

Summarized results (mean + SEM).

Parameter	Celiac disease			P value <0.05: C= vs ctls D= pre/post diet N= neither
	Controls	Baseline	1 year on diet	
Height z-score	0.09 ± 0.3	0.51 ± 0.3	0.88 ± 0.4	D
Target height z-score	-0.4 ± 0.5	-0.4 ± 0.3	-	-
BMI z-score	0.5 ± 0.3	-1.6 ± 0.1	0.89 ± 0.3	C, D
IGF-I (ng/ml)	392 ± 47	208 ± 32	305 ± 35	C, D
IGF-II (ng/ml)	1098 ± 255	952 ± 52	1008 ± 119	N
IGFBP-1 (ng/ml)	61 ± 7	54 ± 8	45 ± 9	N
IGFBP-2 (ng/ml)	306 ± 35	493 ± 41	388 ± 74	C, D
IGFBP-3 (ng/ml)	4216 ± 286	4087 ± 300	4108 ± 281	N
IL-6 (pg/ml)	1 ± 0.1	2 ± 0.6	2 ± 0.7	C
TNF-α (ng/ml)	4 ± 1	2 ± 1	2 ± 0.4	C

Tanner 2 to 3. Mean bone age at diagnosis was 9.4 years, SEM = 0.9 years. Eighteen healthy children (5 male), aged 5.6 to 14.6 (mean 11.1) years, matched for pubertal stage, were evaluated as controls at baseline (Table). Their bone age data were not available.

The authors further examined various IGF/IGF binding protein (IGFBP) molar ratios, simple linear regression analyses and step-wise linear regression analyses to find additional correlates with baseline and treatment values. They concluded, "the data from this study confirm changes in the IGF and cytokine systems at diagnosis of celiac disease which tend to normalize on the gluten-free diet."

Street ME, Volta C, Ziveri MA, et al. Changes and relationships of IGFs and IGFBPs and cytokines in celiac disease at diagnosis and on gluten-free diet. *Clin Endocrinol.* 2008;68:22-8.

Editor's Comment: *There are several limitations to this study in considering the authors' conclusions.*

The discussion section contains many conjectures about the mechanistic links between cytokines, IGF axis, growth, and disease of patients with celiac disease, stretching even to the increased risk of malignancy in patients with long-standing untreated celiac disease. All the data in this paper were associative. Associations are never sufficient to prove causation, as directionality and confounders remain unknown. There were no supporting mechanistic

studies. Likewise, the paper measured serum concentrations. Local (ie, intestinal) concentrations of the cytokines and IGF axis members are more pertinent to disease activity, and changes may not be reflected in the serum levels. Finally, the study's ability to generalize is limited. The subjects all had atypical celiac disease, so the results do not necessarily support conclusions about celiac disease in toto. However, it is this very limitation that makes the findings of this paper intriguing. None of the patients studied had diarrhea, signs of malnutrition or history of celiac crisis. Although the BMI at baseline was significantly lowered, it was still within the normal range. Likewise, the gluten-free diet improved the height z-score, which was already normal, and even better than target height, at baseline. The finding of significant alterations in serum cytokines, IGF-I and IGFBP-2 within this population speaks to the sensitivity of the IGF system to this disease process.

Adda Grimberg, MD

Levothyroxine Therapy on Ventricular Function in Neonates with Congenital Hypothyroidism

Decreased thyroid hormone levels are associated with poor left ventricular contractility and relaxation in hypothyroid adults. These abnormalities can be reversed by levothyroxine substitution therapy. Few studies have been done in neonates with congenital hypothyroidism and to date the results have been conflicting. Only standard echocardiography has been used to assess left ventricular function. Tissue Doppler echocardiography (TDE) is a new method that permits evaluation of regional and global left and right systolic and diastolic ventricular function and color codes the velocity of myocardial movement allowing for more accurate quantification.

Fifty neonates (17 to 28 days of age) who were full term and diagnosed with congenital hypothyroidism (TSH >5.6 mIU/L) with a depressed serum free thyroxine

(FT₄ <10 pmol/L) or total thyroxine (TT₄ <54 nmol/L) were studied. A control group of 35 healthy neonates with normal thyroid function levels matched for age, sex, body surface area, and BMI were studied. None of the subjects had congenital heart disease as assessed by clinical and routine echocardiographic studies. Each neonate was studied with both conventional M-mode pulsed wave Doppler and with TDE. The infants were sedated with oral chloral hydrate for the studies. M-mode echocardiography measured left atrial aortic diameter, left atrial/aortic ratio, left ventricular fractional shortening, and left ventricular ejection fraction. In addition diastolic mitral and tricuspid inflow velocity was measured. The TDE permitted measurement of peak early diastolic mitral annular velocity, peak late diastolic mitral annular

velocity, and peak systolic mitral annular velocity, as well as similar measurements for tricuspid velocity.

Using conventional Doppler echocardiography, markers of left ventricular systolic global function were significantly lower in the infants with congenital hypothyroidism. In addition, early and late mitral and tricuspid valve diastolic function were significantly lower in the infants with congenital hypothyroidism. After a month of levothyroxine (L-T₄) therapy several of the left ventricular parameters improved, but left atrial and aortic diameter did not change. Significantly reduced mitral systolic and early diastolic velocity was found by TDE in the group with congenital hypothyroidism. These significantly increased after therapy, while the peak annular mitral and tricuspid velocity remained unchanged.

Mao et al pointed out that their study was the first comprehensive report of systolic and diastolic function of both ventricles in neonates with congenital hypothyroidism and their data showed impaired left ventricular systolic function which normalized with L-T₄ therapy. Their data also showed that infants with congenital hypothyroidism do not have abnormal left atrial structure. The use of the TDE confirms subclinical impairment of both left and right ventricular contractile function in neonates with congenital hypothyroidism, as well as diastolic dysfunction

of both ventricles. The authors concluded that their data underscore the importance of early detection and treatment of infants with hypothyroidism.

Mao S, Wang Y, Jiang G, Zhao Z. Effects of levothyroxine therapy on left and right ventricular function in neonates with congenital hypothyroidism: a tissue Doppler echocardiography study. *Eur J Pediatr.* 2007;166:1261-5.

Editor's Comment: *This is a very interesting and comprehensive study which shows convincing evidence that there is significant cardiac dysfunction in neonates with congenital hypothyroidism. The presence of a control group adds to the significance of the findings. It is interesting that this study, conducted in China, was performed on infants aged 17 to 28 days, prior to the initiation of L-thyroxine therapy. Details of screening for congenital hypothyroidism in China were not presented. It is disturbing that treatment of a hypothyroid infant would be delayed as long as 28 days. One would hope that with improvement in screening techniques such a delay could be reduced. Clearly the authors have presented significant information demonstrating the need for early identification and treatment of this disorder.*

William L. Clarke, MD

Uterine Development in Turner Syndrome

Bakalov and associates performed a cross-sectional study evaluating uterine development in 86 women with Turner syndrome (TS), aged 18 to 45 years, who were participating in a comprehensive NIH study. All subjects had a karyotype by G-banding consistent with TS in at least 70% of 50 white blood cells. The women were evaluated by either transabdominal (n=68) and/or by transvaginal (n=20) ultrasonography. Longitudinal and anterior posterior fundal diameters were calculated as well as the maximal transverse uterine diameter. Normative data were used to characterize uterine maturity. Historical and treatment data including pubertal development, age of initiation of hormone replacement therapy, type of estrogen used, years of estrogen use, and history of growth hormone therapy were recorded. In the case of spontaneous menarche, the time interval from menarche to the development of amenorrhea was noted.

The mean age of the study population was 31.8 ± 7.3 years. Most subjects (93%) had a karyotype consistent with TS, while 6 (7%) had mosaicism. None had a Y chromosome (intact or abnormal), 15% had spontaneous menarche at age 12.2 ± 1.7 years, but had developed amenorrhea by their late teens. All other subjects (73/86) had started estrogen at an average age of 15.7 ± 4.1 years. Thirty percent (26/86) had also been treated with growth hormone. Almost one quarter (24.4%; 21/86) had a fully developed uterus both in size and shape, while

many (44%; 36/86) had a smaller size uterus (transitional) and 31.4% (27/86) had an immature (cylindrical shaped) uterus. Regression analysis demonstrated that uterine size was influenced significantly by age, years of estrogen use, current use of hormone replacement therapy, history of spontaneous menarche and the type of estrogen medication. There was no correlation between age of first exposure to estrogens and the size of the uterus. The degree of uterine maturity was positively associated with years of estrogen use, history of spontaneous menarche, and negatively associated with the lack of current hormone replacement therapy.

The authors reviewed recent studies from Germany¹ which showed that only mosaic females develop normal uterine size and that karyotype was the only significant predictor of normal uterine development. Findings in the current study were significantly different and 57% of the subjects with a mature uterus had a 45,X karyotype. This may be explained by an average longer duration of estrogen exposure. The authors stated that these findings are encouraging for those women with TS who wish to carry a successful pregnancy. A recent review of women with TS in the US participating in oocyte donation programs found that 69% became pregnant and these pregnancies resulted in the birth of a live infant.²

Bakalov VK, Shawker T, Cenicerros I, Bondy CA. Uterine development in Turner syndrome. *J Pediatr.* 2007;151:528-31.