Understanding the Mechanisms to Maintain Glucose Homeostasis: A Review for Managed Care

This supplement to *The American Journal of Managed Care* explores mechanisms involved in physiologic blood glucose regulation and imbalances in glucose homeostasis, including the mechanisms by which the kidneys contribute to glucose regulation and the potential impact of glucose imbalance on the kidneys. Specific pharmacologic agents are also discussed, in the context of guidelines from the American Diabetes Association and the European Association for the Study of Diabetes as well as relevant clinical studies. An extensive update on the newest drugs for the management of type 2 diabetes mellitus and managed care aspects of diabetes care is also included.

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Disclosures

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Release date: January 12, 2012
Expiration date: January 12, 2014
Estimated time to complete activity: 2.5 hours
Type of activity: Knowledge

This activity is supported by an educational grant from Bristol-Myers Squibb and AstraZeneca LP.

Intended audience: Pharmacists

Statement of Educational Need

The core pathophysiologic defects in type 2 diabetes mellitus (T2DM) include insulin resistance in the muscle and liver and β-cell failure. However, there are other contributing defects in T2DM that affect the regulation of glucose balance in the body, and these include accelerated lipolysis in adipocytes, incretin deficiency/resistance in the gastrointestinal tract, hyperglucagonemia in α-cells, increased glucose reabsorption in the kidneys, and insulin resistance in the brain. The involvement of all these organ systems is part of a system that helps to maintain glucose balance, an important part of homeostasis. The body regulates glucose levels within a tight window, maintaining levels at around 85 to 90 mg/dL. This is a very finely tuned system, and in any given individual the fasting glucose levels change by less than 1 to 2 mg/dL. However, when this system falters, the resulting hypo- or hyperglycemia leads to adverse consequences.

Hyperglycemia is not only the biochemical marker by which the diagnosis of diabetes is made, but it is also responsible for the development of microvascular complications, as seen in the DCCT and UKPDS trials. In addition, hyperglycemia has been shown to contribute to macrovascular disease, albeit to a lesser extent, as seen in the EDIC trial. But, most importantly, it is a self-perpetuating cause of diabetes that leads to glucose toxicity, which then contributes to insulin resistance in the muscle, liver, and adipocytes, as well as impairment in insulin secretion. In such states of hyperglycemia, it is known that elevated glucose levels worsen insulin resistance in the liver, upregulate key enzymes involved in gluconeogenesis, down-regulate glucose transport in muscle, inhibit the insulin signal transduction system, and impair insulin secretion.

These defects in glucose regulation were thought to be the result of defects of only a few organs. However, new evidence has shown that the progression of hyperglycemia to the development of T2DM can be attributed to an octet of defects. One of these defects involves the kidneys. The kidneys play a vital role in normal human physiology by helping to maintain fluid and electrolyte balance, acid-base balance, excretion of metabolic waste products and foreign chemicals, regulation of arterial pressure, secretion of hormones, and glucose balance (via glucose reabsorption and/or gluconeogenesis). New research into the role of the kidneys in glucose regulation has enhanced the understanding of the process involved in glucose reabsorption and release, including the role of sodium-glucose cotransporters (SGLTs) and facilitated glucose transporters (GLUTs) in glucose reabsorption.

In light of these new understandings of the kidneys' role in maintaining glucose balance and the pathophysiologic derangements that contribute to the development of T2DM, healthcare professionals involved in diabetes care need to be educated on these findings. A better understanding of the myriad ways whereby glucose balance is maintained should provide a platform for the rational management of hyperglycemia in the patient with diabetes. A review of the physiology and mechanisms by which the kidneys help to maintain glucose homeostasis, kidney physiology in states of hyperglycemia, and the resulting injury that can occur if balance is not restored can be of benefit to all clinicians in their daily encounters with patients with glucose imbalance, such as those with diabetes.

Overall Educational Objectives

Upon completion of the educational activity, the participant should be able to:

- Explain the pathophysiology of diabetes and the different mechanisms involved in maintaining glucose balance
- Describe the role of therapies and where they fit into the treatment paradigm based on defects of glucose homeostasis
- Examine newer and emerging agents, their potential role in diabetes management, and implications for managed care

Activity Fee

The activity is free for participants submitting evaluation forms and posttests online for Pharmacy Credit (ACPE). For participants submitting evaluation forms and posttest for Pharmacy Credit via fax or mail, there is a nominal fee of $10.00.

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