Changes in plasma levels of inflammatory molecules during puberty in overweight and obese children and their association with co-morbidities

Project: 353

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The increasing prevalence of pediatric overweight and obesity throughout the world, including Switzerland, is associated with an unprecedented increase in the incidence of serious metabolic diseases in children, such as type 2 diabetes mellitus (T2DM) and non-alcoholic steatohepatitis (NASH). The pathophysiological mechanisms through which increased adiposity causes these diseases and their prodromal syndromes (insulin resistance, fatty liver and other components of the "metabolic syndrome") are thought to involve activation of the innate immune system and development of a chronic inflammation-like state. In addition, reproductive-axis function is known to influence innate immune system function. Therefore, the goals of this project were to use multivariate statistical analyses to investigate the interrelationships among adiposity, pubertal development (Tanner stage), plasma levels of innate-immune signaling molecules, and signs of T2DM and NASH risk in a cross-sectional sample of ~100 Swiss children, 6-16 y of age.

The clinical material was provided by our collaborator Dr Dagmar l'Allemande-Jander, Pädiatrische Klinik, Ostschweizer Kinderspital St. Gallen. The plasma assays were performed at the ETH by my post-doctoral fellow, Dr. Lori Asarian, and Dr l'Allemand-Jander's student, Iso Hutter. Budgetary constraints required us to trim the originally proposed list of signaling molecules to those we deemed of greatest scientific interest.

As of spring 2009, assays for the following 9 immune signaling molecules were completed: tumor necrosis factor-alpha (TNF-a), soluble TNF-α receptor (s TNF-aR), interleukin 1-alpha (IL-1a), IL 1-beta (IL-1β), IL-6, IL-8, IL-1 receptor antagonist (IL-1ra), and retinal binding protein (RBP), and we conducted a preliminary data analysis using analysis of variance. Independent variables were sex and adiposity/metabolic health, rated with pediatric body mass index (BMI) and metabolic signs, as follows: (A) healthy children with normal or moderate overweight (BMI < 27.5), (B) overweight or obese children (BMI > 27.5) who had no co-morbidities, (C) B plus risk of T2DM (e.g., elevated blood glucose), and (D) C plus risk of NASH (e.g., elevated liver enzyme ALAT or gGT). Surprisingly few significant results were obtained. Plasma levels of Leptin, RBP and IL-1ra all increased across adiposity/metabolic health categories, with greater changes in boys than girls, such that significant increases in leptin levels were detected in (B)-(D) boys and only (D) girls, significant increases in IL-1ra levels were detected in (C) and (D) boys and only (D) girls, and significant increases in RBP levels were obtained in only in (D) boys.

We expect that a fuller analysis of the data using multivariate regression and including the Tanner stages as well as reproductive hormone levels might reveal more effects. Unfortunately, because Dr l'Allemande-Janders and Mr Huter changed positions and professional responsibilities and Dr Asarian and I left the ETH, this was not done.

The literature indicates that similarly obese and metabolically at-risk adults would show more and larger innate-immune changes than we observed. Thus our data suggest that children, especially girls, may be relatively protected from obesity-related innate immune activation. This is an important result worthy of basic-research and clinical follow-up.