Steroid Treatment Promotes Insulin Resistance in Pediatric ALL Survivors

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Over the past 40 years, the five-year survival rates for pediatric acute lymphoblastic leukemia (ALL) have gone from less that 5% to now exceeding 85% through successful advances in treatments. ALL is the most common cancer in children, and is a cancer of the lymphocyte population of white blood cells. Typically, ALL is treated in three broad phases: 1) induction therapy to kill the majority of leukemic cells in the blood and bone marrow; 2) consolidation therapy once the leukemia is in remission; and 3) maintenance therapy for several years to kill any remaining residual leukemic cells. While treatments are successful in curing leukemia, survivors have an increased risk for adverse long-term effects such as obesity and cardiovascular disease.

In agreement with other studies, Dr. Eric Chow (Chow *et al*., 2007) and colleagues from the Clinical Research Division previously demonstrated an increased risk of obesity and hypertension in childhood ALL survivors several years post-treatment. 40% of survivors were overweight or obese 5 years after diagnosis compared to 25% of the normal population. Importantly, the greatest risk was associated with those treated with higher doses of glucocorticoids. As an essential part of ALL treatment, glucocorticoids (typically prednisone and dexamethasone) help induce lymphoblast cell death. Glucocorticoid treatment can also reduce insulin sensitivity of cells and affect the function of pancreatic β-cells that secrete insulin. Furthermore, chronic steroid usage has been shown to result in hyperglycemia and obesity in people without cancer. Insulin resistance increases blood glucose, as cells take up less glucose, for the same given level of insulin. To investigate the physiologic relationship between high-dose glucocorticoid treatment and insulin resistance, Drs. Eric Chow, Stephanie Lee, Jeannine McCune, and K. Scott Baker of the Clinical Research Division and colleagues from Seattle Children's Hospital and the University of Washington directly measured insulin sensitivity in ALL survivors.

In the current study, Dr. Chow and colleagues chose participants who were diagnosed with ALL at less than 22 years old, were treated between 1990 and 2010 at Seattle Children's Hospital, and were in first continuous complete remission. For the study, the researcher compared two cohorts of patients between 2007 and 2010: 1) 31 on-therapy individuals who had received at least one month of glucocorticoid-based maintenance therapy; and 2) 29 off-therapy individuals who had completed therapy at least one year prior to enrollment. Insulin resistance was measured using homeostatic

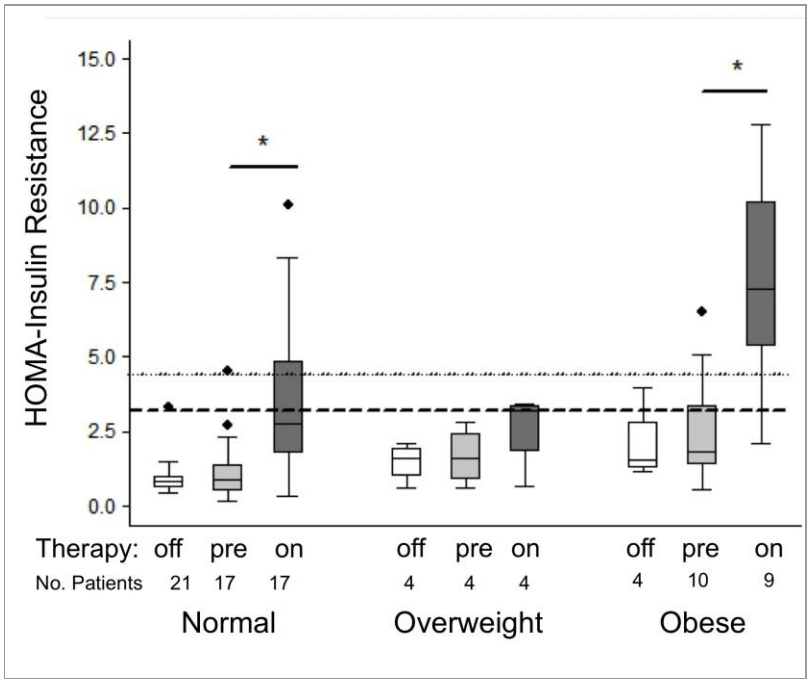
model assessment (HOMA-IR), a simple mathematical model that calculates insulin sensitivity from blood glucose and insulin levels measured in participants. For those on-therapy, blood glucose and insulin measurements were taken immediately prior to starting glucocorticoids and again after 3-5 days of glucocorticoid treatment. Body mass index (BMI) z-scores were also obtained, standardized to pediatric normative data.

During cancer therapy, both off- and on-therapy groups had increases in BMI z-scores as described in the literature previously ($P < 0.05$). HOMA-IR was not statistically different for off- and on-therapy groups (median 1.26 *vs.* 0.93, $P = 0.38$). However, in both groups higher BMI category was associated with increased baseline HOMA-IR values ($P < 0.05$, see figure). Notably, HOMA-IR values increased significantly compared to pre-treatment values in patients on-therapy (median 3.39 *vs.* 1.26, $P < 0.01$). While HOMA-IR values increased with steroid exposure for all BMI categories and tended to be greater at baseline among those with greater BMI z-scores, changes in HOMA-IR in response to steroid exposure was not correlated with any demographic or treatment characteristic, including current BMI.

During critical growth stages, ALL patients receive half or more of their glucocorticoids on the maintenance phase of therapy. Although small in sample size, this study demonstrates high-dose glucocorticoid therapy is associated with insulin resistance, which may be an important contributing factor to obesity in select ALL survivors. Decreased physical activity due to fatigue related to ALL treatment could also contribute to weight gain and insulin resistance in these patients.

Chow EJ, Pihoker C, Friedman DL, Lee SJ, McCune JS, Wharton C, Roth CL, Baker KS. 2012. Glucocorticoids and insulin resistance in children with acute lymphoblastic leukemia. *Pediatric Blood Cancer*. Epub ahead of print, doi: 10.1002/pbc.24364.

Also see: Chow EJ, Pihoker C, Hunt K, Wilkinson K, Friedman DL. 2012. Obesity and hypertension among children after treatment for acute lymphoblastic leukemia. *Cancer* 110:2313-20.



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Insulin resistance values (HOMA) increased in pediatric ALL survivors on-therapy during glucocorticoid treatment (dark gray) compared to on-therapy pre-treatment (medium gray) and off-therapy (white) patients (*, $P < 0.01$). Results are divided by body mass index (BMI) category. The dashed line indicates the values of the upper 25% of normal weight U.S. children (HOMA > 3.29) and the dotted line the upper 2.5% (HOMA > 4.39).