

positively correlated with the daily corticosteroid doses. Fasting serum insulin levels were elevated in the renal failure patients, with the highest levels being in the posttransplant group.

Fasting and OGTT glucose responses did not change throughout the observation period. However, fasting and stimulated insulin levels were 2-fold increased compared with baseline after the first year of rhGH therapy in the dialysis and RT patients, as well as in the controls. Insulin levels in the conservatively treated group became significantly elevated only after the second treatment year. Four patients, 2 on conservative treatment, 1 on dialysis, and 1 RT recipient, developed transient impairment of oral glucose tolerance as defined by the National Diabetes Group of the National Institutes of Health.

In conclusion, the authors observed a selective increase in fasting and glucose-stimulated insulin secretion without a change in glucose tolerance in patients with CRF after RT, but also in short normal children in response to rhGH therapy. This phenomenon was exaggerated in patients on dialysis and after RT, and persisted for up to 5 years of rhGH treatment. Although the absence of increased glucose intolerance during long-term rhGH treatment is

reassuring with respect to the diabetogenic potential of rhGH, the persisting hyperinsulinemia, combined with the dyslipidemia associated with CRF, raises concerns that rhGH therapy may contribute to the long-term risk for premature atherosclerosis in patients with childhood-onset CRF.

Haffner D, et al. *Pediatrics* 1998;43:209-215.

Editor's comment: *This interesting study demonstrates that the effects of rhGH on glucose-stimulated insulin secretion are not different for children with CRF and those with idiopathic short stature. The authors point out that associated hyperinsulinemia may be of particular concern in children with uremia and other factors, including dyslipidemia, which may contribute to atherosclerosis. These data are compatible with those reported on US patients and summarized in GGH (1996;12[4]:49-53) by Dr. Richard Fine. He points out in his review that there have been no clinical consequences associated with the hyperinsulinemia, as corroborated by the German Study Group. However, the long-term effect of such treatment remains to be shown.*

William L. Clarke, MD

Familial Hyperinsulinism Caused by an Activating Glucokinase Mutation

Hyperinsulinism (HI) is relatively common. It is the most common cause of hypoglycemia. Affected individuals are at risk for seizures and permanent brain damage. Glaser et al describe a family with HI associated with a mutation in the glucokinase gene. Glucokinase is an enzyme with low affinity for glucose that controls the rate-limiting step of beta-cell glucose metabolism.

A mutation of the glucokinase gene has been detected in a 31-year-old white male, his 2 children, his sister, and his father. The mutation was sought in the proband after he became unconscious with low plasma glucose (38 mg/dL)

and elevated insulin levels. Counter regulatory hormone responses were normal, and so were pancreatic CT and MRI findings. The proband's 2 children had hypoglycemic seizures and also were diagnosed with HI. Urinary amino acids and urinary and plasma carnitines were normal, as was a pancreatic ultrasound. The proband's sister was diagnosed as having hypoglycemia at the age of 15 years; she had low fasting blood glucose and high plasma insulin levels, and later developed multiple sclerosis. Oral glucose tolerance tests in the proband and his sister showed hypoglycemia 3 hours after taking glucose. During hypoglycemia, their plasma insulin and C-peptide concentrations were elevated. In the proband and his sister, exogenous insulin administration resulted in a decrease in plasma glucose and plasma C-peptide concentrations. The proband's sister's children were normal. The proband's father had symptoms of hypoglycemia, which were controlled by diet. At the age of 48 years, the father developed insulin-dependent diabetes mellitus. All the affected family members were treated with diazoxide 100 to 300 mg/d. This same mutation was not detected in 37 unrelated white families, including 6 with an apparently autosomal dominant form of hyperinsulinism.

The *Val455Met* mutation in the glucokinase gene results in an increased affinity of glucokinase for glucose, resulting in a higher rate of glycolysis and therefore a higher rate of insulin secretion. This represents a

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clinically and biochemically distinct autosomal dominant form of familial hyperinsulinism.

Glaser B, et al. *N Engl J Med* 1998;338:226-230.

Editor's comment: Identification of this mutation in the glucokinase protein is another step in understanding glucose homeostasis. It is clear that different mutations within the same gene give rise to different phenotypes requiring different therapies. The Val203Ala mutation within the same gene results in loss of function and gives rise to maturity-onset diabetes mellitus. That particular glucokinase mutation has been identified in about 50% of individuals with gestational diabetes. By contrast, this new type of mutation leads to hyperinsulinism and hypoglycemia. This contrast illustrates that the domain of mutations within a gene can lead to striking differences in phenotypes.

Judith G. Hall, MD

2nd Editor's comment: Most patients with familial HI have a defect in the sulfonylurea protein resulting from a

SUR gene mutation. An excellent article to review in conjunction with this article is by Permutt et al, entitled "FHI: An Inherited Disorder of Spontaneous Hypoglycemia in Neonates and Infants" (*Diabetes Reviews* 1996;4:347-353). Permutt et al provide the foundation to better understand the etiologies and variations of familial HI, previously called leucine-sensitive hypoglycemia and/or nesidioblastosis.

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Births After Intracytoplasmic Injection of Sperm Obtained by Testicular Extraction From Men With Nonmosaic Klinefelter's Syndrome

Klinefelter's syndrome results from the presence of an extra X chromosome (47,XXY) in males. It is a relatively common sex chromosomal abnormality, occurring in about 1 in 500 males. Some individuals with Klinefelter's syndrome are mosaics, ie, they have both 46,XY and 47,XXY cells. Individuals who are mosaic (46,XY/47,XXY) may have some degree of spermatogenesis and may be fertile, compared with nonmosaic Klinefelter men (47,XXY), who typically have azoospermia and infertility.

Palermo et al have reported 2 couples in which the nonmosaic Klinefelter's syndrome males had undergone testicular sperm extraction (followed by in vitro fertilization by intracytoplasmic injection of single sperm) and thereby were able to father healthy newborn infants.

In the case reports, the men were 32 years and 34 years old and their wives were 32 and 33 years old. Both women were healthy and normal, while both men had nonmosaic Klinefelter's syndrome (47,XXY). Both men had gynecoid habitus, gynecomastia, and bilateral atrophic testes. The first man had bilateral varicocele; the second man had a moderate-size left varicocele. Both men had high serum gonadotropin and low serum testosterone levels. Both men had only Sertoli cells on testicular biopsies. Three semen analyses of the first man showed normal volumes and fructose and a single abnormal nonmotile sperm in 1 semen specimen.

Analysis of the 3 semen samples from the second man revealed low volume, normal fructose, and no sperm.

Both women were given leuprolide (a gonadotropin-releasing hormone agonist) subcutaneously to inhibit gonadotropin secretion and then a combination of human menopausal gonadotropin and follicle-stimulating hormone intramuscularly. Oocytes (15 to 40) were retrieved by ultrasonographically guided transvaginal needle aspiration after intramuscular administration of chorionic gonadotropins.

Simultaneous testicular biopsies were performed in the men. Both men had received testolactone 3 months before having a testicular biopsy. After intracytoplasmic sperm injection and fertilization of oocytes, embryos (3 for each woman) were selected and transferred. Both couples refused preimplantation diagnosis.

Both women received daily intramuscular injections of 50 mg progesterone in oil until fetal heartbeats were confirmed by ultrasound. The ultrasound of the first woman at 32 days of embryo transfer revealed 2 asymmetric uterine sacs, only one of which had a fetal heartbeat. Ultrasound of the second woman showed 2 intrauterine sacs, both with fetal heartbeats. Amniocentesis at 20 weeks showed a fetal karyotype of 46,XY in the first pregnancy and fetal karyotype of 46,XX and 46,XY in the second pregnancy.