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Obesity, Dyslipidemia and Insulin Resistance in Survivors of Childhood Cancer

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Abstract

Background: With the increased survival rates following the treatment of childhood cancer, it becomes equally important that the need for evidence based surveillance of long term effects of cancer therapy is addressed. This includes the risk of development of metabolic syndrome features like obesity, altered lipid and sugar profile, which was attempted in the present study.

Materials and Methods: In this cross sectional case study, 50 survivors of childhood cancer aged between 5 – 18 years were recruited. Positive history of obesity, diabetes mellitus, dyslipidemia, and stroke in family were recorded and their anthropometry was noted with calculation of their Body Mass Index (BMI). Fasting lipid profile, blood sugar, and serum insulin levels were tested; the Homeostatic model assessment of Insulin Resistance (HOMA IR) value and the Fasting Glucose to Insulin Ratio(FGIR) were derived as markers of insulin sensitivity. The data were analyzed using SPSS (version 17.0).

Results: In these fifty children, the risk factors studied for dyslipidemia and insulin resistance due to chemotherapy were: age at diagnosis, sex, radiation exposure, steroid, and L-asparaginase use during the treatment for cancer. Among the fifty survivors, 7 were found obese, 32 normal, and 11 underweight as per the age specific BMI charts. Their metabolic parameters showed that 12 had raised cholesterol levels, 8 had raised triglyceride levels, and 4 had lowered HDL-C levels. Nine survivors also had raised HOMA-IR levels. However, these metabolic derangements were not found to be statistically significant (p value>0.05) and no correlation was found between the risk factors and obesity, dyslipidemia, or insulin resistance.

Conclusion: As against the prior evidence, there was no risk of developing obesity, dyslipidemia, and insulin resistance in survivors of childhood cancers.

Keywords: Dyslipidemias, Insulin Resistance, Obesity, Survivors of childhood cancer

Introduction

With rapid strides in the advances made in the treatment of childhood cancer, there is a marked improvement in the outcome and prognosis of childhood cancers and with it there is an increasing population of survivors of childhood cancer (1, 2, 3). Recent advances have also shown that the treatment of childhood cancers does not end with the completion of the formulated protocols and these children need follow up throughout their adulthood to evaluate the long term effects of the chemotherapy and radiotherapy. Previous study has shown that the prevalence of obesity and overweight among the survivors was not higher than that of the general population but they are at risk of obesity and overweight and this is of greater concern in them due to an increased risk of long term sequelae, including cardiovascular disease, hypertension, and metabolic syndrome (4, 5, 6). This formed the basis for the present study which aimed to focus on survivors of pediatric cancer and the prevalence of obesity, dyslipidemia, and impaired glucose tolerance in this study population. Studies have also shown that there are risk factors which predispose this population of children towards obesity and other metabolic complications; however, there are very few Indian studies available

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at present, analyzing the risk factors for the above said complications. Hence, this study was undertaken among survivors of childhood cancer to evaluate the prevalence of obesity, dyslipidemia, and insulin resistance and to identify the risk factors predisposing these complications.

Materials and Methods

The study was conducted at a tertiary care teaching hospital with patients from coastal Karnataka and northern districts of Kerala. The institutional ethical clearance was obtained before initiating the study (KMC27082009). This was a cross sectional observational study where fifty (50) children selected by convenient and time-bound sampling, The children aged between 5 and 18 years of age who were successfully treated for childhood cancers. Any child with any prior endocrine problem or on chronic steroid intake for other chronic medical conditions was excluded. Written informed consent was obtained from the parents/guardians of the patients before enrolment. None of the patients declined enrolment. The study pro forma included details of diagnosis, age at diagnosis, treatment protocol, chemotherapy, radiotherapy, , and family history of obesity, dyslipidemia, and diabetes mellitus. Patients' weight and height were recorded by a single observer. The body mass index (BMI) was calculated and survivors were classified as underweight (below 95% percentile) as per Agarwal's chart (7). A fasting blood sample was obtained from all patients to measure lipid profile (Serum triglyceride level, LDL, VLDL, HDL, and total cholesterol), blood glucose, and serum insulin levels. The timing of the sample coincided with the timing of the mandatory follow up investigation in the patients. Blood glucose was estimated by enzymatic colorimetric method using glucose-peroxidase method (GODPAP). Serum triglycerides were estimated by enzymatic calorimetric test (GPO-PAP); total cholesterol by cholesterol oxidase and peroxidase method (CHOD-PAP); HDL by enzymatic calorimetric test; and LDL by Friedwald's Formula. Serum insulin was estimated by chemiluminescent assay. Abnormalities in fasting levels lipid profile were considered abnormal as per the values given by Khalil (8) .The Homeostasis Model of Assessment of Insulin Resistance (HOMA –IR) and Fasting Glucose Insulin Ratio (FGIR) were calculated from the Serum insulin level and fasting blood glucose level as markers of insulin resistance. The HOMA IR cut off of 3.16 was used and used FGIR was < 7(9).

Statistical analysis

Data were analyzed using SPSS (version 13.5). Fisher's Exact Test was used for categorical variables and T test was used for continuous variables. P value less than 0.05 was taken as statistically significant.

Results

When the demography of the study population was plotted, majority of the children were survivors of Acute Lymphoblastic Leukemia (80%); survivors of childhood lymphomas formed the next group (10%), and the remaining were survivors of CNS (4%) and abdominal malignancies (6%). Given that the identified risk factors for obesity, dyslipidemia, and impaired glucose tolerance were female sex, steroid, L-Asparaginase use in chemotherapy protocols, radiation exposure, and early age at diagnosis, these factors were studied in detail in the current investigation. In all the fifty children, the analysis was done to assess these risk factors and their association with BMI, total cholesterol, triglycerides, HDL-C levels, HOMA IR, and FGIR. Table I depicts the overview of the study population.

With respect to their BMI as per Agarwal's BMI charts for age, 7 children were obese, 32 were normal, and 11 were underweight. When the laboratory

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parameters were analyzed, 12 had raised cholesterol, 8 had raised triglyceride levels, 6 showed elevation in LDL-C, 4 children had lowered HDL-C levels, and 9 had elevated HOMA –IR values.

Association between BMI and risk factor exposure*:* Table 2 shows the association between BMI and the risk factors identified earlier. According to Table II, 2 patients were female, 6 were diagnosed below 9 years of age, 6 had steroid as part of their chemotherapy, 5 had exposure to cranial radiation, and 6 had been treated with Lasparaginase as a part of the chemtherapy protocol. Statistical tests; however; did not show any significant association between the risk factors and BMI.

Association between dyslipidemia and risk factor exposure**:** According to Table II, 12 patients had raised serum cholesterol levels. The mean of cholesterol level was 165.74mg/dl and the maximum cholesterol value was 241mg/dl in the survivor population. Among the 12 patients with raised cholesterol, 5 were female, 9 were diagnosed below 9 years of age, 10 had steroids in the regimen, 7 had exposure to cranial radiation, and 9 were treated with L-asparaginase. No statistically significance difference was observed either. The association of raised triglyceride levels was studied with respect to the risk factors and it was found that 8 patients had raised triglyceride levels, with mean level of 75.72mg/dl and a maximum value of 147 mg/dl. Among these 8 patients, 3 were female, all 8 were diagnosed at an age below 9 years, all received steroids, 5 had exposure to cranial radiation and 7 were treated with L-asparaginase. Despite these observations, no statistically significant association was observed between raised triglyceride levels and the risk factors. In Table III, a comparison was made between the lipid profiles of the survivor population as against the general Indian children population no statistically significant difference was found though in this study the range was slightly higher among the survivor group with respect to the lipid profile.

Association between markers of insulin resistance and risk factor exposure: In this study, serum Insulin levels were analyzed and raised insulin levels were found in 6 survivors and low insulin levels were found in 12 survivors (Range 0.70 to 22 mIU/ml). Comparing the fasting sugar values, 11 children with low insulin levels, 30 with normal insulin levels, and 5 with raised insulin levels had normal FBS. One child with low insulin levels, 2 with normal insulin level, and 1 with high insulin level had high FBS. Then, HOMA IR values were calculated, with the cut off being 3.16. Table IV shows the relationship between the risk factors in the survivor population and their HOMA IR values. Nine patients had raised HOMA-IR values, of whom, 4 were female, 6 were diagnosed below 9 years of age, 8 had steroids in the regimen, 7 had exposure to cranial radiation, and 8 were treated with L-asparaginase. Similar to the above analyses, there was no statistically significant association between raised HOMA-IR and the risk factors.

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Table I: Demography and laboratory parameters of the study population

Parameter		Number of survivors Total no - 50	Percentage
Sex	Male	32	64%
	Female	18	36%
Age at Diagnosis	<9 years	39	78%
	>= 9yrs	11	22%
BMI	Underweight	11	22%
	Normal	32	64%
	Overweight	7	14%
Total cholesterol	Normal	38	76%
	Raised	12	24%
Triglycerides	Normal	42	84%
	Raised	8	16%
HDL - C	Normal	46	92%
	Lowered	4	8%
Serum Insulin	Normal	32	64%
	Raised	6	12%
	Lowered	12	24
HOMA IR	Normal	41	82%
	Raised	9	18%

Table II. Association between the risk factors induced by cancer chemotherapy and BMI and markers of Dyslipdemia

Risk factors studied		**BMI**			**p value**	**Total Cholesterol**		**p value**	**Serum Triglycerides**		**p value**
		Obese n = 7	Normal n = 32	Underweight n=11		Raised n = 12	Normal n = 38		Raised n= 8	Normal n = 42	
Sex	Female	2	12	7	>0.05	5	13	0.220	3	15	>0.05
	Male	5	20	4		7	25		5	27	
Age at diagnosis	Below 9 yrs	6	26	7	0.447	9	30	0.544	8	32	0.086
	9 and Above 9 yrs	1	6	4		3	8		0	10	
Steroid Use	Used in treatment	6	29	10	0.167	10	35	0.780	8	40	0.599
	Not used	1	3	1		2	3		0	2	
Radiation exposure	Radiotherapy received	5	15	10	7.05	7	24	0.779	5	27	0.599
	Not received	2	17	1		5	14		3	15	
L Asparaginase	Used in treatment	6	24	8	0.444	9	29	0.602	7	32	0.691
	Not used	1	8	3		3	9		1	10	

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Table III: Lipid Profile comparison between cancer survivor population and general Indian children

Parameter	Lipid profile in survivor population		Lipid profile in general Indian Children		
	Mean value +/- 1SD	Range	Mean value +/- 1SD	Range	Cut off values used
Total Cholesterol(mg/dl)	165.74±32.10	96-241	134.5±27.1	84-247	190
Triglycerides (mg/dl)	75.72±33.32	29-147	91.1±29.85	27-185	150
HDL-C(mg/dl)	52.02±15.05	24.8-101	34.15±13.05	12-86	20
LDL-C (mg/dl)	98.564±28.25	48-169.5	80.1±21.65	32-202	130

Table IV: Association of the risk factors induced by cancer chemotherapy and marker of insulin resistance (HOMA-IR level)

Risk factors		HOMA IR values Cut off – 3.16		p value (NS- not significant >0.05)
		Raised Total no - 9	Normal Total no - 41	
Sex	Female	4	14	NS
	Male	5	27	
Age at diagnosis	Below 9 yrs	6	30	NS
	9 and Above 9 yrs	3	11	
Steroid Use	Used in treatment	8	36	NS
	Not used	1	5	
Radiation exposure	Radiotherapy received	7	25	NS
	Not received	2	16	
L Asparaginase	Used in treatment	8	29	NS
	Not used	1	12	

Discussion

Fifty survivors of childhood cancer were enrolled in this study. Males formed the majority (64%) of study population. Most of the survivors (78%) were diagnosed and treated below 9 years of age. Out of these fifty survivors, 7 were overweight (14%), 11 were underweight (22%) and the rest were within the normal range. Among the overweight, majority (5 out of 7) were males but this difference was not statistically significant. In a similar study, obesity was found to be common in survivors of acute lymphoblastic leukemia by the end of therapy (10). The findings of another study by Nathan et al., revealed that the prevalence of obesity was not more as compared to the general population after cancer treatment (4), which is in line with our study. Oeffinger et al., in their study found an increased prevalence of obesity in females treated at a young age (11), while Van Donegn et al., reported that 28% of male survivors were

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found to be obese; he also noted that 33% of those diagnosed below the age of 6 and 21% of those diagnosed after the age of 6 years were obese; however, they reported no statistically significant correlation (12). These findings lend strength to the conclusions of this study where a similar result was obtained. In the present study, prevalence of underweight was 11 out of 50 (22%). According to the study done by Nathan et al., on pediatric cancer survivors, only 2.7% were classified as underweight (4). The increased prevalence of underweight survivors in our study correlated with CCSS report on BMI in long term adult survivors of childhood cancer (13)where it was reported that the cancer survivors were less likely to be obese and more likely to be underweight than their siblings. However, this study was done on adult survivors > 5 years after chemotherapy was completed and the current study was done on survivors of >1 year disease free period. This study also stated that underweight survivors were more likely to report adverse health and major medical conditions (13), which is why early detection and frequent monitoring of the metabolic profile of these children needs to be done. The molecular basis and explanation for these alterations found in the BMI was supported by Ross et al., (14). The results of this study showed that there is a genetic variation in leptin receptor gene. This variation leads to abnormalities in the BMI in survivors of childhood acute lymphoblastic leukemia. When the other risk factors were studied, 6 of the 7 obese were diagnosed before the age of 9 years and 5 of them received cranial radiotherapy but this association was not statistically significant. In a study done by Garmeyet al, younger age at diagnosis was a significant risk for obesity (13) but this was not seen in the current study. There was no statistically significant association between overweight and other risk factors such as steroid use, cranial radiotherapy, and L-Asparaginase use. According to Van Dongen et al., patients treated with combination of prednisolone and dexamethasone had, as a late effect, the highest prevalence of obesity (12). In the current study, 6 out of 7 obese survivors had received steroids though this was not statistically significant. Upon analysis of the metabolic profile, in the present study, 12 survivors out of 50 (24%) had raised cholesterol and 8 (16%) had raised triglyceride levels. Comparing the risk factors in these 12 survivors with raised cholesterol, it was found that 10 were treated with steroids. In line with findings of earlier studies, changes in serum cholesterol was consistent with treatment protocols using corticosteroids. Another risk factor of L-Asparaginase use was studied by Cohen et al., (15). They concluded in children with ALL, mean cholesterol level of long term survivors was significantly higher than the normal range (177 mg/dL, p=0.045) and 20% of these patients had raised cholesterol levels after L-asparaginase use. Nine of the 11 survivors with raised cholesterol had received treatment with L-Asparaginase, though no statistical significance was found. Mohapatra et al.,(2016) concluded that there was no significant association between cranial radiotherapy or age at diagnosis and obesity or dyslipidemia (16). In their study, 32% of the survivors were obese or overweight and the prevalence of insulin resistance (17%), hypertriglyceridemia (20%), and low HDL (37%) was comparable to the present study as well as to the prevalence in children in historical population-based studies from India (16). When the serum Insulin levels of the survivors were analyzed; raised insulin levels were found in 6 survivors and low insulin levels were found in 12 survivors (Range: 0.70 to 22 microU/ml). Raised HOMA-IR was found in 9 (18%) out of 50 patients, though no statistical significance difference was observed. Oeffinger et al., compared risk factors for insulin resistance in survivors of childhood ALL and found that female survivors

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treated with cranial radiotherapy had significantly high HOMA-IR (17). In the present study, among 9 children with raised HOMA-IR, 7 received cranial radiotherapy at a high dose; however, it did not lead to a statistically significant difference. Another study was done on 248 survivors by Neviille et al in Australia and hyperinsulinemia/impaired glucose tolerance was detected in 39 of 212 (18%) patients (18). they demonstrated that untreated hypogonadism and abdominal obesity were independent risk factors for the development of various types of glucose intolerance. In the present study, 10 children had a FGIR<7 and 9 had elevated HOMA IR (>3.16). With reference to a study by Keskin et al., (19), it was concluded that HOMA IR was a more reliable index than FGIR for assessing insulin resistance; hence, it was used in the present study as the marker for insulin resistance. In contrast to prior established facts that the risk factors due to childhood chemotherapy cause obesity and altered sugar and lipid profile, the present study did not show any such findings and this can be explained by the newer and milder treatment protocols for childhood cancers, where the chemotherapeutic protocols are decided individually for each child, as well as the increased awareness of parents and children.

Limitations

1. The study had a small sample size and only 50 survivors were included; hence detailed sub-classification into pre and post pubertal children could not be done.
2. Overweight and obesity usually depend on multiple factors and genetic factors have a significant influence on the body composition. Hence, a study with sibling matched controls will be most appropriate, as would be more accurate assessment of body composition using newer and more advanced methods.
3. In addition, the studied abnormalities such as obesity and dyslipidemia depend on the life-style (diet, physical activity) and living conditions (socioeconomic status) too. This could have played a role in achieving non-significant correlation between the risk factors and abnormalities as the possibility of the patient family being well informed of the risks; hence altering their life-style in order to avoid these abnormalities.

Conclusion

Contrary to prior studies, no risk of developing obesity, dyslipidemia, and insulin resistance was found among the survivors of childhood cancers due to their exposure to various risk factors (gender, age at diagnosis, radiation exposure, steroid use, and Lasparaginase use) while receiving childhood chemotherapy. A high number of survivors of childhood cancer develop complications such as obesity, dyslipidemia, and insulin resistance post cancer chemotherapy. The major identified risk factors are cranial radiotherapy, age at diagnosis, sex, steroid usage, and L-asparaginase usage. There is no statistically significant correlation between the risk factors and the complications of metabolic syndrome as reported earlier.

Conflict of interest

Authors declared no conflict of interst.

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