Choice of Glucose-lowering Therapy—A Metabolic Fulcrum-based Approach

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Abstract

Choosing the appropriate glucose-lowering therapy for the optimal management of type 2 diabetes is always challenging. Existing guidelines either do not offer any recommendations as to which particular drug to use as second- or third-line therapy, or make the issue too confusing for a primary care physician to follow. We suggest a simple, metabolic fulcrum-based approach, which classifies persons with type 2 diabetes as being eubolic, as being predominantly catabolic, or as having "maladaptive anabolism." This metabolic triage, performed using phenotypic features, with or without supporting investigations, allows the rational choice of therapy, which helps achieve glycemic targets in a more efficient manner.

Keywords

AGIs, DPP4i, GLP1RA, metabolic phenotype, metabolic triage, metformin, phenotypic approach, SGLT2 inhibitors, sulfonylureas

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With multiple classes of glucose-lowering drugs now available, the opportunity to achieve effective diabetes control has never been brighter. The American Diabetes Association (ADA) and European Association for Study of Diabetes (EASD) list seven classes of drugs in their recommendation.[1] Metformin, pioglitazone, sulfonylureas, dipeptidyl peptidase-4 (DPP4) inhibitors, glucagon-like peptide-1 receptors agonists (GLP1RA), sodium glucose cotransporter-2 inhibitor (SGLT2i), and basal insulin are included in their treatment plan. The International Diabetes Federation (IDF) also includes alpha-glucosidase inhibitors (AGIs) and premixed insulin in its therapeutic algorithm,[2] while bromocriptine and colesevelam find a place in the management strategy of American Association of Clinical Endocrinologists (AACE).[3]

Challenge of Choice

At the same time, however, this opportunity creates a challenge for physicians, who shoulder the responsibility of making rational, evidence-based prescription, which is safe, well-tolerated, and effective. Current treatment guidelines offer a choice of second- and third-line therapies, leaving the physician to take a "patient-centered" decision. No clear-cut guidance is available to help inform this decision, and the physician often relies upon a strategy of trial and error. In many resource-limited settings, reference investigations are not available, and the physician bases his decision upon experience, rather than evidence.

We propose a simple, metabolic fulcrum-based approach to the choice of glucose-lowering therapy, which can be practiced not only by primary care physicians but also by specialists. This metabolism-based analysis allows delineation of people with diabetes into various groups, each suited to a particular therapeutic approach.

Phenotypic Approach

Phenotype, defined as the sum of external attributes, includes a number of variables, which include anthropometric variables, such as age, gender, and weight. Weight is an important aspect of health, which influences the choice of glucose-lowering therapy. Specific life stages, such as preconception, pregnancy, and lactation, are also included in phenotype variables. Other biologic variables include cardiovascular health, hepatic function, renal function, and bone health (see *Table 1*).

Based on available evidence, a phenotypic framework can be crafted to allow the rational choice of glucose-lowering therapy. The multiple variables listed in modern, comprehensive guidelines, however, make it challenging for the primary care physician to understand and implement the recommendations in practice.

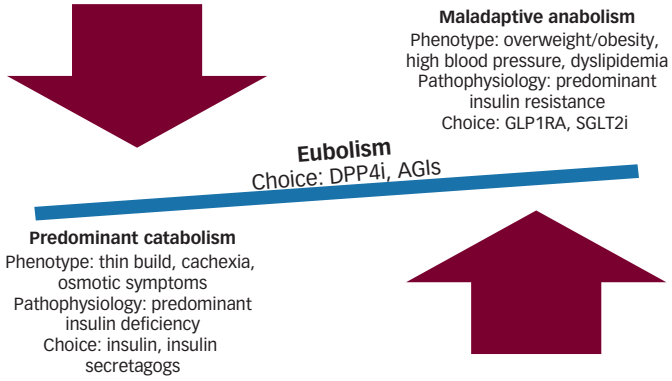
Metabolic Fulcrum

We propose simpler, metabolic fulcrum-based systematics, based upon a basic classification of metabolic status, to help inform the choice of glucose-lowering therapy (see *Figure 1*). The term "metabolism," derived from the Greek word for change, "metabole," refers to all life-sustaining chemical reactions that occur in a living organism. Healthy metabolism, or eubolism, can be visualized as a balance between the opposing processes of catabolism (breakdown of organic matter) and anabolism (building up of tissues).

Table 1: Phenotypic Variables Related to the Choice of Glucose-lowering Therapy

Life Stage
• Age
• Gender
• Preconception/pregnancy/lactation
Glucotype
• Fasting hyperglycemia
• Postprandial hyperglycemia
• Risk for hypoglycemia
• Glycemic variability
Cardiovascular Health
• Resting pulse rate
• Blood pressure
• Lipid status
• Myocardial health (ejection fraction)
• Coronary health
Comorbid Conditions
• Renal status
• Hepatic status
• Bone health

Figure 1: Metabolic Triage and Choice of Glucose-lowering Therapy



AGIs = alpha-glucosidase inhibitors; DPP4 = dipeptidyl peptidase-4 inhibitors; GLP1RA = glucagon-like peptide-1 receptors agonists; SGLT2i = sodium glucose cotransporter-2 inhibitor.

Metabolic Triage

If so, all individuals can easily be classified as belonging to one of three metabolic categories: a eubolic, a predominantly catabolic, or a predominantly anabolic. A healthy person, with signs of neither catabolism nor excessive anabolism, may be termed a eubolic. Evidences of catabolism, including asthenia, weight loss, cachexia, and malnutrition, qualify a person with diabetes as having severe insulin deficiency. Presence of weight gain and stigmata of metabolic syndrome justifies the label "maladaptive anabolism" and represents an insulin-resistant condition.

This systematic arrangement allows a "metabolic triage" of diabetes and lends itself well to the choice of glucose-lowering therapy. While this approach does not preclude the use of investigations to inform the choice of therapy, it can be practiced with minimal investigations as well.

Strengths and Limitations

Such an approach, though not yet evidence-based, follows the precepts of logical empiricism. It poses many challenges, which must be met if its full potential is to be realized. The definitions of "maladaptive anabolism" and "catabolism" need uniformity. Similarly, consensus is required regarding the exact placement of various drugs. Our model, however, is characterized by its dynamism and flexibility. All descriptors are relative and subject to change: these characteristics mirror the meaning of "metabole" itself.

This malleability allows the application of this metabolic fulcrum-based approach to the choice of glucose-lowering therapy in diabetes. Such usage strengthens, rather than detracts from, existing treatment guidelines.[1–3] It helps the patient and physician choose a rational therapy and facilitate faster achievement of glycemic targets in a more-efficient manner. ■

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