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ABSTRACT

Endocrinology has recently witnessed several important developments:

- The Epidemiology of Diabetes Interventions and Complications study, a follow-up to the landmark Diabetes Control and Complications trial, found that strict glucose control early in the course of type 1 diabetes reduces the risk of microvascular and cardiovascular complications and provides prolonged benefits even if intensive control is not so tightly maintained.
- Inhaled insulin preparations are now available for mealtime coverage.
- We now have two new injectable medications for diabetes; pramlintide (Symlin) and exenatide (Byetta) are good adjuncts for patients with both type 1 and type 2 diabetes who have trouble reaching their hemoglobin A_{1c} target, and they can help control and even reduce weight.
- Thyroxine (T_4), instead of being merely a "prohormone," has been found to have direct actions on cells, leading to rapid clinical effects and possibly oncogenesis and angiogenesis.
- The therapeutic range for thyrotropin (TSH) may be much narrower than traditionally believed: some have proposed that the normal range should be redefined as 0.4 to 2.5 mIU/L.
- New evidence shows that vitamin D is important for more than calcium control and may help prevent type 1 diabetes.

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*Dr. Reddy has indicated that he was on the speakers' bureaus of the GlaxoSmithKline, Lilly, Novartis, Sanofi-Aventis, and Takeda corporations. Subsequent to Dr. Reddy's lecture, he accepted a position with Merck.

RECENT STUDIES in endocrinology have shed new light on diabetes management, the therapeutic range of thyroid hormones, the possible role of thyroxine (T_4) in cancer, and the importance of vitamin D in preventing type 1 diabetes. This article discusses these new developments and highlights their clinical implications.

INTENSIVE CONTROL IN DIABETES

The Epidemiology of Diabetes Interventions and Complications (EDIC) study,[1] a 7-year observational follow-up of participants from the landmark Diabetes Control and Complications Trial (DCCT),[2] found that intensive control of blood glucose levels early in the course of diabetes seems to protect against microvascular and cardiovascular complications of diabetes years later.

The DCCT,[2] published in 1993, randomized more than 1,400 patients with type 1 diabetes mellitus to receive either intensive therapy (with either an external insulin pump or three or more daily insulin injections and guided by frequent blood glucose monitoring) or conventional therapy (one or two daily insulin injections). Patients were followed for a mean of 6.5 years. Each treatment arm consisted of two groups: the primary prevention cohort, which consisted of patients with no retinopathy at baseline, and the secondary prevention cohort, which consisted of patients who started out with mild retinopathy.

In the primary prevention cohort, patients receiving intensive therapy had a 76% lower incidence of retinopathy compared with patients receiving conventional therapy. In the secondary prevention cohort, intensive therapy slowed the progression of retinopathy by 54%. In both cohorts combined, intensive therapy also led to a 39% reduction in the

occurrence of microalbuminuria compared with conventional therapy.

Throughout the DCCT, the mean hemoglobin A_{1c} level was 9.1% in patients on conventional therapy vs 7.3% in patients on intensive therapy. Soon after the DCCT ended, hemoglobin A_{1c} levels began to rise in patients in the intensive therapy group and fell in the conventional therapy group, so that by the end of the first year of the EDIC study, the groups had only a 0.4% difference, and by 5 years, the levels were not significantly different.

Despite the similarity of blood glucose control between the two groups throughout the EDIC study, microvascular complication rates continued to be lower in the cohort that had been assigned to intensive therapy in DCCT, reflecting the level of glucose control of the previous years.

The incidence of cardiovascular disease was also significantly lower during the EDIC study in the cohort who had received intensive therapy during the DCCT. During the mean 17 years of follow-up of both studies, 46 cardiovascular disease events occurred in 31 patients in the intensive therapy cohort vs 98 events in 52 patients in the conventional therapy cohort, reflecting a 42% lower risk of any cardiovascular disease event and a 57% lower risk of myocardial infarction, stroke, or death from cardiovascular disease.[3]

Controlling diabetes early on may help years later

Nephropathy and persistent microalbuminuria were found to be associated with genetic factors in addition to glucose control. Three markers of the angiotensin-converting enzyme gene were evaluated in patients participating in the DCCT and were found to be associated with the development of nephropathy.[4]

NEW DIABETES TREATMENTS

Most of our life is spent in a postprandial state. Intuitively, one might think that glucose given intravenously would stimulate a stronger insulin response than oral glucose, but the opposite is true: the gastrointestinal system is one of our biggest endocrine organs, secreting hormones that regulate glucose metabolism. Now drugs have been developed that mimic or augment the action of these hormones.

Targeting incretins

Ingested carbohydrates, amino acids, and proteins stimulate the gastrointestinal tract to release hormones called incretins, which include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP).

GLP-1, secreted by the L cells of the ileum, acts as an "ileal brake" by inhibiting gastric emptying and glucagon secretion and by stimulating insulin secretion. GLP-1 is secreted within minutes after an oral glucose challenge, so some kind of signal must travel rapidly from the stomach to the ileum.

The brain also has receptors for the gastrointestinal peptides, which may directly affect appetite and satiety.

GLP-1 has a half-life of less than 2 minutes; it is rapidly inactivated by dipeptidyl peptidase-4, an important protease both for clearing GLP-1 and for immune function.

Giving GLP-1 to rats causes beta-cell hypertrophy, and there is some hope that it may improve diabetes by extending beta-cell survival. Experimental evidence also indicates that GLP-1 improves cardiac output and enhances cardioprotection.[5]

Patients who undergo gastric bypass surgery sometimes develop hypoglycemic episodes a few years later; some speculate that increased GLP-1 levels are to blame.

GLP-1 also is the mother peptide of a number of other proteins, and will probably prove important in several areas of medicine.

Nauck et al[5] randomized 10 patients with poorly controlled type 2 diabetes to receive (in addition to their other diabetes medications) either intravenous GLP-1 or placebo. In all patients given GLP-1, but not in any patients given placebo, plasma glucose reached normal fasting concentrations, insulin increased significantly over basal levels, and glucagon was reduced.

Pharmaceutical research is currently focused in three directions: developing GLP-1 analogues that are resistant to protease breakdown, developing a pill to inhibit dipeptidyl peptidase-4 so that the body's GLP-1 half-life can be extended, and developing GLP-1 receptor agonists that are not peptides, also to avoid rapid breakdown.

Exenatide (Byetta) is a GLP-1 analogue

derived from the venom of the gila monster, a lizard that eats only a few times a year. The drug mimics GLP-1 and is not easily broken down by dipeptidyl peptidase.[4]

Exenatide 5 to 10 μg given twice daily subcutaneously was found to improve glycemic control vs placebo in patients with type 2 diabetes who could not achieve control with maximal doses of metformin,[6] a sulfonylurea,[7] or with metformin and a sulfonylurea combined[8] (all subjects continued to take metformin or a sulfonylurea, or a combination of both during the trial). Patients taking exenatide progressively lost weight during the studies, which continued for up to 90 weeks.[9]

The drug is approved for use in patients with type 2 diabetes who are concurrently receiving metformin, a sulfonylurea, or both and have not achieved good glucose control.

Amylin: A new pharmaceutical target

GLP-1 and GIP also trigger beta cells in the pancreas to secrete insulin and another important peptide, amylin.[10]

First described in 1987, amylin is physiologically similar to insulin and is secreted from beta cells in a like manner following meals. Physiologically, it suppresses glucagon secretion, delays gastric emptying, and increases satiety. Patients with type 2 diabetes have a reduced amylin response following a meal compared with healthy controls, and those with type 1 diabetes have a much lower baseline level and no response from meals.[11]

Pramlintide (Symlin), a synthetic analogue of amylin, is cleared primarily through the liver and has a plasma half-life of 50 minutes. It can be injected three times a day before each meal. It initially causes nausea, but this tends to wear off after weeks of use. Low doses are used with type 1 diabetes and higher doses with type 2 diabetes.

Patients with type 1 or type 2 diabetes taking insulin along with pramlintide have better postprandial glucose control and less weight gain than patients taking only insulin. Some patients report that the drug enables them to achieve good glucose control following meals for the first time. Whitehouse et al[12] found that for patients with type 1 diabetes taking insulin, adding pramlintide at mealtimes led to lower hemoglobin A_{1c} levels without inducing weight gain or increasing the risk of severe hypoglycemia.

Pramlintide is approved for use in patients with type 1 diabetes and type 2 diabetes who are receiving insulin.

The success of these medications has given us proof of the concept that these are important pathways in glucose regulation. Under consideration by the US Food and Drug Administration (FDA) are oral agents that inhibit dipeptidyl peptidase 4 and result in raised levels of GLP-1 and GIP. These drugs (sitagliptin and vildagliptin) are in the approval stage at the FDA.

Inhaled insulin

Inhaled insulin has been under development since the mid-1980s. Exubera, an inhaled product, was approved by the FDA and was recently made available. (See review in June issue, *CCJM*).[13] This product is in the form of lyophilized microspheres in a blister pack that is inserted into an inhaler device about the size of a cucumber. The user turns on a blower motor and inhales the insulin deep into the bronchial tree.

Gamma scintigraphic imaging shows that delivery systems such as this distribute the drug well throughout the lungs.[14] The epithelial surface of the lungs is about the size of a tennis court, offering a potentially huge area for drug absorption. However, about 10 times more insulin is needed for delivery by inhaler than by subcutaneous injection to get the same response.

Inhaled insulin is for mealtime use; patients still need basal injections

Interestingly, smokers absorb inhaled insulin more rapidly than nonsmokers, possibly because of vascular changes in their bronchial tree.[15]

Efficacy of aerosolized insulin, as measured by hemoglobin A_{1c}, is very similar to that of subcutaneously injected insulin.[16] Because inhaled insulin is rapid-acting, it is for mealtime use, and subcutaneous insulin still needs to be used for basal coverage.

Patient satisfaction is higher with the inhaled delivery system than with the injectable form. Whether it becomes popular will probably depend on its price and insurance coverage.

Concern has been raised about possible long-term adverse effects of inhaled insulin on

the lungs.[17] A small decline in pulmonary function was observed in some of the preapproval studies, and for this reason the FDA suggests that patients undergo pulmonary function testing at baseline and at intervals during therapy. There are some theoretical concerns about insulin as a growth factor and about greater immunogenicity in patients with type 1 diabetes. There have been no adverse clinical sequelae, but certainly post-marketing surveillance will be necessary.

THYROXINE (T_4) IS BIOLOGICALLY ACTIVE

Recent evidence may change our thinking about how thyroid hormone works.

Classic understanding is that although thyroxine (T_4) and triiodothyronine (T_3) are secreted by the thyroid gland, only T_3—as it is secreted from the thyroid and converted from T_4 in the muscle, liver, and other organs—is active. Within cell nuclei are T_3 receptors that lead to gene expression and hormonal action.

Without having direct actions, T_4 should take days to have an effect, and patients who take T_4 preparations should not notice if they skip a day or two of medication. However, patients often report that they can feel a difference at once if they forget their drug.

Proposed new TSH range: 0.4–2.5 mIU/L

New evidence offers a possible explanation for this phenomenon: thyroid hormone appears to also have nongenomic activity, including roles in calcium metabolism, muscle function, angiogenesis, and neural cell function. These actions take place within seconds to minutes of exposure to thyroid hormone. This rapid action strongly suggests that T_4 may be interacting with a membrane receptor.

Is there a thyroid hormone-cancer link?

Davis et al,[18] in a series of experiments, demonstrated the role of T_3 and T_4 on angiogenesis in chick chorioallantoic membranes. Each hormone stimulates angiogenesis. Tetraiodothyroacetic acid (tetrac), an analogue of T_4, inhibits the surface binding of T_4 and reduces the enhanced angiogenesis effect of T_4. Fibroblast growth factor also stimulates angiogenesis, and blocking it with an antibody inhibits the angiogenesis caused by T_4, suggesting that the mechanism of angiogenesis by T_4 is mediated through fibroblast growth factor.

Mitogen-activated protein (MAP) kinase is an important enzyme in signal transduction of a number of growth factors. It can be activated by integrins, which are peptides at the cell membrane that are believed to be important in modulating cell responses and to play a role in oncogenesis, metastasis, and angiogenesis. By experimentally blocking MAP kinase, the angiogenesis caused by T_4 and fibroblast growth factor is also blocked. T_4 is believed to interact with a subtype of the integrin receptor, activating MAP kinase and promoting angiogenesis.

Hercbergs[19] observed 10 years ago that a patient with non-small cell carcinoma of the lung underwent spontaneous remission after prolonged hypothyroidism. He later attempted[20] to induce hypothyroidism with propylthiouracil in 22 patients with glioblastoma who had already undergone therapy unsuccessfully and were no longer candidates for subsequent therapy. Eleven patients became hypothyroid; they had a median survival time of 10.1 months vs 3.1 months in patients who did not become hypothyroid ($P = .03$). Patients who had at least a 40% drop in T_4 levels survived longer. Patients did not become clinically hypothyroid.[20]

It is difficult to be certain how to interpret this experiment. It is possible that a lower metabolic rate in hypothyroid patients slows tumor growth. Or it could be that the lower T_4 level reduces angiogenesis. If the latter proves true, perhaps in the future thyroid hormone analogues will be developed that block angiogenic effects but do not affect other important aspects of thyroid function.

WHAT IS A NORMAL THYROTROPIN LEVEL?

Defining normal levels of thyrotropin (TSH) is of great interest to endocrinologists. For most laboratory measurements, the normal range is arbitrarily defined as 2 standard deviations above and below the mean value for a population of apparently healthy people. However, although the normal range for TSH is considered to be 0.4 to 5.5 mIU/L, each person tends to have a tight normal range that varies very little over time.

Furthermore, it is valid to use the definition of 2 standard deviations above and below the mean only if the data are normally distributed, ie, if they fall in a symmetric bell-shaped curve. However, the distribution for biologically normal TSH is not symmetric but skewed towards the left, so that the median and mode are around 1.5 mIU/L. Such a skewed distribution makes one question whether those above the 75th percentile are truly healthy or whether they should be considered hypothyroid.

Bjoro et al[21] tested nearly 1,000 healthy people in Norway for TSH and thyroid peroxidase antibodies (which are similar to microsomal antibodies) and found that antibody levels were lowest in patients with a TSH level of 0.2 to 2.0 mIU/L and increased as TSH levels either increased or decreased.

Wartofsky and Dickey[22] proposed in 2005 that the normal range for TSH levels should be changed to 0.4 to 2.5 mIU/L. This would also affect the target therapeutic range, which would be 0.5 to 2.0 mIU/L. Therefore, in the future many endocrinologists may be treating patients who have a TSH level of 5.0 mIU/L and mild symptoms as hypothyroid and offering them thyroid medications to bring their level to the 0.5 to 2.0 mIU/L range.

It is critical for patients to be consistent about taking their thyroid medications. They should also stay with the same formulation. Thyroid hormone has a very narrow therapeutic range, and although different formulations may vary by only a few micrograms, this may be enough to alter TSH levels and bring the patient out of therapeutic range.[23]

VITAMIN D

New information about vitamin D indicates it has more actions than calcium and bone regulation and is making some experts question whether the recommended daily allowance is too low.

Vitamin D_2 (a plant-based product) and vitamin D_3 (which is synthesized in skin from sun exposure) are 25-hydroxylated in the liver, then 1-alpha-hydroxylated in the kidney to become the active form of vitamin D (1,25-dihydroxycalciferol). Vitamin D becomes inactivated with 24-hydroxylation.

Vitamin D is measured as 25-hydroxyvitamin D. Deficiency is defined as less than 30 nmol/L, and 30 to 50 nm/L is considered insufficient. Most senior citizens in American and Europe are deficient, which might play a role in osteoporosis.

Health effects

We have long understood that vitamin D is important as a regulator of calcium homeostasis and bone metabolism, and deficiency plays a role in hypocalcemia and rickets. But vitamin D has also recently been implicated in a wide range of diseases, including autoimmune disorders, cancer, and the metabolic syndrome. It modulates immune function by suppressing overaggressive reactions. Vitamin D analogues are being used in psoriasis because of the effects of vitamin D on cell growth and differentiation.

Does vitamin D prevent type 1 diabetes?

Increasing evidence implicates vitamin D deficiency or insufficiency in the development of both type 1 and type 2 diabetes mellitus. In mice with a genetic tendency to develop type 1 diabetes, supplementing the active form of vitamin D delays its onset.[24] Evidence also suggests that vitamin D protects against diabetes in people.

Thyroid hormone preparations are not equivalent

Epidemiologic data show that the incidence of type 1 diabetes is higher in countries further from the equator, leading to speculation that sun exposure and vitamin D may play a role: Scandinavian countries have a much higher prevalence of type 1 diabetes than Israel or India have, for example.

Hypponen et al,[25] in a birth-cohort study, evaluated more than 10,000 children born in 1966 in northern Finland. Vitamin D supplementation was associated with a significantly reduced risk of developing type 1 diabetes, and children suspected of having rickets in the first year of life had a three times higher risk of developing type 1 diabetes than other children. Finland has had an increasing incidence of type 1 diabetes at the same time that vitamin D supplementation recommendations have been reduced.

Experiments on beta cells have shown that 1,25-dihydroxyvitamin D is necessary for normal insulin secretion and biosynthesis and

protects beta cells from cytokine-induced damage. Vitamin D down-regulates antigen presentation by dendritic cells, and by indirectly inhibiting the development of Th-1 lymphocytes and inducing Th-2 lymphocytes, interleukin 2 and interferon-gamma production is inhibited and interleukin 4 is increased.

The level of 1,25-dihydroxyvitamin D that leads to these effects is much higher than what is normally seen in the circulation. Some believe that 1-alpha-hydroxylation occurs within target organs so that local levels may be higher than circulating levels.

To achieve by supplementation high enough levels of vitamin D to be beta-cell-protective and immunomodulatory, hypercalcemic effects would also occur. Future pharmaceutical efforts may focus on vitamin D analogues that would provide benefits without causing hypercalcemia.

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