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Premature Atherosclerotic Cardiovascular Disease in Childhood Cancer Survivors

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Abstract

Survival rates of childhood cancer have increased over the last 30 years, revealing a population with unique characteristics and risks. The effects of radiation and cardiotoxic chemotherapy predispose these children to both early and late cardiovascular disease. Cranial radiation also increases the likelihood of growth hormone deficiency, which leads to metabolic disturbances. Childhood cancer survivors are less likely to be active than their healthy siblings, and have a lower aptitude for physical activity. These issues are additive to the usual risks experienced by the general population, thereby significantly increasing the likelihood of premature cardiovascular disease. Early and regular screening and risk factor management in this population is recommended.

Keywords

Atherosclerosis; childhood cancer survivors; cardiovascular disease; growth hormone; metabolic syndrome

1. Introduction

Over 12,000 youth are diagnosed with cancer each year in the United States [1]. With improved treatments for childhood cancers, in the current era (1999–2006), 5-year survival rates have increased to 82% [2] resulting in over 325,000 childhood cancer survivors in the US [3] (1 in 600 children under the age of 14 years). This number is likely to increase as the incidence of the major childhood cancers continues to grow, in the face of ever-improving outcomes [3]. Childhood cancer survivors (CCS) are 8–10 times more likely to die from cardiac causes than age-matched controls [4, 5]. Radiation therapy and some chemotherapeutic and biologic agents are known causes of cardiotoxicity, independently and especially in combination [6]. A report of necropsy studies in youth demonstrated severe stenosis in at least one coronary artery after >35 Gy of cardiac radiation [7]. Anthracyclines are widely used antineoplastic agents as they are very effective, yet are independently

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associated with elevated risk of early [8, 9] and delayed cardiovascular (CV) disease and death [4, 10]. The developing cardiovascular system of children is especially vulnerable to cancer therapy [11]. The most common long-term cause of non-cancer death in childhood cancer survivors is cardiac disease [5, 6, 12]. While congestive heart failure from anthracycline exposure and chest radiation therapy accounts for some deaths, most are related to traditional atherosclerotic cardiovascular disease (CVD) such as myocardial infarction, stroke, and other vascular diseases [6].

Adult cancer survivors demonstrate that these CV events are associated with the development of metabolic syndrome, insulin resistance, as is the case with atherosclerotic CVD in the general population, but with greater frequency and at a younger age. Many are asymptomatic even with severe coronary artery disease (CAD). Risk factors usually associated with aging such as obesity [13, 14], hypertension [15–17], and diabetes mellitus [14] are noted prematurely after cancer therapy. We will focus on these factors and describe their prevalence, monitoring, and treatment in CCS.

2. Obesity

In non-cancer adult populations, premature CVD is closely associated with obesity [18]. Adults with increasing weight have an increased incidence of early CV events and death [18, 19]. Currently in the United States, nearly 30% of youth are overweight and obese [20], which is associated with hypertension [21], low levels of high-density lipoprotein cholesterol (HDL-c) and elevated triglycerides [22, 23], abnormal glucose metabolism [24], insulin resistance [23, 25, 26], inflammation [27–30], and functional abnormalities of the vasculature [31]. Children who are obese are likely become obese adults, with insulin resistance [32] and lipid abnormalities [33]. Childhood cancer survivors (CCS) have been found to have an even higher incidence of obesity over the general population [34–36]. This has necessitated the establishment of simple yet reliable measurements of corporal adiposity. Body mass index, based on height and weight requires minimal training to perform, and is regularly employed to evaluate adiposity in adults and children, with good agreement in repeated measurements in adults [37–40]. Dual-energy x-ray absorptiometry (DXA) has been employed in research for its ease of acquisition and accuracy [41], and is now considered a “gold standard” for estimating body composition, but is mostly limited to research studies due to cost and complexity [42–46]. A number of studies in adult survivors of childhood cancers found no difference in rates of obesity compared to healthy siblings when using body mass index (BMI) [15], yet waist circumference and visceral fat content were increased in some cancers [47–49]. Conversely, the Childhood Cancer Survivors Study, a large retrospective cohort study, demonstrated an increased incidence of obesity with an accelerated rate of increase in BMI when comparing adult survivors of acute lymphoblastic leukemia (ALL) to healthy controls [34]. In a study of 319 CCS during childhood, we compared the body composition of pediatric CCS to 208 healthy control subjects. As shown in table 1, CCS were not significantly different from healthy controls in regards to weight, BMI, or BMI percentile, however, CCS had greater adiposity, demonstrated by waist circumference, ratio of waist-to-height, and percent fat mass (PFM_{DXA}) measured by DXA, while lean body mass (LBM) was significantly lower in CCS as a whole, and in leukemia survivors specifically, but not in survivors of solid tumors.

Central nervous system (CNS) tumor survivors also demonstrated greater abdominal subcutaneous and visceral fat. BMI greater or equal to the 85th percentile for age and sex-specific criteria for overweight/obesity was similar between CCS and healthy control subjects (31.4 and 32.2% respectively), with significantly greater numbers of those with a waist circumference greater or equal to the 75th percentile in the CCS population compared to controls (11% vs. 6.7%; OR 2.1; 95% CI 1.4–3.2; $P < 0.001$). Waist-to-height ratio of greater or equal to 0.5, which predicts greater CV risk, was found in 24% of the CCS group compared to 11.2% of controls (OR 2.5; 95% CI 1.5–4.1; $P < 0.001$). Hypertension was not significantly different between CCS and controls (10.7% CCS vs. 7.2% controls, $P = 0.2$) [50].

As demonstrated in our pediatric study when evaluating adiposity, the tool employed may influence the prevalence of obesity. In this young population, waist circumference or body composition measures by DXA may be more accurate measure of adiposity than BMI [50].

The pathophysiology of obesity in CCS is multifactorial, with genetic predisposition, female sex, history of cranial radiation, and history of exposure to steroids each adding to this risk [35, 51–57]. By suppressing appetite and increasing energy expenditure, leptin, a cytokine produced by adipocytes, controls energy metabolism at the level of the hypothalamus [58, 59]. Obese adults and children develop resistance to leptin, as evidenced by high leptin concentration in otherwise healthy individuals [60–63]. Abnormalities in leptin receptors, with high leptin concentrations have been found in CCS [64, 65]. Late onset growth hormone (GH) deficiency, which can lead to obesity, can be a result of radiation exposure in the hypothalamic-pituitary axis [51, 54, 66–69]. GH plays a significant role in fat cell differentiation, fat cell size [67] and resistin concentrations [66], each of which help regulate insulin sensitivity [65]. With decreased levels of GH, CCS are at increased risk of insulin resistance, type 2 diabetes mellitus, and obesity [67–70]. Young adults who have undergone cranial radiation for ALL have an elevated risk of increased abdominal, visceral, and total adiposity; increased risk of metabolic syndrome; abnormal metabolism, and decreased lean body mass [71]. In our pediatric study of CCS we found a high prevalence of GH deficiency, which explained a large proportion of the increased adiposity in this cohort [72].

Some cancer patients experience cachexia, including fatigue, abnormal metabolism, weakness, and decreased lean body mass [50], which may predispose cancer survivors to premature CV disease similar to fetal malnutrition in healthy populations [73–78]. Prolonged and continuous courses of high-dose steroids, used in induction and intensification stages of cancer therapy, stimulate hunger and decrease lean body mass [52, 56], and when that follows the muscle wasting and malnutrition of cancer, survivors will have a greater tendency for obesity later in life [6].

3. Hypertension

Hypertension, one of the criteria utilized to define metabolic syndrome [79, 80], is a common risk factor for heart failure [81] and ischemic CAD in adults [82, 83]. CCS are twice as likely as their healthy siblings to be hypertensive [15]. Hypertension is uncommon in children prior to diagnosis of cancer [84], yet during chemotherapy, some patients

experience transient hypertension [85]. In a study of pediatric ALL patients, blood pressure returned to normal after therapy, with only 1% requiring antihypertensive medications [85]. Others found a similar pattern of hypertension during induction, but also found persistence of hypertension at the end of therapy, and systolic hypertension at 5 years from diagnosis [86]. In studies of patients undergoing allogeneic hematopoietic cell transplantation hypertension was reported in up to 70% within 2 years after transplantation, and persisted in 34% after 2 years [87]. Insulin resistance and obesity foster the development of metabolic syndrome [79, 88], and the incidence of both are high in long-term survivors of childhood ALL [13, 17, 50]. In our pediatric study, blood pressure was not different between CCS and controls at a median of 10 years after therapy [50]. The degree of systemic arterial pressure elevation is dependent on the patient's cardiovascular status, age, type of cancer, and specific medication and dose used. Elevated blood pressures are present within hours of starting chemotherapeutic agents, and resolve rapidly when medication is discontinued [89]. The mechanism is thought to be a consequence of inhibiting the VEGF receptors, but is not completely understood. Arteriolar vasodilation after exposure to intrinsic nitric oxide is reduced by VEGF inhibition, which decreases concentrations of nitric oxide, resulting in vasoconstriction, increased peripheral systemic vascular resistance, and this leads to increased systemic blood pressures [90].

Some medications utilized for cancer treatment can directly cause renal damage (ifosfamide and methotrexate), leading to hypertension [91, 92]. Abdominal radiotherapy, used in Wilms tumor, neuroblastoma, is associated with hypertension [15, 93–95]. Hypertension in these cases may be due to renal artery stenosis induced by the radiation therapy, or radiation nephropathy [91, 94]. Graft-versus-host disease, acute or chronic, may result in chronic kidney disease or permanent glomerular injury causing hypertension [96].

In the general population, hypertension is seen with aging, related to lifestyle practices and behaviors or genetic predisposition. CCS are not exempt from these risk factors, which may compound the effects of radiation and chemotherapy. Blood pressure should be monitored regularly as hypertension is prevalent among CCS, and the risk of CVD increases with hypertension.

4. Dyslipidemia

Lipid derangements typically associated with metabolic syndrome such as increased triglycerides and low HDL-c are seen in adult CCS with and without obesity [47, 97, 98]. Some studies have found this pattern in CCS during childhood [50, 99]. The classic atherogenic lipid profile (high total cholesterol and low density lipoprotein cholesterol (LDL-c) is not common in cancer survivors, although leukemia and CNS tumor survivors have elevated total cholesterol, LDL-c, triglycerides, and triglyceride-to-HDL ratios compared to healthy control subjects [50]. In our pediatric study, we found that total cholesterol, LDL-c, and triglycerides were higher in CCS than controls as shown in Table 2 [50]. Although lipid screening in children and adolescents remains insufficiently implemented, despite recently updated guidelines from the National Heart, Lung, and Blood Institute [100], there is ample indication to perform lipid screening in CCS.

Possible mechanisms of dyslipidemia in CCS include radiation therapy with or without GH deficiency, and corticosteroid therapy [101–104]. Some of the chemotherapy medications may also cause serum lipid abnormalities. Cyclophosphamide causes impaired vascular lipoprotein lipase and hypertriglyceridemia in animal models [105, 106]. Asparaginase is associated with a risk of pancreatitis and very high triglyceride levels [107]. The increased likelihood of premature atherosclerosis secondary to dyslipidemia, combined with direct damage to the myocardium from cardiotoxic cancer treatments, has significant potential late untoward CV consequences to CCS.

5. Endocrine dysfunction

Endocrine dysfunction, a well described complication of childhood cancer treatments, compounds the CV risk of the direct cardiotoxic effects of therapy. CCS who have undergone cranial radiation or specific surgical resection of intracranial tumors (i.e. transsphenoid) have an increased propensity of hypopituitarism including isolated GH deficiency [108, 109]. Radiation exposure has been implicated in an increased risk of diabetes mellitus (DM) and insulin resistance [14, 17, 49, 50]. For those exposed to cranial radiation, GH deficiency is one of the earliest and most common endocrine disorders [6, 72], which may present even after limited exposure, leading to dyslipidemia, obesity, and altered cardiac structure and function [47, 101, 110–113]. Replacement therapies for GH deficiency may improve quality of life and reduce CVD risks [114, 115], making consideration and evaluation for such disorders important, even years after therapy. Even in the absence of poor growth velocity, such investigations should be considered, especially in those exposed to cranial radiation. Cancer survivors are almost twice as likely as their healthy siblings of having DM, even after controlling for adiposity [14]. CVD risk in those with diabetes mellitus is equivalent to those with previous myocardial infarction (MI) in the general population [116], and in those aged 45–64 years of age, DM triples the risk of CVD [117]. One long-term study of over 200 survivors over the age of 40 years demonstrated that 4% had DM, and an addition 7% had impaired glucose tolerance, and 4% had hyperinsulinemia [49]. In our pediatric study, CCS were more insulin resistant than controls, even after adjustment for adiposity (Table 2) [50].

6. Lifestyle (Physical functioning and activity levels)

Certain modifiable lifestyle behaviors, including illicit drug use, alcohol consumption, physical inactivity, and smoking, should be assessed in CCS. Physical inactivity [118–122] and smoking [82, 123–125] are well-accepted risk factors for CV disease. CCS have been reported to be less active than their healthy siblings and more likely to report a sedentary lifestyle [126].

We studied 183 CCS and 147 healthy siblings with similar weight, height, BMI percentile, age, and minutes of physical activity each week [127]. Physical aptitude testing demonstrated that CCS had lower performance in every marker except grip strength when compared to healthy age matched siblings. Figure 1 demonstrates these findings, adjusted for BMI percentile, height, and sex, as a function of physical activity measured in minutes per week. The difference in the timed up and go (TUG) test and the 6 minute walk (6MW)

was most notable for those with a history of CNS tumor, while the greatest difference in quadriceps strength was found in those with a history of bone and soft tissue sarcomas [127].

In the same study population, we also showed that CCS children engaged in less physical activity than controls; moreover, as shown in Figure 2, we studied the interaction of the effect of physical activity for each cardiovascular risk factor in and found a stronger association between physical activity and abdominal visceral fat, abdominal subcutaneous fat, waist circumference, and percent fat mass in CCS than in controls [128].

7. Vascular changes and Cerebrovascular accidents

CCS as a whole have a relative risk of cerebrovascular accidents (CVA) that is nearly 10 times higher than in healthy siblings [129], with the greatest risk in brain tumor survivors [129] and this is highest in CCS who received > 50 Gy of cranial radiation [130].

Although CVA is rare in children, in our pediatric population of CCS, we assessed early signs of subclinical atherosclerosis using ultrasound imaging of the carotid and brachial arteries, comparing 319 CCS to 208 healthy, age-matched siblings [131]. Brachial artery endothelial-dependent dilation was significantly lower than controls in leukemia survivors (8.2% vs. 7.5% respectively $p=0.016$). In addition, CCS had significantly lower carotid diameter distensibility (14.32% vs. 15.1% respectively $p=0.003$) and carotid cross-sectional distensibility (32.7% vs. 30.72% respectively $p=0.002$) compared to controls, suggesting that stiffer carotid arteries in CCS during childhood may lead to increased risk for later CVA. These findings correlate to arterial changes early in life that increase the risk for premature atherosclerotic CVD in CCS [131].

8. Screening for premature ASCVD

The following are a list of recommended screenings and follow-up suggested by the Children's Oncology Group (COG). Annual measurements of height, weight, and BMI with discussion of lifestyle including diet and physical activities, with counseling as needed [132]. As discussed earlier in this document, despite being inexpensive, easy to perform, and reproducible, BMI may not be an adequate measurement of changes of adiposity in CCS youth. Periodic DEXA screenings may be helpful in this population. Blood pressure should be monitored annually for those treated with cranial, chest, or abdominal radiotherapy, those treated with certain medications including methotrexate, cisplatin/carboplatin, ifosfamide, or nephrectomy [132]. In addition, survivors with any criteria for metabolic syndrome including decreased levels of HDL, hyperglycemia, hypertriglyceridemia, hypertension, or increased waist circumference should undergo periodic screening for the other markers of metabolic syndrome [132]. A lipid profile should be obtained every 2 years [132]. For those treated with cranial radiation therapy, nutritional status should be monitored every 6 months, with attention to signs of insulin resistance or DM, including following fasting glucose levels [132, 133], 2-hour oral glucose challenge and hemoglobin A1C [134, 135]. Metabolic screening usually begins at age 45 years in the healthy population without additional risk factors [135]. However, CCS have an elevated risk of DM and CVD, and metabolic screening early after cancer therapy, and continue on every 2 years, or more frequently if

additional risk factors are present [132, 133]. Of note is that the current COG guidelines for CV risk factor screening are relatively vague and do not include recommendations for GH deficiency evaluations or carotid artery US screening.

9. Treatments

Lifestyle and behavioral changes play a key role in decreasing CV risk in this population, similar to the general population, and should play a central role in the treatment plan from early in childhood. Diets low in sugar, salt, fats, and calories, and high in fiber should be encouraged [136–138], as should physically active lifestyles, with avoidance of smoking and excess drinking of alcohol. When lifestyle changes are inadequate, standard medical treatment of DM, dyslipidemia, and hypertension [133] in CCS are theoretically as effective as for the general population, and should be aggressively incorporated in CCS care. Although GH replacement therapy has many positive effects on CVD risk factors and metabolism, its use remains controversial with concerns of precipitating recurrent or secondary cancers [139]. Large multicenter reviews found it actually lowered the incidence [140] except in survivors of ALL and CNS tumors where it may actually increase the risk [141]. Cancer treatment protocols that reduce the overall and specific organ radiation and chemotherapeutic doses help decrease the insult to the survivor and reduce CV risk.

10. Conclusions

Improvements in childhood cancer survivorship over the past three decades have led to a growing population of CCS with premature development chronic diseases, in particular CVD. Protocols to decrease cardiotoxic chemotherapy and radiation doses are undergoing continual refinement. As we become more successful in curing childhood cancers, the next critical step in the transition of CCS from childhood to adulthood is to address the consequences of the cure.

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Figure 1.

Physical performance outcomes among survivors and siblings as a function of weekly minutes of physical activity: (A) 6-minute walk test; (B) timed up-and-go test; (C) grip strength; (D) quadriceps strength (90°); (E) quadriceps strength (120°); (F) quadriceps strength (180°). Reprinted with permission from Elsevier. © 2013 American Society of Clinical Oncology. All rights reserved. Hoffman M et al: J Clin Oncol 31. (22), 2013: 2799–2805.

Fig. 2.

CCS/control status physical activity level (low vs. high PA) interaction plots for waist circumference, percent fat mass, abdominal subcutaneous fat, and abdominal visceral fat. These plots assess whether the difference between high and low PA was the same for CCS and controls for each of these four cardiovascular risk factors. CCS, childhood cancer survivors; PA, physical activity. Reprinted with permission. © 2014 Wiley Periodicals, Inc. DOI 10.1002/pbc.25276. All rights reserved. Slater M et al: *Pediatr Blood Cancer*. Epub ahead of print. 2014.

Table 1

Comparison of Body Composition between CCS and Controls

	CCS (n=319)		Leukemia (n=110)		CNS (n=82)		Solid Tumors (n=127)		Controls (n=208)	
	mean $\pm$ SE	p	mean $\pm$ SE	p	mean $\pm$ SE	p	mean $\pm$ SE	p	mean $\pm$ SE	p
Height (cm)	158.2 $\pm$ 0.6	0.01	156.4 $\pm$ 1.0	<0.001	156.2 $\pm$ 1.0	0.04	158.7 $\pm$ 0.9	0.31	159.9 $\pm$ 0.7	
Weight (kg)	57.2 $\pm$ 1.1	0.85	55.4 $\pm$ 1.7	0.48	58.1 $\pm$ 2.0	0.39	55.4 $\pm$ 1.4	0.92	57.0 $\pm$ 1.2	
Body Mass Index (kg/m ²)	22.4 $\pm$ 0.3	0.08	22.2 $\pm$ 0.5	0.15	23.1 $\pm$ 0.6	0.08	21.8 $\pm$ 0.5	0.68	21.8 $\pm$ 0.4	
Body Mass Index Percentile	67.5 $\pm$ 2.0	0.51	68.0 $\pm$ 2.8	0.25	71.0 $\pm$ 3.2	0.71	64.6 $\pm$ 3.6	0.66	66.1 $\pm$ 2.4	
Waist (cm)	73.1 $\pm$ 0.9	0.02	72.8 $\pm$ 1.2	0.03	74.7 $\pm$ 1.6	0.01	70.7 $\pm$ 1.1	0.67	71.1 $\pm$ 1.0	
Waist (cm) to Height ratio (cm)	0.5 $\pm$ 0.005	0.001	0.46 $\pm$ 0.007	0.06	0.48 $\pm$ 0.009	0.07	0.45 $\pm$ 0.008	0.36	0.4 $\pm$ 0.006	
Percent Fat Mass (DXA)	28.1 $\pm$ 0.8	0.007	28.6 $\pm$ 1.1	0.004	29.9 $\pm$ 1.2	0.002	26.3 $\pm$ 1.4	0.52	25.9 $\pm$ 0.9	
Lean Body Mass (DXA) (kg)	38.4 $\pm$ 0.5	0.01	37.0 $\pm$ 0.9	<0.001	37.3 $\pm$ 0.9	0.06	38.6 $\pm$ 0.8	0.37	39.9 $\pm$ 0.6	
Abdominal Visceral Fat (CT) (cm ³)	22.3 $\pm$ 1.1	0.17	22.5 $\pm$ 1.3	0.09	25.5 $\pm$ 2.3	0.01	18.4 $\pm$ 1.2	0.51	21.0 $\pm$ 1.2	
Abdominal Subcutaneous Fat (CT) (cm ³)	85.2 $\pm$ 4.5	0.07	83.5 $\pm$ 6.2	0.09	97.6 $\pm$ 8.5	0.01	73.1 $\pm$ 6.4	0.81	77.0 $\pm$ 4.9	

All measures adjusted for age-at-study, gender, race, and Tanner score

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Table 2
Comparisons between CCS and Controls for CV Risk Factors and Insulin Resistance

	All CCS (n=319)		Leukemia (n=110)		CNS (n=82)		Solid Tumors (n=127)		Controls (n=208)	
	mean $\pm$ SE	* p	mean $\pm$ SE	* p	mean $\pm$ SE	* p	mean $\pm$ SE	* p	mean $\pm$ SE	
Total Cholesterol (mg/dL)	154.7 $\pm$ 2.1	0.004	149.8 $\pm$ 2.8	0.03	159.3 $\pm$ 4.2	0.008	152.3 $\pm$ 3.4	0.23	148.3 $\pm$ 2.5	
LDL-Cholesterol (mg/dL)	89.4 $\pm$ 1.9	0.002	86.7 $\pm$ 2.6	0.01	91.6 $\pm$ 3.7	0.02	88.8 $\pm$ 3.3	0.10	83.7 $\pm$ 2.2	
HDL-Cholesterol (mg/dL)	47.3 $\pm$ 0.8	0.21	46.1 $\pm$ 1.0	0.33	46.6 $\pm$ 1.4	0.29	47.6 $\pm$ 1.3	0.29	48.4 $\pm$ 1.0	
Triglycerides (mg/dL)	91.8 $\pm$ 5.5	0.03	85.9 $\pm$ 5.3	0.38	109.1 $\pm$ 11.1	0.004	80.5 $\pm$ 3.7	0.48	84.0 $\pm$ 5.9	
Triglycerides to HDL ratio (mg/dl)	2.2 $\pm$ 0.15	0.006	2.0 $\pm$ 0.15	0.19	2.7 $\pm$ 0.33	0.007	1.9 $\pm$ 0.13	0.13	1.8 $\pm$ 0.16	
Non-HDL Cholesterol (mg/dl)	107.4 $\pm$ 2.2	<001	103.8 $\pm$ 2.8	0.02	112.6 $\pm$ 4.1	0.002	104.6 $\pm$ 3.4	0.10	99.9 $\pm$ 2.5	
Insulin (mU/L)	10.6 $\pm$ 0.6	0.7	10.9 $\pm$ 0.8	0.54	12.2 $\pm$ 1.4	0.20	9.1 $\pm$ 0.7	0.49	10.3 $\pm$ 0.7	
HOMA-IR	2.3 $\pm$ 0.1	0.8	2.3 $\pm$ 0.2	0.58	2.6 $\pm$ 0.3	0.25	2.0 $\pm$ 0.1	0.42	2.2 $\pm$ 0.2	
M _{hbm} (mg/kg/min)	12.1 $\pm$ 0.3	0.002	11.5 $\pm$ 0.5	0.002	11.6 $\pm$ 0.6	0.04	12.4 $\pm$ 0.5	0.05	13.4 $\pm$ 0.4	

All measures adjusted for age-at-study, gender, race and Tanner score

* p-value for comparison between CCS (or subgroup) with controls, based on adjusted regression models

Euglycemic hyperinsulinemic clamps not performed on 3 cases (2 CNS, 1 Solid Tumor) and 1 control, due to pre-existing diagnosis of diabetes

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