

10^{-7} M, and the suppression was gone by 24 hours. Four hours of 10^{-7} M adiponectin caused a 74% reduction in the LH secretion stimulated by 10^{-8} M gonadotropin-releasing hormone (GnRH). At 4 hours GnRH receptor expression was halved by adiponectin at concentrations of 10^{-9} to 10^{-7} M, but only the highest concentration of adiponectin significantly reduced GnRH receptor expression at 24 hours.

Rodriguez-Pacheco et al also examined the pituitary adiponectin system. Expression of adiponectin and its 2 receptors (AdipoR1 and AdipoR2) were demonstrated by RT-PCR in extracts of rat and human pituitaries. Returning to the rat pituitary cell culture model, the authors found that 4 hours of adiponectin exposure at concentrations of 10^{-9} to 10^{-7} M increased its own expression by almost 70% (at the highest dose only), but did not alter the expression levels of either of its 2 receptors. However, after 24 hours' exposure, adiponectin (10^{-8} M only) increased its own expression (by 300%), decreased expression of AdipoR1 (by 10^{-8} M only), and increased expression of AdipoR2 (by 10^{-7} M only).

Rodriguez-Pacheco F, Martinez-Fuentes AJ, Tovar S, et al. Regulation of pituitary cell function by adiponectin. *Endocrinology*. 2007;148:401-10.

Editor's Comment: Rodriguez-Pacheco et al showed that short-term adiponectin exposure suppressed both basal and stimulated (by ghrelin [but not GHRH] and GnRH) secretion of GH and LH, respectively, by rat pituitary cells *in vitro*. They further laid the groundwork for a pituitary adiponectin autocrine/paracrine system in which both adiponectin and its receptors are expressed and further modulated by adiponectin exposure. Thus, adiponectin seems to serve like the classic adipokine leptin, in centrally linking growth, anabolic, and reproductive

function to fat cell activity. These relationships warrant *in vivo* confirmation. From the evidence so far, it seems that neither endocrine leptin nor endocrine adiponectin underlie the old clinical observation that obesity suppresses GH secretion; circulating leptin levels are increased in obesity but leptin stimulates GH release, and although adiponectin suppresses GH secretion, as shown in this paper, circulating adiponectin levels are reduced in obesity.

Nonetheless, adiponectin attracts tremendous clinical interest. Adiponectin seems to do what clinicians are desperately seeking to accomplish in the obesity epidemic: adiponectin acts as an insulin-sensitizing, anti-atherogenic, anti-inflammatory, anti-angiogenic, and anti-tumoral agent. The sooner we learn about adiponectin physiology, the sooner it can inspire novel therapeutic approaches.^{3,4} For example, it turns out that thiazolidinediones up-regulate adiponectin. Adiponectin's reported insulin-sensitizing activities are multiple and peripheral: it enhances hepatic insulin action and decreases endogenous glucose production; it increases glucose uptake by adipocytes and myocytes, and it increases fatty acid oxidation in muscle. If the *in vitro* findings of this paper are confirmed *in vivo*, then we can add one more mechanism to the list: adiponectin centrally inhibits secretion of the counter-regulatory GH. Further, adiponectin was shown to decrease body weight in mice by stimulating energy expenditure.⁵ Not everything from fat is bad.

Adda Grimberg, MD

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Vitamin D Receptor in Idiopathic Short Stature

Stature is a highly heritable trait, but beyond those genes known to cause specific disorders in which short stature is a major component, the genetic factors responsible for variation in height are poorly understood. As reported by Dempfle et al, genome-wide linkage scans of adult height have been performed in at least 22 separate samples and the results summarized in 12 publications. Although these studies, most of which have been performed on relatively small samples, yielded divergent results and no chromosomal region was highlighted across all scans, evidence for linkage is convincing for some regions, in particular regions on chromosomes 6, 7, 9, and 12.

Building on these studies, Dempfle et al carried out a genome-wide scan on 92 families, each with 2 affected children with idiopathic short stature (ISS), which they defined as including constitutional delay of growth and puberty, familial short stature, and ISS in its more narrow meaning. For inclusion, each family had one child whose

height was below the 5th percentile and a second child with height less than the 15th percentile. Only Caucasian families were included, and all but 2 parents were of German origin.

Linkage analysis using 511 short tandem repeat markers revealed the highest LOD score (3.18 [and only LOD score >3]), which is usually accepted proof of linkage, at chromosome 12q11. This is the region to which adult height has been linked and which contains the vitamin D receptor (VDR) gene that has been previously implicated as a factor in adult height variability. In fact, as noted in a 2005 GGH abstract,¹ a single nucleotide polymorphism (SNP) at the VDR locus has been associated with variation in adult stature. The same association was found in ISS in this investigation.

The VDR polymorphism involves the substitution of a G base for an A base at a particular nucleotide; it is called the G allele. The G allele was detected more often

than the A allele in children and adolescents with ISS. The substitution maps to the VDR start codon where it abolishes the first translation initiation site, resulting in a peptide lacking 3 amino acids, which increases the transcriptional activity of the gene. The more active allele was over-transmitted to affected children in the sample giving estimates of relative risks for ISS of 1.33 and 1.9, respectively, for heterozygotes and homozygotes for the allele. The authors suggested that on the population level, the G allele might be responsible for 34% of ISS cases.

The genomic scan did not detect evidence of linkage to other sites that have been implicated by other investigators in ISS, including the SHOX and NPR2 loci.

Dempfle A, Wudy SA, Saar K, et al. Evidence for involvement of the vitamin D receptor gene in idiopathic short stature via a genome-wide linkage study and subsequent association studies. *Hum Molec Genet.* 2006;15:2772-83.

Editor's Comment: Readers may ask: if linkage to the VDR locus and association with the G allele of VDR has been established for adult height, why repeat the genomic scan in children with ISS? The reason is that the findings in the adult study could be explained by the effects of several genes, each having a small impact on stature or a small number of genes having a larger impact. Finding a similar effect in a small subset of individuals, ie, those with ISS, argues for a larger effect of a smaller number of genes, of which VDR is one. The next step will be to delineate how the more transcriptionally active VDR allele actually affects linear bone growth.

William A. Horton, MD

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Hyperinsulinemia, Impaired Glucose Tolerance, and T2DM in Cancer Survivors

The occurrence of hyperinsulinism and type 2 diabetes mellitus (T2DM) has been identified in survivors of childhood malignancy, particularly after bone marrow transplantation (BMT). Only small numbers of patients had been studied and evaluated long-term. The recent study of Hoffmeister et al¹ dealing with a population of children followed after hematopoietic cell transplantation, showed a 3-fold increase rate for T1DM and T2DM. The study of Neville et al focused on the predisposing factors and early markers of DM, a critical issue for the development of prevention strategies. This group studied 248 survivors of childhood cancers; half of them were adults at the time of evaluation. The median duration after diagnosis was 12.9 years. They grouped hyperinsulinism (HI), impaired glucose tolerance (IGT), and T2DM

together for analysis of potential risk factors. Body mass index (BMI) and abdominal adiposity were potential markers. In this population, which is often growth-retarded, the waist-to-height (W/H) ratio correlated well with the volume of visceral fat as measured by CT scan. A ratio of >0.5 was considered a good predictor of complications of obesity.

The mean BMIs of both prepubertal and pubertal subjects were similar compared with controls, but the mean W/H ratio was higher, with a doubling of the percentage in children with abdominal adiposity. In all groups, there was a tendency for accumulating abdominal fat. In pubertal and adult subjects, abdominal adiposity was predictive for the occurrence of biochemical markers for metabolic abnormalities (insulinemia and lipid profiles). Fasting insulin

concentrations were higher in prepubertal and pubertal subjects, compared with their controls. Hyperinsulinism, IGT, or DM were detected in 18% of pubertal and adult subjects. Eleven percent of this group had IGT/DM ($p < 0.001$). In the group with BMT, conditioning with total body irradiation (TBI) increased the risk (Table).

This study confirms the risk factors previously identified, with a strong focus on the BMT group. Total body irradiation turns out to be a major risk factor for metabolic abnormalities. Differences with previously reported studies could be accounted for by the prospective approach, the

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