LEUKEMIA/LYMPHOMA

Screening Survivors of Childhood Acute Lymphoblastic Leukemia for Obesity, Metabolic Syndrome, and Insulin Resistance

Hasan Karakurt, Nazan Sarper, Suar Çakı Kılıç, Sema Aylan Gelen, and Emine Zengin

Department of Pediatrics, Division of Pediatric Hematology, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey

Acute lymphoblastic leukemia (ALL) survivors were screened for risk factors of cardiovascular disease. Forty-four ALL survivors in first remission were enrolled. Twenty-six also received 12–18 Gy cranial radiotherapy (RT). Patients’ body mass indexes (BMIs) at diagnosis and during the study were compared. Metabolic syndrome (MS) evaluation was performed in patients, parents, and siblings older than 6 years. Homeostasis Model Assessment (HOMA) index of the survivors was also calculated. In survivors with impaired fasting glucose levels, oral glucose tolerance test (OGTT) was performed. Thyroid functions and IGF-1 and/or IGFBP-3 levels of the survivors who received cranial RT were evaluated. Median age of the survivors was 11.5 years (6–23). At diagnosis, mean BMI percentile was 46.7 (3–95) and mean z-score was $-0.09 \pm 1.14$; during the study, these values rose to $71.1 \pm 25.6$ (3–100) and $0.8 \pm 0.94$, respectively ($P < .001$). One patient (2.2%) and nine survivors (20%) were obese at diagnosis and during the study, respectively ($P = .005$). Survivors had significantly higher BMI percentile and BMI z-score compared to their siblings ($P = .006$ and $P = .011$, respectively). The study group was small and we could not show a correlation of the patients’ obesity with RT, thyroid functions, IGF-1, and IGFBP-3 levels. In three survivors (6.8%), there was MS. Maternal and paternal MS was not found as a risk factor for MS of the survivors ($P = .1$, $P = .5$, respectively). The HOMA index revealed insulin resistance (IR) in 12 (27.2%) of the survivors, whereas OGTT revealed abnormal glucose regulation and/or IR in four. As a conclusion, ALL survivors have high risk for obesity and MS.

Keywords ALL, insulin resistance, late effects, metabolic syndrome, obesity

INTRODUCTION

An overall survival rate for acute lymphoblastic leukemia (ALL) of children younger than 18 years is now about 85% [1]. Improved survival has focused attention on long-term sequel of treatment. Among these sequela, components of the metabolic syndrome (MS), obesity, and hypertension are particularly well documented [2–4]. A Childhood Cancer Survivor Study covering a large cohort showed that after 25-year follow-up, ALL survivors had severe or life-threatening chronic medical conditions 3.7 times more than their siblings. Following musculoskeletal problems, the second
frequent medical condition was cardiovascular, including congestive heart failure and coronary artery disease on medication, myocardial infarction, cardiac arrest, and cerebrovascular accidents. Nonirradiated and nonrelapsed survivors were 2.0 times as likely to report a severe life-threatening condition and 1.9 times as likely to report two or more chronic medical conditions, compared with their siblings, although survivors were younger than their siblings (median age of the survivors 26 years, siblings 31 years) [5].

In this study, the aim was screening ALL survivors for obesity, MS, insulin resistance (IR), and investigating their relation with cranial radiotherapy (RT), familial obesity, and familial MS. During screening, recommendations about healthy diets and physical activity were given to the survivors to prevent cardiovascular disease and development of type 2 diabetes mellitus (DM).

METHODS

Approval of the local ethics committee and written informed consent of the survivors, siblings, and the parents were obtained for the study.

Study Group

All childhood ALL survivors who were diagnosed between June 2000 and May 2007, who had been off-treatment for at least 3 years, and were older than 6 years during the study were informed about the study by telephonic calls. Due to foundation of the hematology clinic in 2000 with only four beds, the number of patients was small in those years. Patients received a modified Berlin–Frankfurt–Munster (BFM-95) chemotherapy protocol. Twenty-six patients also had 12–18 Gy cranial RT. Relapsed patients and patients who underwent hematopoietic stem cell transplantation were not included.

Data Collection

Demographic data were obtained from hospital records.

Definitions and Methods of Measurements

All measurements were performed by a senior research assistant of pediatrics with equipment sensitive to 0.5 kg and 0.5 cm. Weight and height were measured without shoes and with light clothes. Waist circumference (abdominal circumference midway between the lowest rib and the top of the iliac crest at the end of expiration) was measured with a nonelastic tape with the subject in a standing position. Waist circumferences of children were evaluated using reference values of Turkish children [6]. Values >90th percentile were regarded as representing abdominal obesity.

Body mass index (BMI = weight/square of height) was calculated using computer program of the Centers for Disease Control and Prevention (CDC). To standardize BMIs of the survivors, BMI was converted to percentiles for age and sex using national reference values and converted to z-scores from the CDC website [7, 8]. Obesity and overweight for children and adolescents were defined as BMI ≥95th percentile (z-score >1.65) and ≥85th percentile to <95th percentile (z-score >1 to <1.65) for age and sex, respectively; for adults, obesity and overweight BMI ≥30 and ≥25 to <30, respectively. In our national reference values, there were percentiles of BMI, but there were no z-scores, so we used CDC values. Height and weight of Turkish and US children were similar [7].

The investigator used standard sphygmomanometer with mercury to measure blood pressures. During blood pressure measurements, survivors were in sitting position after a period of at least 5 minutes. Appropriate cuff size was used. If blood
pressure was >95 percentile for age, blood pressure measurements were repeated in the next two visits, and mean of three measurements was used. Measurements according to International Diabetes Federation (IDF) MS criteria were performed in the survivors, parents, and in the siblings elder than 6 years, and whose age was close to the patient [9].

IR of the patients was evaluated with Homeostasis Model Assessment (HOMA) index. HOMA index = fasting insulin (µU/mL) × fasting blood glucose (mg/dL/405). IR was defined as HOMA index ≥3.16 for puberty; ≥2.5 for prepuberty, and postpuberty [10, 11]. (Tanner stage I prepuberty, stage II–IV puberty, and stage V postpuberty.)

Impaired glucose tolerance was defined as fasting glucose level ≥100 mg/dL and/or 120-minute glucose level 140–200 mg/dL. In survivors with impaired fasting glucose, oral glucose tolerance test (OGTT) was performed and insulin levels were determined. After a 3-day high-carbohydrate diet (300 g/day) and an overnight fast, a standard OGTT (1.75 g/kg or a maximum of 75 g glucose) was performed. Blood samples were obtained at baseline and at 30, 60, 90, and 120 minutes after glucose administration, for glucose and insulin measurements. Subjects were defined as having IR if fasting insulin level was greater than 15 µU/mL during prepuberty, 30 µU/mL at puberty, and greater than 20 µU/mL after puberty, and/or peak insulin level greater than 150 µU/mL and/or 120 minute level greater 75 µU/mL. Diabetes was defined as a fasting glucose level ≥126 mg/dL or 120-minute glucose level ≥200 mg/dL [12, 13].

Laboratory Assays
Blood samples for serum glucose, insulin, triglyceride, and high-density lipoprotein (HDL) were obtained after 8–12 hours of fasting and were analyzed the same day in the local laboratory using Abott aeroset. Serum glucose was measured with hexokinase enzyme reaction at 340 nm wavelength; HDL and triglyceride were measured after enzymatic calorimetric reaction at 500 nm wavelength by spectrophotometric method. Insulin levels were measured using the electrochemiluminescence method with BIODPC Immulite 1000. In patients exposed to RT, thyroid functions (TSH, TT4), growth hormone insulin-like-growth factor (IGF-1), and IGF-binding protein (IGFBP-3) were also measured with electrochemiluminescence using Roche Modüler E-170 immunologic analyzer system. IGF-1 and IGFBP-3 lower than −2 standard deviation score (SDS) were evaluated as deficiency according to national percentiles [14].

Statistical Analysis
Statistical analyses were performed using the SPSS software version 16. The variables were tested using Kolmogorov–Smirnov to determine whether or not they are normally distributed. Descriptive analyses were presented using medians for the abnormally distributed or means and standard deviations for normally distributed. The chi-square test or Fisher’s exact test was used to compare categorical variables in different groups. The Wilcoxon test was used to compare BMI percentiles and BMI z-scores in diagnosis and during the study. Independent sample t-test was used to compare BMI z-score and BMI percentiles of the survivors and siblings. One-way ANOVA was used to compare laboratory parameters of the survivors and the family members. When an overall significance was observed, pairwise post hoc test (Scheffe’s test) was performed. The Kruskal–Wallis test was used to compare the HOMA index at different stages of puberty. Mann–Whitney U-test was performed to test the significance of pairwise difference using Bonferroni correction to adjust for multiple comparisons. An overall P-value of less than .05 was considered significant.
RESULTS

Between June 2000 and May 2007, 75 pediatric patients with ALL were accepted to the unit. There were 14 relapse (five of them still alive in second remission) and four deaths due to other causes (two hepatotoxicity, one infection, and one apneic seizure). Five patients who were younger than 6 years during the study were not enrolled due to lack of standards for MS and BMI percentiles. Fifty-two patients with no event and still living in our region and were older than 6 years were eligible for the study. Eight survivors were either lost to follow-up or their personal contact details were changed or their families refused to participate due to being off work. Out of 52 eligible survivors, 44 were enrolled. Twenty-five male and 19 female survivors with median age 6 years (2.5–17.5) at diagnosis and 11.5 years (6–23) during the study were enrolled. Mean time following diagnosis was 5.4 (3–10) years. Forty-four mothers, 43 fathers (one father was dead), and 32 siblings were enrolled. Twenty-five percent ($n = 11$) and 48% ($n = 21$) of the patients were obese/overweight at diagnosis and during the study, respectively. At diagnosis, only two patients (4.5%) had obesity whereas nine survivors (20%) had obesity ($P = .005$). The BMI $z$-scores of the survivors was significantly higher compared to $z$-scores at diagnosis ($P < .001$; Figure 1). Mean age of the siblings was 16.3 ± 5.8 years (range 7–29 years, median 16.5 years). Out of 32 siblings, gender of 21 was matched to the survivors. Survivors had significantly higher BMI $z$-score and BMI percentile compared to their siblings ($P = .011$ and $P = .006$; Figures 2 and 3).

When BMI of all the patients of the Center was evaluated at diagnosis, median and mean BMI percentile was 51.56 (0.90–89.90) and 51.82 ± 31.09, respectively, in relapsed patients ($n = 14$), whereas in patients alive in first remission ($n = 57$) median and mean BMI percentile was 45 (0.7–99.90) and 48.99 ± 31.46, respectively. Difference was not significant between relapsed patients and patients in first remission ($P = .82$).

![FIGURE 1] Comparison of the BMI $z$-scores of the survivors at diagnosis and during the study.
FIGURE 2 Comparison of the BMI z-scores of the survivors and siblings.

FIGURE 3 Comparison of the BMI percentiles of the survivors and siblings.
TABLE 1  Frequency of Obesity and Metabolic Syndrome Criteria in Survivors and Their Families

<table>
<thead>
<tr>
<th>Frequency of Obesitiy and Metabolic Syndrome Criteria</th>
<th>Survivors</th>
<th>Sibling</th>
<th>Mother</th>
<th>Father</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 44</td>
<td>n = 32</td>
<td>n = 44</td>
<td>n = 43</td>
<td></td>
</tr>
<tr>
<td>Obesitiy BMI &gt;95%</td>
<td>9 (20.5%)</td>
<td>5 (15.6%)</td>
<td>21 (47.7%)</td>
<td>15 (34.9%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>8–33%</td>
<td>3–28%</td>
<td>33–62%</td>
<td>20–49%</td>
</tr>
<tr>
<td>Overweight BMI between 85% and 95%</td>
<td>12 (27.3%)</td>
<td>4 (12.5%)</td>
<td>13 (29.5%)</td>
<td>22 (51.2%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>12–38%</td>
<td>1–24%</td>
<td>16–43%</td>
<td>36–66%</td>
</tr>
<tr>
<td>Increased waist circumference</td>
<td>17 (38.6%)</td>
<td>14 (43.8%)</td>
<td>36 (81.5%)</td>
<td>29 (67.4%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>24–53%</td>
<td>27–61%</td>
<td>70–93%</td>
<td>53–81%</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>2 (4.5%)</td>
<td>1 (3.1%)</td>
<td>11 (25%)</td>
<td>19 (44.2%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0–10%</td>
<td>0–9%</td>
<td>12–37%</td>
<td>29–59%</td>
</tr>
<tr>
<td>Low HDL</td>
<td>14 (31.8%)</td>
<td>6 (18.8%)</td>
<td>23 (52.3%)</td>
<td>18 (41.9%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>18–46%</td>
<td>5–32%</td>
<td>38–67%</td>
<td>27–57%</td>
</tr>
<tr>
<td>Fasting blood glucose &gt;100 mg/dL</td>
<td>8 (18.2%)</td>
<td>2 (6.3%)</td>
<td>12 (27.3%)</td>
<td>12 (27.9%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>7–30%</td>
<td>0–14%</td>
<td>14–40%</td>
<td>14–41%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>1 (3.1%)</td>
<td>13 (29.5%)</td>
<td>13 (30.2%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0</td>
<td>0–9%</td>
<td>16–43%</td>
<td>16–44%</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>3 (6.8%)</td>
<td>0</td>
<td>21 (47.7%)</td>
<td>16 (37.2%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0–14%</td>
<td>0</td>
<td>33–62%</td>
<td>23–52%</td>
</tr>
</tbody>
</table>

Frequency of no parameter was significantly different between the survivors and the siblings. The frequency of overweight in fathers and obesity in mothers was significantly higher compared to the survivors and the siblings. The frequency of increased waist circumference, hypertriglyceridemia, hypertension, and metabolic syndrome was significantly higher in parents compared to the survivors and the siblings. The frequency of low HDL and fasting blood glucose >100 mg/dL was significantly higher in parents compared to the siblings.

At diagnosis, in patients having an event (relapse + toxic death = 18), BMI percentile was median 63.50 (0.90–100) and mean 56.98 ± 29.97. When compared with patients without event (n = 57), there was no significant difference (P = .38).

The BMI percentile of ALL patients diagnosed in June 2000–May 2007 (n = 75) was compared with patients diagnosed in June 2007–December 2011 (n = 71). The BMI percentiles were median 46.3(0.70–100), mean 50.91 ± 31.10 and median 50.30(0–99.90), mean 48.69 ± 33.27 (P = .64), respectively.

The frequency of the obesity and MS criteria of the survivors and their families are shown in Table 1.

Out of 21 mothers with MS, three had children with MS (3/21, 14.2%). Out of 16 fathers with MS, two had children with MS (2/16, 12.5%). MS of the survivors had no correlation with maternal and paternal MS (P = .1, P = .5). Laboratory parameters of the MS of the survivors and their families are shown in Table 2. Fathers had significantly high triglyceride and low HDL levels compared to the family members.

Twenty-six of the survivors had cranial RT; only five survivors were exposed to 18 Gy and the rest to 12 Gy. In survivors exposed to RT and not exposed to RT, obesity/overweight ratio was 13/26 (50%) and 8/18(44%), respectively. MS incidence in patients exposed to RT and not exposed to RT was 2/26 (7.6%) and 1/18(5.5%), respectively. We could not show a correlation between obesity/overweight and MS with RT (P = .7 and P = 1, respectively). Among survivors exposed to RT, only three (11.5%) had thyroid dysfunction with elevated TSH and normal T4. Among survivors exposed to RT, five were obese and only one of these five survivors had thyroid dysfunction. There was no correlation between obesity and thyroid dysfunction (P = .4). Out of 26 survivors exposed to RT, 12 survivors (46.1%) had both IGF-1 and IGFBP-3 deficiency. Out of these 12 survivors, five (41.6%) were obese/overweight. IGF-1 and IGF-3 deficiency was not found as a risk factor for obesity (P = .4).
TABLE 2  Laboratory Parameters of the Metabolic Syndrome of the Survivors and Their Families

<table>
<thead>
<tr>
<th></th>
<th>Survivors (n = 44)</th>
<th>Siblings (n = 32)</th>
<th>Mother (n = 44)</th>
<th>Father (n = 43)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>80.02 ± 40.13</td>
<td>83.6 ± 30.9</td>
<td>117.9 ± 65.4</td>
<td>170.9 ± 107.4</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>49.4 ± 10.1</td>
<td>52.1 ± 10.9</td>
<td>50.3 ± 13.0</td>
<td>42.2 ± 10.0</td>
<td>.001†</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>93 ± 8</td>
<td>86.7 ± 7.2</td>
<td>103.6 ± 48.7</td>
<td>99.6 ± 19.1</td>
<td>.047†</td>
</tr>
</tbody>
</table>

* Difference was significant between father and survivor; father and sibling; father and mother (P < .001, P < .001, P = .007; respectively).
† Difference was significant between father and survivor; father and sibling; father and mother. (P = .035, P = .003, P = .012; respectively).
‡ Difference was not significant between the pairs.

HOMA index revealed that in 12 (27.2%) of the survivors, there was IR and in eight (17%) there was impaired fasting glucose (≥100 mg/dL). In three (6.6%) of the survivors, there was both IR and impaired fasting glucose. Incidence of IR was significantly increased with progression of pubertal stage (Table 3). Among eight survivors with impaired fasting glucose, OGTT revealed abnormal glucose regulation and/or IR in four. There was no survivor with type 2 DM.

DISCUSSION

ALL is the most common childhood malignancy with marked improvement in survival over the last three decades. Some toxicity and long-term sequelae of treatment are currently inevitable as cardiotoxicity of antracyclines; cranial RT-induced neurocognitive, neuropsychologic deficits, CNS tumors; epipodophyllotoxin, antracyclin-induced secondary acute myeloblastic leukemia. Screening survivors for obesity, MS, and IR and to change these cardiovascular risk factors may prevent long-term morbidity and mortality of the survivors.

In growing children, the BMI changes significantly with age, and BMI percentiles by age and z-scores are used to classify the appropriateness of weight in children. In the present study, we found that survivors had significantly increased BMI percentiles and z-scores compared to BMI at diagnosis of leukemia. In a study screening schoolchildren in our district, the prevalence of obesity was 6.8% and overweight was 11.5%, which were lower than ALL survivors [15].

TABLE 3  HOMA Index and Insulin Resistance (IR) Regarding Stage of Puberty

<table>
<thead>
<tr>
<th>Tanner stage</th>
<th>Prepuberty Stage 1 (n = 20)</th>
<th>Puberty Stage 2–4 (n = 17)</th>
<th>Postpuberty Stage 5 (n = 7)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HOMA index ± SD</td>
<td>1.69 ± 1.73 (0.4–8.6)</td>
<td>3.07 ± 2.68 (0.7–11.7)</td>
<td>3.07 ± 1.07 (2.0–4.7)</td>
<td>.006*</td>
</tr>
<tr>
<td>(Min–max) Reference value</td>
<td>&gt;2.5</td>
<td>&gt;3.16</td>
<td>&gt;2.5</td>
<td></td>
</tr>
<tr>
<td>Number of patients with insulin resistance (%)</td>
<td>1 (5%)</td>
<td>7 (41.2%)</td>
<td>4 (57.1%)</td>
<td>.007**</td>
</tr>
</tbody>
</table>

* Kruskal–Wallis test revealed significant difference in survivors at different stages of puberty. Bonferroni correction and Mann–Whitney U-test showed that the difference was significant between prepuberty and postpuberty (P = .002).
** Fisher’s exact test showed that the difference was between prepuberty, puberty; prepuberty and postpuberty (P = .011, P = .009, respectively).
In 1986, Zee and Chen at St. Jude Children’s Research Hospital provided the first report of excess weight gain of 414 ALL survivors. Significant increases in BMI occurred during the first year off-therapy, at the end of which 35% of the children were overweight and 12% were obese [16]. In a review by Rogers et al. [17], the reported prevalence of overweight/obesity in ALL survivors ranged between 11% and 57%. We found that there was overweight/obesity in 25% of the patients at diagnosis. At least 3 years off-therapy, overweight/obesity percentage increased to 48%. Many other studies also found a similar increase [18–20]. Trimis et al. [21] reported that after a mean interval of 5.9 years since completion of therapy, 25% of survivors were obese and 44% were overweight. Their findings were very similar to ours, and both studies revealed early onset overweight and obesity. To avoid a bias, we also evaluated BMI of children that were not enrolled in our study due to events (relapse, toxic death, etc.) or some other reasons. There was no difference in BMI at diagnosis compared to enrolled patients. Also, there was not a correlation between BMI of patients with and without event. By comparing BMI at diagnosis in patients diagnosed between 2000–2007 and 2007–2011, we also showed that in ALL patients followed in our Center there was not a trend for changes in BMI at diagnosis by years; however, there is a trend for obesity in ALL survivors.

In Childhood Cancer Survivor Study, the BMI of 1765 adult survivors of childhood ALL were compared to 2565 adult siblings, and increased obesity was found in survivors. Obesity was not associated with treatment consisting of chemotherapy only or with cranial RT doses of 10–19 Gy. Cranial RT $\geq$ 20 Gy was associated with an increased prevalence of obesity especially in females treated at a young age [19]. But Gofman and Ducore did not find significant association between obesity at follow-up and craniospinal RT. They reported that patients who were older at diagnosis were more likely to be obese at follow-up [20]. In our study, out of nine obese children, six were younger than 6 years at diagnosis and four did not have cranial RT. We also found no difference in overweight/obesity between survivors who had only chemotherapy versus chemotherapy plus cranial RT. Razzouk et al. reported that the overall percentage of survivors who were overweight or obese approximated rates prevalent in the general population of the United States. Young age (<6 years) and overweight/obesity at diagnosis were the best predictors of obesity at adult height. The BMI increase did not differ significantly between children that received RT or not, nor between patients that received 18 or 24 Gy of cranial RT [22]. In the last two decades, prophylactic or therapeutic doses of cranial RT in the first line therapy of ALL are reduced to $\leq$ 18 Gy in BFM protocols. In our cohort, 21 patients received 12 Gy and five patients received 18 Gy. New studies may show that reduced cranial RT doses may not contribute to excessive weight gain in ALL survivors.

Some studies reported overweight/obesity at diagnosis and maternal obesity/overweight as predictive factors for overweight/obesity of ALL survivors [18]. We did not find any association with overweight/obesity of parents or siblings. During therapy, there are risk factors for excessive weight gain. Among chemotherapeutic agents, corticosteroids and L-asparaginase interact with glucose metabolism, and can cause IR and decrease in insulin secretion, respectively. Patients are physically inactive during long treatment period. Steroid-induced myopathy and vinca alkaloids induced neuropathy are additional risk factors for inactivity. Steroids also cause polyphagia. We observe that during maintenance chemotherapy, patients are partially off school and in the follow-up period parents are overconservative and limit survivors from outdoors and overfeed them. True estimation of the nutrition practice of the family is not easy. In low economic status, proportion of carbohydrates and fat in the diet is high because protein-rich foods as meat and dairy products are more expensive in our country. Regular sports activities in our
Components of MS according to IDF are central obesity, fasting glucose, dyslipidemia, and hypertension. Abdominal obesity increases the risk of cardiovascular and cerebrovascular disease and type 2 DM. Adipose tissue is considered as an endocrine organ and as a source of inflammatory mediators and has role in the development of IR. MS screening showed a frequency of 6.8% in survivors, and there was no association with familial MS. In our city, 2.3% of school children had MS according to IDF criteria. One-third of the obese children had MS [15]. In survivors, two out of nine obese children had MS. In a study of 52 ALL survivors who had received no cranial RT, three subjects had MS similar to our MS frequency [23]. In Trimis et al.'s [21] study, patients who received chemotherapy only had a twofold increase (8%), and those who received chemotherapy + 18 Gy cranial RT had fivefold increase (22%) in MS as compared to healthy children in the population. In Turkish women >20 years (mean 39.4 year) prevalence of metabolic syndrome was 31.9% in a study performed in 2006 [24]. This prevalence was lower than our mothers. In Turkish population, prevalence of overweight and obesity in women were 20.4% and 22.1%, respectively; the same prevalences were 17.4% and 7.8% in men [25]. In our study, mothers and fathers had a higher frequency for obesity and overweight in both sexes.

IR is defined as an impaired ability of plasma insulin at usual concentrations to adequately promote peripheral glucose disposal, suppress hepatic glucose, and inhibit very low-density lipoprotein output. The HOMA is a simple method to measure IR [10]. IR is the precursor of type 2 diabetes and it begins in childhood. Exercise and diet programs and metformin can prevent type 2 diabetes [13]. We found that 27.2% of the survivors had increased HOMA index.

In a recent study, derangements in adipokines were found as factors that change body composition and cause IR in ALL survivors. They suggested that emerging central leptin resistance causes store of energy instead of burn of energy. This resistance may be a result of hypothalamic damage or downregulation of hypothalamic leptin receptors. Leptin was strongly associated with IR in overweight and obese survivors [4]. Karaman et al. found that in female ALL survivors who received cranial RT, leptin levels were higher than their age-matched healthy controls, and there was a significant correlation with serum leptin levels and BMI–SDS of these irradiated female survivors [26]. In healthy subjects, IR increased immediately at the onset of puberty (T2), but returned to near prepubertal levels by the end of puberty (T5). IR was strongly related to BMI, triceps skin fold thickness, and waist circumference, and this relationship was independent of Tanner stage or sex. [27]. We evaluated IR with reference values of pubertal stage and found increased incidence with progression of pubertal stage.

Cranial RT may cause deficiency in growth hormone and thyroid hormones [28]. Franco et al.[29] had shown that growth hormone therapy reduces abdominal visceral fat content, total and LDL-cholesterol concentrations, and improves insulin sensitivity. IGF-1 has an important role in mediating the effects of growth hormone and its main transporter is IGFBP-3. Serum IGF-1 and IGFBP-3 levels increase as the child grows, reach a peak value at puberty, and decrease with aging. Growth hormone is the main regulator of their production [14]. We found decreased IGF-1 and/or IGFBP-3 levels in about half of the irradiated patients according to reference values. Argüelles et al. studied IGF system longitudinally, in 26 prepubertal children with ALL at diagnosis and 6, 18, 24, 30, and 36 months after beginning treatment. Serum IGF-1, IGF-2, and IGFBP-3 levels were significantly decreased at diagnosis. Normalization of IGF-2 and IGFBP-3 occurred 6 months after diagnosis, and normalization of IGF-1, 1 year after terminating therapy. Free IGF-1 was elevated throughout the study. There was no difference between children irradiated with 12 Gy or not irradiated [30]. Birkebaek
et al. studied growth hormone and IGF-1 and IGFBP-3 in 38 ALL patients after 14 years of diagnosis. Eighteen were irradiated with 24 Gy. Eleven patients (nine in the irradiated group) had growth hormone (GH) deficiency with two provocative tests. IGF-1 was significantly lower and IGFBP-3 was higher in GH-deficient survivors compared to the group with sufficient GH response ($P < .02$) [31].

A simple 16-week home-based exercise program was effective in improving cardiometabolic risk factor status and fitness in young adult survivors of childhood ALL. Fasting plasma insulin ($P = .01$), HOMA-IR ($P = .002$), waist circumference ($P = .003$), waist-to-hip ratio ($P = .002$), fat percent ($P = .04$), and supine diastolic blood pressure ($P = .03$) decreased during the program, while weight and BMI remained unchanged [32].

A limiting factor of the study was the number of the patients, which reduced the statistical power. Due to financial reasons, we could not compare thyroid functions and IGF-1, IGFBP-3 of the irradiated survivors with survivors that received only chemotherapy.

As a conclusion, we found that ALL survivors have higher risk for obesity and MS compared to the population and their siblings. Screening of the survivors and giving recommendations about healthy diet and physical activity may be useful for prevention of cardiovascular disease and type 2 diabetes.

**Declaration of Interest**

The Research Fund of Kocaeli University supported the study. The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

**REFERENCES**


[11] Madeira IR, Carvalho CN, Gazolla FM, et al. Cut-off point for homeostatic model assessment for insulin resistance (HOMA-IR) index established from receiver operating characteristic (ROC) curve...


