METABOLIC CARDIOVASCULAR DISEASE SURABAYA UPDATE (MECARSU)
SURABAYA METABOLIC SYNDROME UPDATE (SUMETSU)
SURABAYA DIABETES UPDATE (SDU)
SURABAYA OBESITY UPDATE (SOBU)

SYMPOSIUM

CABANG SURABAYA CABANG SURABAYA

Proceeding

THE QUADRUPLE JOINT SYMPOSIUM - 2018

1. SURABAYA METABOLIC SYNDROME UPDATE (SUMETSU)
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THEME: CARDIOMETABOLIC HEALTH TOWARD–2020
CHALLENGES in PREVENTION and TREATMENT of OBESITY, MetS, CMR, and the CMDs

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Basal Insulin Concept: How to Treat The Target in T2DM Patients with Basal Insulin

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Worldwide, both underdiagnosis and undertreatment leave many patients exposed to long periods of hyperglycemia and contribute to irreversible diabetes complications. Early glucose control reduces the risk of both macrovascular and microvascular complications, while tight control late in diabetes has little or no macrovascular benefit.

Insulin therapy offers the most potent antihyperglycemic effect of all diabetes agents, and has a unique ability to induce diabetes remission when used to normalize glycemia in newly diagnosed patients. When used as a second-line therapy, basal insulin is more likely to safely and durably maintain A1C levels d+ 7% than when insulin treatment is delayed. The use of basal insulin analogs is associated with a reduced risk of hypoglycemia and weight gain compared to NPH insulin and pre-mixed insulin. Patient self-titration algorithms can improve glucose control while decreasing the burden on office staff.

Mechanism Diabetes Mellitus

Diabetes mellitus (DM) is a set of related diseases in which the body cannot regulate the amount of sugar (specifically, glucose) in the blood. The blood delivers glucose to provide the body with energy to perform all of a person's daily activities. The liver converts the food a person eats into glucose. The glucose is then released into the bloodstream. In a healthy person, the blood glucose level is regulated by several hormones, primarily insulin. Insulin is produced by the pancreas, a small organ between the stomach and liver. The pancreas also makes other important enzymes released directly into the gut that helps digest food. Insulin allows glucose to move out of the blood into cells throughout the body where it is used for fuel. People suffered diabetes either do not produce enough insulin (type 1 diabetes) or cannot use insulin properly (type 2 diabetes), or both (which occurs with several forms of diabetes). In diabetes, glucose in the blood cannot move efficiently into cells, so blood glucose levels remain high. This not only starves all the cells that need the glucose for fuel, but also harms certain organs and tissues exposed to the high glucose levels.

Pathophysiology

Type 1 diabetes

T1DM is the result of a combination of genetic and environmental influences. It most commonly results from autoimmune destruction of insulin-producing β-cells in the pancreas. Eisenbarth proposed that one or more environmental factors, such as enteroviruses, dietary factors or toxins, might trigger the development of T-cell

dependent autoimmunity in genetically susceptible individuals[1] Autoimmunity is manifested by detectable antibodies to ICA512/IA-2, insulin autoantibody (IAA) and glutamic acid decarboxylase (GAD). Insulitis with gradual β-cell destruction leads to pre-diabetes and finally to overt DM. These patients are susceptible to other autoimmune diseases, such as Hashimoto's thyroiditis, celiac disease, Addison's disease, and myasthenia gravis. Forty genetic loci have been associated with T1DM by a genome-wide association study and meta-analysis[2,10]. A number of genetic loci in the major histocompatibility (HLA) region are associated with increased susceptibility to developing T1DM, including the alleles DR3/4, DQ 0201/0302, DR 4/4, and DQ 0300/0302. The risk of T1DM is approximately 5% if there is an affected first-degree relative and slightly higher if the affected parent is the father rather than the mother. To date, interventional trials have failed to delay the onset or prevent T1DM in those genetically at risk. Ongoing research by international networks is exploring ways to prevent, delay or reverse the progression of T1DM [3].

Type 2 diabetes

Chronic fuel surfeit is the primary pathogenic event that drives the development of type 2 diabetes in genetically and epigenetically susceptible people[3,4]. Many chronic ally overnourished and overweight or obese individuals, however, do not develop diabetes at all or develop it very late in life. They remain resistant to type 2 diabetes and safely partition excess calories to subcutaneous adipose tissue (SAT) rather than to the heart, skeletal muscle, liver, and islet β cells, owing to the following mechanisms: successful islet β-cell compensation; maintenance of near-normal blood nutrient concentrations; development of minimal insulin resistance; increased expansion of SAT relative to visceral adipose tissue (VAT); and limited increase in liver fat.[5.6] In this way, key organs of the body avoid nutrient-induced damage. Susceptible over nourished individuals develop type 2 diabetes owing to the failure of these adaptive responses to safely dispose of the fuel surfeit. The following metabolic defects are crucial to the development of type 2 diabetes: inability of islet β -cells to compensate for the fuel surfeit; increased glucagon secretion and reduced incretin response; impaired expansion of SAT, hypoadiponectinaemia, and inflammation of adipose tissue; increased endogenous glucose production; and development of peripheral insulin resistance. Importantly, the fuel surfeit is not safely deposited into SAT, such that it has to be disposed of elsewhere. The "elsewhere" is less healthy VAT and "ectopic" storage in organs, such as the liver, heart, skeletal muscle, and pancreas, which causes widespread tissue damage. Worsening islet β-cell function can lead to the need for insulin therapy [7.8,9,10].

Therapy insulin

Ideally, the principle of insulin use is the creation of as normal a glycemic profile as possible without unacceptable weight gain or hypoglycemia. As initial therapy, unless the patient is markedly hyperglycemic and/or symptomatic, a "basal" insulin alone is typically added. Basal insulin provides relatively uniform insulin coverage

throughout the day and night, mainly to control blood glucose by suppressing hepatic glucose production in between meals and during sleep. The latter two are associated with modestly less overnight hypoglycemia (insulin glargine, insulin detemir) than NPH and possibly slightly less weight gain (insulin detemir), but are more expensive. Of note, the dosing of these basal insulin analogs may differ, with most comparative trials showing a higher average unit requirement with insulin detemir (11, 12).

The choice of initial insulin. The ADA and EASD recommend starting insulin treatment with basal insulin based on both the efficacy and relative safety of this approach (12,13). The 4Â T results suggest that "good control" should be judged based on not only A1C reductions but also on hypoglycemia risk. In choosing a basal insulin, clinicians should consider the following key questions (13).

- How rapidly does the basal insulin improve glycemic control?
  Both insulin glargine and insulin detemir are potent antihyperglycemic agents that rapidly reduce glycemia and can sustain target glucose levels long-term. In the glargine clinical trials, baseline A1C levels were generally >Â 8.5%. A1C levels close to 7% were achieved within 3Â months and sustained for the duration of these studies (6Â months to a year) (12).
- How well are the glycemic effects of basal insulin sustained over time?
  in the ORIGIN trial, basal insulin can maintain glucose at target levels for long periods and can even halt diabetes progression. A 3-year, open-label observational study with insulin glargine use in every-day clinical practice demonstrated sustained A1C reductions of 1.6% for 3Â years; mean A1C remained stable at 7.0% for the duration of that time (12, 15)
- What are the rates of symptomatic, severe, and nocturnal hypoglycemia with basal insulin?
  Rates of hypoglycemia are lower with the basal insulin analogs glargine and detemir than with neutral protamine Hagedorn (NPH) insulin. In a treat-to-target study of glargine vs NPH, symptomatic hypoglycemia was reduced by 21% (PÂ =Â 0.02) and nocturnal hypoglycemia by 42% (PÂ <Â 0.001). Severe hypoglycemia occurred in 2.5% of glargine patients and 1.8% of NPH patients (12,16).
- How satisfied are patients with basal insulin, and what are the quality of life data?
  Users of basal insulin analogs report greater satisfaction than patients treated with other agents (17). In a pooled analysis of glargine clinical trial results, mean improvements in Diabetes Treatment Satisfacüon Questionnaire change (DTSQc) were significantly greater with glargine than with comparators, which included oral antidiabetic drugs, NPH, and premixed insulin (mean scores 13.5 vs. 12.1, PÂ <Â 0.001). Treatment satisfaction was associated with positive changes in A1C and FPG (PÂ <Â 0.001) as well as a minimally negative impact on weight (PÂ =Â 0.02) (12, 17).

Having titrated the basal insulin against the fasting glucose, the inability to achieve glycaemic control despite normal or near-normal fasting glucose usually

means that excessive glycaemic excursions may be occurring during the day *following either breakfast or the main evening meal.* Therefore, a prandial insulin injection before the meal most consistently contributing to the greatest postprandial *glycaemic excursions is a logical first step in progressing insulin therapy, thereby* allowing for a more gradual intensification of insulin therapy governed by structured self-monitoring of blood glucose. Adjustments in the doses of both the basal and *prandial insulin may be required during this process. Additional injections of prandial* insulin may eventually be required, leading to a full basal–bolus regimen based on disease progression (12,14,17).

Conclusions

Insulin therapy offers the most potent antihyperglycemic effect of all diabetes agents, and has a unique ability to induce diabetes remission when used to normalize glycemia in newly diagnosed patients. When used as a second-line therapy, basal insulin is more likely to safely and durably maintain A1C levels ≤ 7%. The use of basal insulin analogs is associated with a reduced risk of hypoglycemia and weight gain, sustained glycemic control, rapid achieved glycemic targets, satisfied patient and increased quality of life.

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