

10 and 20 minutes of treatment, glargine phosphorylated both IR and IGF1R, and detemir phosphorylated IR but not IGF1R. Glargine further led to increased phosphorylation of both Akt and ERK, representing the 2 major signaling cascades of IR and IGF1R, without changes in the total protein amounts; phosphorylation was maximal at 20 minutes and decreased by 60 minutes. In a test of relative potencies, cells were treated for 30 minutes with each hormone at 50 ng/mL. Glargine and insulin both significantly increased the amount of phosphorylated Akt in comparison to untreated cells, while detemir and IGF-I did not significantly alter Akt phosphorylation. Insulin alone significantly increased ERK phosphorylation.

The authors concluded that at the supra-physiologic doses tested, glargine and detemir have significant IGF-I-like mitogenic activity, which is not shared by insulin. The authors' warning bears repeating: current evidence shows that neither IGF-I nor insulin (and hence, one would expect the insulin analogues as well) can cause malignant transformation. However, IGF-I does increase the aggressivity of already transformed cells. Thus,

the question raised by this paper is whether long-term exposure to the insulin analogues can likewise affect cancer behavior.

Weinstein D, Simon M, Yehezkel E, Laron Z, Werner H. Insulin Analogues Display IGF-I-like mitogenic and anti-apoptotic activities in cultured cancer cells. *Diabetes Metab Res Rev.* 2009; 25:41-49.

Editor's Comment: *It would take a colossal leap to answer the underlying question based on the data of this pilot study. However, the results are intriguing enough to suggest more rigorous investigations are warranted. The high prevalence of both cancer and diabetes in our society, plus the widespread long-term use of these modified insulin analogues, makes the question an important one to answer. If—and this is a big if—it pans out that one or more of the insulin analogues is more stimulatory for cancer behavior, then cancer risk will become yet another factor clinicians must consider in selecting the particular insulin regimen for an individual patient.*

Adda Grimberg, MD

Continuous Glucose Monitoring and Intensive Treatment of Type 1 Diabetes

The Juvenile Diabetes Research Foundation (JDRF) Continuous Glucose Monitoring Study Group reported their findings of a multicenter clinical trial which randomly assigned 322 adults and children with type 1 diabetes to continuous glucose monitoring (CGM) or a control group which performed blood glucose monitoring with a glucose meter. All subjects were followed for 6 months to determine whether CGM helped to produce a sustained lowering of HbA1c and a reduction in hypoglycemia. The subjects were stratified by age: 8 to 14 years, 15 to 24 years, and over 25 years of age, and by HbA1c $\leq 8\%$ and $> 8\%$. Individuals with HbA1c of $< 7\%$ or $> 10\%$ were excluded. Subjects had to be using an insulin infusion pump, or at least 3 daily insulin injections, to control their diabetes and could not have had experience with CGM for the 6 months prior to the trial. The final study group included subjects who used either the Dexcom 7® (Dexcom™), the Mini-Med Paradigm® Real Time Insulin Pump and Continuous Glucose Monitoring System (Medtronic), or the FreeStyle Navigator® (Abbott Diabetes Care) according to the manufacturer's instructions which included specific calibration procedures and replacement of the sensors every 3 to 7 days.

Subjects were instructed to verify the accuracy of CGM determinations with self blood glucose meters before making treatment decisions. Subjects were also given written instructions on how to use the data generated by the CGM and blood glucose meters to make real-time adjustments in insulin doses. Target pre-meal blood glucose values were identical for the study group and the control group, 70 to 130 mg/dL (3.9

to 7.2 mmol/L); target peak post-prandial values were < 180 mg/dL (10 mmol/L), and bedtime overnight values 100 to 150 mg/dL (5.6 to 8.3 mmol/L). Subjects were seen at weeks 1, 4, 8, 13, 19 and 26 with one telephone contact between each visit to review glucose data and adjust diabetes management. After visits at 13 and 26 weeks, the control group used a blinded CGM for one week in order to compare continuous glucose profiles with the treated group. HbA1c was measured at 13 and 26 weeks and adverse events including severe hypoglycemia (defined as requiring assistance from another person and/or the use of glucagon), hyperglycemia with ketoacidosis, or other events were recorded.

The trial included 322 subjects (CGM group $n=165$; control group $n=157$); 114 patients were between 8 to 14 years of age (CGM group $n=56$, control group $n=58$), 100 subjects between 15 to 24 years of age (CGM group $n=57$, control group $n=53$) and 98 participants were over 25 years of age (CGM group $n=52$, control group $n=46$). A significant between group difference in the change in HbA1c from baseline to 26 weeks was seen in subjects who were 25 years of age or older, but not in those 15 to 24 years of age, or 8 to 14 years of age. In addition, in the CGM group over 25 years of age there were improvements in all measures of glycemic control including pre-meal and post peak-meal glucose values. The secondary analysis showed more patients in the CGM group had a reduction of 10% or more in mean HbA1c and more patients achieved their target HbA1c of $< 7.0\%$. Among subjects 15 to 24 years of age, the mean decrease in HbA1c from baseline to

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