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The World Health Organisation (WHO) Guidelines on Intensification of Anti-Diabetic Treatment in Developing Countries

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The last few years have witnessed the introduction of new anti-diabetics with a lower risk of hypoglycemia than sulphonylureas. Some of these drugs (SGLT-2 inhibitors and liraglutide) may also confer cardiovascular and renal protection. These medications are currently recommended as second line in type 2 diabetes mellitus (T2DM) not controlled by metformin alone (1,2). The WHO recently updated its 2013 guidelines, taking into account not only safety and efficacy, but also availability and cost of medications. Financial constraints are particularly important in developing countries, and in countries (like the USA) where patients pay out of pocket for their prescriptions. The WHO document, involving a team of 12 experts, is based on a review of the literature published between 2007 and 2017. The focus is on second line treatment and use of insulin, and there are 5 recommendations.

2nd Line Treatment of T2DM

Recommendation 1. Sulphonylureas should be used in T2DM patients not controlled by metformin alone, or when metformin is contraindicated (recommendation: strong; level of evidence: intermediate).
The authors notice that the new anti-diabetics have glucose-lowering efficacy similar to sulphonylureas. More data are needed to assess the reduced risk of hypoglycemia of the new drugs in patients at low cardio-vascular risk. These considerations, and the higher cost, do not allow at present to recommend the large-scale adoption of the new anti-diabetics.

3rd Line Treatment of T2DM

Recommendation 2. Human insulin should be used in T2DM patients who fail to achieve adequate glycemic control on metformin and sulphonylurea (recommendation: strong; level of evidence: low)
Recommendation 3. If insulin treatment is not possible (e.g. patients living alone and unable to self-administer insulin), a gliptin, a SGLT-2 inhibitor or a thiazolidinedione should be added (recommendation: weak; level of evidence: low).
Human insulin should be used if the association metformin + sulphonylurea fails to achieve adequate glycemic control. Human insulin and analogs appear similar in terms of hypoglycemic efficacy. According to the authors, the lower risk of hypoglycemia of the analogs is not backed by sufficient data on clinical endpoints to favor their use over human insulin.

Insulin Treatment in T1DM and T2DM

Recommendation 4. Human insulin (both regular and NPH) should be used in adults with type 1 diabetes mellitus (T1DM) and in T2DM patients who need insulin (recommendation: strong; level of evidence: low).
Recommendation 5. Long-acting insulin analogs should be considered in adults with T1DM or T2DM and recurring significant hypoglycemia while receiving human insulin (recommendation: weak; level of evidence: intermediate).
Although some data support a superior efficacy and a lower risk of hypoglycemia of the analogs in T1DM, the net clinical benefit is too modest to recommend their use in all patients with T1DM and T2DM in resource poor countries.

Discussion

Points of strength of the WHO guidelines: concordance with other international recommendations, emphasis on life-style, and confirmation of metformin as first line treatment.

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The guidelines have some **limitations**: the evidence supporting the recommendations is not strong, and there is a bias towards cost containment. An accompanying editorial expresses concern on sulphonylureas as second line agents, particularly in individuals at higher risk of hypoglycemia, like the frail elderly and patients with kidney disease. The better hypoglycemic profile of gliclazide over other sulphonylureas should have been highlighted. The cardiovascular protection conferred by the SGLT-2 inhibitors in patients with previous ischemic events should also have been mentioned, due to the potential to reduce diabetes macrovascular complications and costs. The WHO emphasizes cost containment in order to increase the number of patients in developing nations who receive treatment for T2DM, as shown by their statement that « … the main aim of WHO is to respond to health needs of populations, and not of specific groups of patients … ». The cost of the new anti-diabetics may overwhelm the resources available and deny treatment to part of the population, because, particularly in developing nations, financial sustainability goes along with fair access to health care. The use of biosimilars could reduce costs of producing insulin and make it more accessible.

In conclusion, the WHO's aim of fair and sustainable access to pharmacological treatment of T2DM underlies the decision to position the new anti-diabetics as third line treatment, behind sulphonylureas and human insulin. The WHO document places limited emphasis on the extra-glycemic benefits shown by some of the new anti-diabetics. In the future, reductions in cost and reductions in chronic complications of diabetes with inherent savings may promote easier access to new hypoglycemics and insulin analogs in resource poor countries.

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