Abstract
The heterogeneity of diabetes mellitus, and the various metabolic abnormalities associated with it, are well known. Current management guidelines used to help choose glucose-lowering drugs in diabetes mellitus describe various drug classes in detail, but do not take the overall metabolic profile into consideration. To help physicians choose appropriate oral therapy, we propose a discrete metabolic score, based upon the presence and absence of metabolic comorbidities included in the definition of metabolic syndrome. This communication describes how to choose an appropriate oral antidiabetic drug using such a score. The metabolic score based decision making aid should be able to prove its utility in all health care settings, especially resource constrained societies.

Keywords: DPP-IV inhibitors, GLP-1RA, metformin, metabolic syndrome, SGLT2-inhibitors, sulfonylureas.

Introduction
If diabetes is a heterogeneous condition, diabetes management is even more diverse. Availability of newer therapeutic tools and conflicting opinions regarding suitability of various pharmacological regimes often combine to make diabetes management unnecessarily complicated.

While various guidelines and algorithms have been crafted to address this issue, they have certain limitations. Some guidelines are country-specific, while others appeal to a global audience. Some deal with the overall management of diabetes, while others focus on specific aspects of the condition. Of the guidelines that deal with the pharmacological management of glycaemia in persons with diabetes, two are read and discussed across the globe. These are the ADA- EASD (American Diabetes Association, European Association for Study of Diabetes) and the AACE (American Association of Clinical Endocrinologists) guidelines. ADA-EASD guidelines promote a person-centred care, and describe various second line and third line drug options.1 The AACE follows an HbA1c-based triage to decide the intensity of anti-diabetes regimes, and classifies drug classes according to safety.2

Limitations of Current Guidelines
Neither of these guidelines, however, discusses the appropriateness of various drugs according to patient characteristics. While evidence-based medicine does have its merits, these guidelines do not adequately highlight the role of traditional clinical skills in medical decision-making. The conventional teaching of eliciting a history, conducting a physical examination, arriving at a provisional diagnosis ordering investigations, and confirming the diagnosis seems to be ignored in these articles. For experts in the field, who are armed with sufficient expertise and experience to interpret published literature in an appropriate manner, this may not be a shortcoming. For students and general practitioners, however, this represents a major void. Unfortunately, therefore, the guidelines do not serve the very target they hope to reach. By proxy, therefore, they are unable to help the vast majority of people with diabetes, who seek treatment from general physicians.

In developing countries, which face the "cruel dual" challenge of seemingly limitless diabetes, and certainly limited resources, the situation is compounded by difficulty in access to required biochemical investigations and monitoring facilities.3 Modern treatment guidelines often do not take this psychosocial reality into account, though national guidelines such as those of India are gradually trying to meet this need.4

The Metabolic Score
We propose here, a simple aid to help decision making, based upon the "metabolic score". This aid is based upon the definition of the metabolic syndrome, and draws inspiration from the recently coined terms 'metabolically healthy obesity' (MHO) and 'metabolically unhealthy obesity' (MUO).5-7 The distinction between metabolically healthy and unhealthy obese persons is drawn according to the presence or absence of various components of metabolic syndrome. Similarly, we use the presence or absence of the components of metabolic syndrome to create two sub-phenotypes of diabetes (Table-1, 2). Each

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component is given equal weightage, to create a discrete score. The same score can be used to distinguish diabetes with metabolic syndrome (DMS+) from diabetes without metabolic syndrome (DMS-), or create new onomastic categories: metabolically complicated diabetes (MCD) and metabolically uncomplicated diabetes (MUD). MCD will have a relatively greater number of concomitant metabolic abnormalities as compared to those with MUD.

**Scoring Systems**

It must be noted here that the metabolic score can be a continuous or a discrete one. Reducing different metabolic dimensions into a single variable as a summary score is more appealing. However it is assumed that each item included in the score is equally important (unless weighting is used) and can be exchanged with any other item. For example, 1 SD increase in blood pressure is assumed equivalent with 1 SD increase TG or 1 SD decrease in HDL-cholesterol. Its limitations are that any such score is highly unlikely to reflect the complete clinical picture, and validation in different patient sub-populations and datasets will be a real challenge.

A continuous metabolic score may be preferable to the binary metabolic classification which we have used. This can be a sum of individual rankings, sum or mean of z-scores, principal components, or sum of standardized residuals. The problems of misclassification and low statistical power of binary scores can be overcome by this approach, but any cutoff level used will have limited sensitivity and/or specificity. At the same time, mis-allocation may occur even if a continuous score is used.

Discrete variables of metabolic syndrome, on the other hand, can be calculated [or rather, counted] in a convenient manner, which is feasible even in a busy practice. We can rate every component as being present or absent, and calculate the metabolic score accordingly. These discrete metabolic parameters can be easily calculated with measuring tapes, sphygmanometer and a laboratory where lipid profile can be done. These facilities are available to almost every clinician who treats diabetes. Therefore we recommend use of discrete variables in resource constrained settings, in spite of their statistical limitations.

**Classes of Drugs**

It is understood that metformin is the drug of choice for initial therapy of type 2 diabetes, in combination with lifestyle modification. There is a wide variety of second and third line options to choose from. The various glucose-lowering drugs available can easily be classified according to their effect on the individual components of metabolic syndrome (Table-3). These properties can be used to select the appropriate drug for an individual patient, based upon his or her metabolic phenotype.

Evidence colligated from research suggests that the newer classes of glucagon-like peptide 1 receptor agonists (GLP1RA) and sodium glucose co-transporter 2 inhibitors (SGLT2i) seem to provide comprehensive metabolic control. Apart from their glucose-lowering activity, they have a beneficial effect upon body weight, lipid profile and blood pressure. While other classes of

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**Table 1:** Metabolic score based on IDF definition of Metabolic syndrome.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Central obesity</td>
<td></td>
</tr>
<tr>
<td>Ethnicity specific values for other groups)</td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td>One</td>
</tr>
<tr>
<td>≥ 94 cm for Europid men</td>
<td></td>
</tr>
<tr>
<td>≥ 80 cm for Europid women</td>
<td></td>
</tr>
<tr>
<td>TG level:</td>
<td></td>
</tr>
<tr>
<td>≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality</td>
<td>One</td>
</tr>
<tr>
<td>HDL cholesterol:</td>
<td></td>
</tr>
<tr>
<td>&lt; 40 mg/dL (1.03 mmol/L) in males and</td>
<td>One</td>
</tr>
<tr>
<td>&lt; 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality</td>
<td>One</td>
</tr>
<tr>
<td>Blood pressure:</td>
<td>One</td>
</tr>
<tr>
<td>systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension</td>
<td>One</td>
</tr>
<tr>
<td>Fasting plasma glucose (FPG)</td>
<td></td>
</tr>
<tr>
<td>≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes</td>
<td>One</td>
</tr>
</tbody>
</table>

TG- Triglyceride; HDL- High Density.

**Table 2:** Metabolic score based on the presence of various components.

<table>
<thead>
<tr>
<th>Score classification</th>
<th>Classification</th>
<th>Alternate classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>High metabolic score</td>
<td>&gt;4 MCD</td>
<td>DMS+</td>
</tr>
<tr>
<td>Moderate metabolic score</td>
<td>3 MCD</td>
<td>DMS+</td>
</tr>
<tr>
<td>Low metabolic score</td>
<td>&lt; 2 MUD</td>
<td>DMS-</td>
</tr>
</tbody>
</table>

MUD: Metabolically uncomplicated diabetes; MCD: Metabolically complicated diabetes; DMS: Diabetes with metabolic syndrome.

Maximum possible score = 5.

Minimum possible score = 2, in a person with diabetes.
glucose-lowering drugs do report such advantages, the evidence is not as robust.

Our proposed algorithm, adds to, and strengthens, instead of conflicting with, existing guidelines. As it does not attempt to change the hierarchy of first line and subsequently chosen drugs, it is syncretic with the existing ADA-EASD recommendations. In fact, it increases their utility by helping the physician choose the appropriate second or third line drug in a timely manner, without going through a lengthy, wasteful process of trial and error.

**Classification and Choice of Drug**

**Metabolically Complicated Diabetes Mellitus**

A simple, discrete, metabolic score can be used to categorize people with type 2 diabetes into two groups, MCD and MUD (Table-2). Persons with MCD should preferentially be offered GLP1RA or SGLT2i, as second line drugs after metformin.12-15 Alpha-glucosidase inhibitors (AGIs) and dipeptidyl peptidase 4 inhibitors (DPP4i) may also be prescribed. DPP-IV inhibitors such as saxagliptin have been studied in long term cardiovascular outcome trials, and found to be safe.16 Those with MUD can be prescribed any of the antidiabetic drug classes according to the patient's needs and preferences.

**Diabetes and Dyslipidaemia**

The association of diabetes and dyslipidaemia is well known. There is always a need for an antidiabetic agent which will normalize lipid levels. GLP1RA, as well as DPP4i like vildagliptin, have been shown to suppress postprandial triglyceride and apolipoprotein B48 elevations after a fat-rich meal. In persons with dyslipidaemia, GLP1RA may be a better drug to use as compared to SGLT2i.17 As of now SGLT2i have shown inconsistent effects on lipid profile. Canagliflozin 300 mg has shown positive effects on lipid profile with increases in high-density lipoprotein by 7.1% to 10.6%, decreases in triglycerides by -2.3% and increases in low density lipoprotein by 7.1%.18-20 Dapagliflozin did not establish similar changes.21 No significant changes in lipid profile were seen after 24 weeks of dapagliflozin therapy.22

It must be noted that GLP-based therapy has been suggested to be more effective in persons with high serum free fatty acids. Serum triglycerides are a surrogate maker of serum free fatty acids, and it stands to reason that GLP1RA should be preferred in persons with high triglyceride levels. On the other hand, insulin is the drug choice for management of severe hypertriglyceridaemia, and this condition is a documented risk factor for pancreatitis.23 These factors must be assessed prior to initiation of therapy.

**Diabetes and Hypertension**

GLP1RA also improve blood pressure, as opposed to older sulfonylureas, which may increase systolic blood pressure.24-32 Modern sulfonylureas do not have any adverse effects on blood pressure.

These pharmacodynamics data help influence the choice
of anti-diabetic drugs in persons who do not respond to, or do not tolerate or have contraindications to, metformin.

**Limitations of Proposed Approach**

The approach that is described here, viz, using metabolic score to decide appropriate drug therapy, has not been validated so far. There is published evidence, however, that persons with diabetes and metabolic syndrome may respond better to GLP1RA than to DPP4i.33

**Conclusion**

This approach is meant to be a simple clinical aid or decision making tool for physicians practicing in settings where access to detailed investigations is not available, and where patients may not be able to follow up at frequent intervals. It is for physicians who feel the need for simplification of current, detailed guidelines, which offer an ever-increasing number of choices, but do not necessarily help one make the appropriate choice.

Based upon the metabolic score, we suggest preferential use of GLP1RA, SGLT2i, and AGIs in persons with a greater degree of metabolic dysfunction, or a higher metabolic score (MCD). Those without metabolic abnormalities, apart from dysglycaemia, may be prescribed any class of glucose-lowering drugs, including sulfonylureas.

This approach provides a framework for discussion and teaching, and can even be used in the most resource-constrained of settings. We hope that it stimulates further research in this direction, so that evidence-based decision making tools can be created to help physicians decide appropriate, and effective, treatment strategies for people with diabetes.

**References**


