

26 weeks was 0.2% in both groups and among those 8 to 14 years of age the mean decrease was 0.37%. There were no statistical differences in the reduction in HbA1c between the CGM group and the control group for both of these ages. There were no significant differences in the incidence of severe hypoglycemic events between the CGM groups according to age; however, severe events were infrequent in both groups. Sensor use was greater among subjects 25 years of age or older with 83% of the subjects using the sensor at least 6 days/week. In the group 15 to 24 years of age 30% used the sensor 6 days/week, and in those 8 to 14 years of age 50% used the sensor 6 days/week. Sensor use was not associated with baseline HbA1c.

The JDRF Continuous Monitoring Study Group concluded that the benefit associated with CGM with regard to improved glycemic control was strongly related to age. Individuals greater than 25 years of age clearly benefitted while those 15 to 24 years of age did not benefit. Those 8 to 14 years of age had greater benefit than those 15 to 24 of age years. The authors further commented that before generalizing these results it is important to remember that all of the subjects in this trial were receiving intensive insulin therapy and that most of them had better than average HbA1c. Of note, the results for subjects using multiple daily injections were similar to the results of those using an insulin pump. The researchers further concluded that CGM may improve HbA1c and enhance the management of type 1 diabetes in adults who have the motivation to use the technology and incorporate it into their daily management.

Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med.* 2008;359:1464-1476.

Editor's Comment: *Many pediatric endocrinologists have been waiting to see the data in this study regarding CGM. Many may see the results as disappointing, but maybe not surprising. Adults with strong motivation to use the CGM 6 days/week seem more likely to utilize the information to improve their glycemic control. Children 8 to 14 years of age—whose diabetes management is mostly directed by their parents—who also may have great motivation receive a greater benefit than adolescents 15 to 24 years of age, but not as much benefit as the adults. The results from the adolescents (who used CGM the least) is not surprising. CGM provides an incredible amount of real-time information regarding glycemia. For many people this information is overwhelming and of such a magnitude that organizing and responding to it is difficult. The JDRF study does not report any psychological, behavioral, or social information regarding the participants. Indeed such factors may have a great influence on subjects' ability to successfully manage their diabetes. It is hoped that such information was collected and that further reports of this data will include such information. Until such information is reported and correlated with the findings, the study remains incomplete.*

Pediatric endocrinologists still do not know for whom CGM will provide the greatest benefit and how such information can best be used by their patients. CGM most likely will not be widely used by the majority of persons with type 1 diabetes; but for a subset of individuals the information from CGM may greatly improve their ability to reduce glycemic variability and their risk of long-term complications.

William L. Clarke, MD

Primary Thyroid Carcinoma in Childhood Cancer Survivors

With modern therapies and supportive care, the number of the childhood cancer survivors (CCS) has increased considerably. However, these patients suffer from the late-onset complications such as endocrine impairments, neuropsychological problems and second malignancies. These late-onset complications often do not become clinically apparent until decades after therapy. Since the likelihood of follow-up decreases with time, it is important for physicians as well as patients and family members to be aware of the late-onset complications over their lifetime.

Patients who received upper-body radiotherapy for childhood cancer have an increased risk of developing primary thyroid cancer later in life. Brignardello et al set forth the recommendations for monitoring the late-onset complications of thyroid carcinoma by thyroid ultrasound screening into young adulthood, and beyond, in CCS. They observed a very high occurrence of thyroid carcinoma as a second malignant neoplasm in a total of 129 CCS who were previously treated with radiotherapy

involving the head, neck, or upper thorax. The patients had had brain tumors, Hodgkin's disease, acute lymphoblastic leukemia and received preventive brain irradiation or total body irradiation for bone marrow transplantation. Thyroid ultrasound surveillance usually began 5 years after radiotherapy and was repeated every third year, if negative. Median follow-up time since the primary childhood cancer diagnosis was 15.8 years (range 6.1 to 34.8 years). Solid thyroid nodules were found in 35 patients included patients with palpable nodules (n=6) as well as those with solid nodules larger than 0.5 cm detected by thyroid ultrasound. Fourteen patients had nodules over 1 cm, 8 of which were not palpable. Fine-needle aspiration was performed in 19 patients, of which 14 had nodules over 1 cm. Cytological examination of specimens resulted in papillary carcinoma diagnosed in 5 patients and follicular carcinoma in 6 patients. In the remaining 8 patients, 7 had a diagnosis of nodular hyperplasia and one had lymphocytic thyroiditis. The

cytological diagnosis of papillary thyroid carcinoma was confirmed by histological examination in all 5 subjects who underwent surgery. Notably, only 2 of these patients had palpable nodules; the other 3 were smaller than 1 cm and were only detected by ultrasound. However, histological examination showed nodal metastases in 2 of them. In all 6 patients with follicular neoplasms who underwent surgery, the histological examination showed a benign lesion (goiter, n=3; follicular adenoma, n=3). Thyroid function was normal in 87 subjects, whereas 42 had primary hypothyroidism (n=37) or central hypothyroidism (n=5).

Brignardello E, Corrias A, Isolato G, et al. Ultrasound screening for thyroid carcinoma in childhood cancer survivors: A case series. *J Clin Endocrinol Metab.* 2008;93:4840-4843.

Editor's Comment: *This is a very interesting article; it provides important information for physicians who care for CCS. Because survival rates of childhood cancer patients have improved markedly in recent years, the risk of developing a thyroid neoplasm clearly increases over many years after radiation therapy involving the head, neck, or upper thorax during childhood. Brignardello et al reported the prevalence of thyroid cancer, thyroid nodules and other thyroid alterations increased in the long-term follow-up of CCS.*

There are 2 other papers on the subject worthy of discussion. In a 2003 retrospective study of all survivors of childhood and adolescent malignancies treated at Memorial Sloan-Kettering Cancer Center, Acharya et al¹ reported 33 patients who developed a clinically apparent thyroid neoplasm after therapeutic radiation. The median age at the time of diagnosis of the primary malignancy was 12.0 years (range, 3.7 to 18.3 years). The most common primary malignancy seen was Hodgkin's disease (n=18 patients), followed by non-Hodgkin's lymphoma (n=10 patients). The median interval from the time of radiation therapy until the recognition of thyroid disease was 13.0 years (range, 6.2 to 30.1 years). Thirteen of 33 thyroid lesions (39%) were malignant (11 papillary carcinomas and 2 follicular carcinomas). All thyroid abnormalities were detected on routine physical examination. Seventeen patients presented with a single nodule, 7 with multiple nodules, 5 with a multinodular goiter, 2 with lobar enlargement, 1 with a diffuse goiter, and 1 with an enlarged cervical lymph node and a normal thyroid gland. Thyroid ultrasound results were abnormal in 18 of 19 patients. Ultrasound revealed the presence of multiple nodules in 33% of patients, whereas only

15% of those patients had multiple nodules that were appreciated on physical examination.

In 2005, Sigurdson et al reported 72 cases with pathologically confirmed thyroid cancer from 14054 survivors (5 years or longer) of cancer during childhood from the Childhood Cancer Survivor Study cohort.² Childhood cancers were diagnosed between 1970 and 1986 with cohort follow-up to 2000. Of the 72 cases with secondary thyroid neoplasms, 56 (78%) were papillary, 11 (15%) follicular, and 5 (7%) of other or unspecified histology; 29 cases had a first diagnosis of Hodgkin's lymphoma and 14 had leukemia. They showed that the risk of subsequent primary thyroid cancer after a first tumor in childhood rose with increasing radiation dose (greatest risk 20–29 Gy), but decreased at doses of more than 30 Gy. Patients younger than 10 years at first cancer diagnosis had a higher risk of thyroid cancer than patients aged 10 years or older.

It is evident from these studies that thyroid nodules, even those greater than 1.5 cm, cannot always be palpated. In the study of Brignardello et al only 2 of the 5 patients with papillary thyroid carcinoma had palpable nodules. In the other 3 cases, the nodules were less than 1 cm, and were only detected by ultrasound. Therefore, the authors recommended monitoring the thyroid cancer by thyroid ultrasound screening in CCS previously treated by radiotherapy involving the head, neck, or upper thorax. Early detection of secondary thyroid cancers could improve the outcome of the patients. However, because thyroid ultrasound also detects many small lesions, the majority of which are benign, a very careful evaluation is needed to ascertain the results of thyroid ultrasound screening.

Brignardello et al emphasized the need for long-term follow-up for all CCS, which clearly must be extended well beyond childhood. Follow-up must

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address transitional strategies to avoid dropout and improve the overall outcome of childhood cancer treatment and survivors. Also it is necessary for physicians, as well as patients and family members, to know that late-onset complications of a cancer survivor can occur even after many years following cancer treatment.³

Yoshikazu Nishi, MD

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Renal and Urinary Tract Anomalies in Congenital Hypothyroidism

Newborn screening for congenital hypothyroidism (CH) is one of the major achievements of preventive medicine, as the condition occurs frequently (1/3000-4000 newborns). An early diagnosis and treatment prevents brain damage and the ensuing mental retardation. It is well known that CH has increased incidence of congenital malformations of heart, gastrointestinal, and skeletal systems. However, the prevalence of congenital renal and urologic anomalies on CH has not been well established.

Kumar et al reported that children with CH have significantly increased risk of congenital renal and urological anomalies. They investigated the prevalence of congenital renal and urologic anomalies in children with CH as compared to children without CH. Analysis of Congenital Malformation Registry data showed 980 children with CH and 3,661,585 children without CH born in New York State (1992-2005). Children with CH had a significantly increased risk of congenital renal and urological anomalies with the odds ratio (OR) of 13.2 (10.6-16.5). The other significantly increased defects and prevalence rates in patients with CH were cardiac, gastrointestinal, and skeletal (Table). Analysis of matched data (CH data from New York State newborn screening; 1,538 children with CH and 3,654,033 children without CH) also confirmed an increase of congenital renal and urologic anomalies with an OR of 4.8 (3.7-6.3). There are limitations of their study; the Congenital Malformation Registry is compiled on the basis of hospital-generated data and is limited to children under 2 years of age. Therefore, there may be an underestimating of the true prevalence of congenital renal and urologic anomalies.

Hydronephrosis, UPJ obstruction, hypospadias, renal dysplasia, and renal agenesis were especially significant. Therefore, they suggested that CH children should be evaluated for the presence of congenital renal and urologic anomalies by a renal ultrasound examination.

Kumar J, Gordili R, Kaskel FJ, Druschel CM, Wordniecki RP. Increased prevalence of renal and urinary tract anomalies in children with congenital hypothyroidism. *J Pediatr*. 2009;154:263-266.

Editor's Comment: This is a very interesting article; it provides important information for physicians who care for patients with CH and elucidates the high incidence of

Prevalence rates of congenital anomalies in hypothyroidism (CH) and in general population (non CH)

Congenital anomalies	CH (RATE/10 000)	Non-CH (RATE/10 000)
Renal		
Dysplastic kidney	30.6	1.7
Renal agenesis	102.0	4.3
Ectopic kidney	30.6	1.7
Hydronephrosis	346.9	21.1
Hydroureter	20.4	1.5
UPJ obstruction	30.6	1.9
Reflux	20.4	0.4
Hypospadias	275.5	39.6
Obstruction meatus	20.4	0.3
Posterior urethral valves	10.2	0.7
Cardiovascular		
Atrial septal defect	622.4	29.0
Ventricular septal defect	602.0	36.6
Coartation of aorta	81.6	4.1
Tetralogy of Fallot	183.7	4.6
Endocardial cushion defect	275.5	3.1
Gastrointestinal		
Duodenal atresia/stenosis	51.0	1.6
Gastroschisis	10.2	1.4
Omphalocele	40.8	1.3
Oral clefts	91.3	12.9
Pyloric stenosis	40.8	17.1
Tracheoesophageal fistula	61.2	2.4
Skeletal		
Craniosynostosis	50.0	4.0
Congenital hip dysplasia	30.6	1.7
Limb reduction	40.8	3.3

Modified from Kumar J, et al. *J Pediatr*. 2009;154:263-266. Copyright © Elsevier 2009. All rights reserved.