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Commentaries

'Treatment-resistant' type 2 diabetes: Which definition for clinical practice?

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Despite being a common feature in clinical practice and a major challenge for healthcare providers involved in the management of Type 2 Diabetes (T2D) [1], the notion of 'treatment-resistant diabetes' is scarcely found in the diabetes literature, which is instead dominated by the classic term 'insulin resistance' [2,3]. In contrast, 'treatment-resistant hypertension' is a well-known concept in the field of arterial hypertension [4]. Resistant hypertension is defined as the persistence of systolic blood pressure ≥ 160 mmHg (or ≥ 150 mmHg in T2D) despite pharmacological treatment with at least three antihypertensive drugs (one of which is a thiazide or loop diuretic) [5]. Based on this definition, a practical approach for managing resistant hypertension has been recommended [6], and the results of large-scale prospective clinical trials, such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), have recently been re-analyzed according to this idea [7]. Yet, there is no such precise definition for 'treatment-resistant T2D', despite the fact that T2D and hypertension are two diseases that share several characteristics [8]. Mimicking the definition used for arterial hypertension, it has recently been proposed that the term 'treatment-resistant T2D' be used to refer to patients with Persistent Poorly-controlled Diabetes Mellitus (PPDM) despite standard care with three oral glucose-lowering medications [9].

Even though a global approach is recommended for the management of T2D [10], the notion of PPDM is restricted to the control of hyperglycaemia, as evaluated by the level of glycated haemoglobin (HbA_{1c}), which is associated with diabetic complications and considered a key marker of glycaemic control in diabetes [10–12]. Yet, this surrogate marker remains a matter of controversy [13]. As previously discussed [9], different target HbA_{1c} values have been proposed in the literature to define PPDM, including $> 8.0\%$ (64 mmol/mol) [14,15], $\geq 9.0\%$ (75 mmol/mol) [16] and even $\geq 10\%$ (86 mmol/mol) [17]. In real-life practice, however, there are numerous arguments in favour of a patient-centered approach and individualized HbA_{1c} targets according to the patient's profile [10–12].

The definition of standard care in T2D, restricted to the control of hyperglycaemia, is also challenging, especially given the commercialization of an increasing number of pharmacological classes, leading to a wide variety of different combination therapies [10–12]. Because of the progressive failure of beta cells, T2D is an evolving disease that requires progressive treatment intensification over time to maintain adequate glucose control [10–12]. To define this topic and to keep it analogous to the definition of resistant hypertension [5], it is here proposed to define treatment-resistant diabetes as PPDM despite triple oral therapy, and before the stage of glucose-lowering injectables (insulin and Glucagon-Like Peptide [GLP]-1 receptor agonists) [9].

It was also decided to select, as triple therapy, a dual background combination of metformin plus a sulphonylurea (SU) plus another oral glucose-lowering agent (whether glitazone, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter type 2 inhibitors). Metformin appears to be unavoidable as it is the first-line pharmacological treatment recommended in all guidelines [10–12]. However, the choice of SU may be challenged because of the controversy concerning this class of drugs over the past five decades [18], such that a recommendation of 'use with caution' has recently been proposed [12]. Based on its efficacy (poor durability of glucose control), safety (risk of hypoglycaemia), weight control (risk of weight gain) and cardiovascular controversy [18], other pharmacological alternatives may be more advantageous. However, the latter are more expensive, recommended only as third-line therapy in some countries and not available or reimbursed in many countries.

SUs, because of their low cost and wide clinical use, have kept their place as the second-line therapy in several T2D management algorithms, including those of the American Diabetes Association (ADA)-European Association for the Study of Diabetes (EASD) position statement (2015) [11], the International Diabetes Federation (IDF, 2012) [19], the UK National Institute for Health and Care Excellence (NICE, 2016) [20] and the Haute Autorité de Santé (HAS; National Health Authority) in France (2013) [21]. This means that even if cautious use is recommended for SUs [12], these agents remain largely prescribed in combination with metformin worldwide. In terms of glucose-lowering efficacy, SUs offer at least the same efficacy as other oral antidiabetic agents, although this may diminish or disappear over time [22].

Finally, in the diabetes literature, numerous trials have tested the addition of a third oral glucose-lowering agent to the metformin plus SU dual background therapy [23]. This is also the case when the addition of an injectable glucose-lowering agent, whether insulin or a GLP-1 receptor agonist, is considered to

improve glucose control in patients with PPDM despite oral antidiabetic therapy [24].

All these arguments support the definition proposed for treatment-resistant diabetes and the inclusion of SU in addition to metformin as background therapy [9]. As stated in the 2015 ADA-EASD position statement: “In certain patients, glucose control remains poor despite the use of three antihyperglycaemic drugs in combination. In any patient not achieving an agreed HbA_{1c} target despite intensive therapy, basal insulin should be considered an essential component of the treatment strategy.” [11].

It is also of interest to compare treatment-resistant diabetes with so-called ‘Psychological Insulin Resistance’ (PIR). Although the concept is clearly different, some connections may be seen between the two. PIR refers to the reluctance of healthcare providers to prescribe, and for patients to take, insulin despite insulin therapy becoming necessary because of PPDM with oral antidiabetic therapy [25,26]. The Barriers to Insulin Treatment Questionnaire seems to be a reliable and valid measure of PIR in patients with T2D [27], and patient PIR can result from a range of personal viewpoints involving cognitive appraisal and/or emotional reactions [28]. More broadly, this patient perspective may manifest as a lack of compliance or adherence to glucose-lowering medications, a common finding in T2D care that can clearly contribute to PPDM [29,30]. As discussed in our previous article on treatment-resistant diabetes [9], poor compliance/adherence to prescribed antidiabetic therapy should always be suspected in patients with PPDM despite standard care, given that it is such a common phenomenon in T2D [29,30]. It is therefore mandatory to also take into account patient preferences when prescribing antidiabetic agents, and to facilitate communication between physicians and T2D patients to promote shared decision-making [31,32].

Patient reluctance or poor medication adherence may lead to physician clinical inertia in the management of glycaemia in T2D patients [32–34]. This may then contribute to a delay of treatment intensification and, in particular, a shift to injectable therapies (especially insulin), thereby aggravating PPDM [35,36]. Moreover, healthcare professionals face many potential barriers to insulin initiation and intensification in primary care. These can be categorized as low motivation (questions concerning efficacy), lack of familiarity with insulin (inadequate experience) and time constraints [37]. Overall, physician-, patient- and healthcare-delivery-system-related factors can all contribute to clinical inertia and PPDM [32].

Furthermore, besides poor patient adherence and physician clinical inertia, disease-specific factors may also contribute to PPDM in T2D, especially when the defect of insulin secretion cannot overcome insulin resistance. Real-life observations have revealed that achieving HbA_{1c} targets becomes more and more difficult as the disease progresses and insulin secretion inexorably fails [38], leading to a higher risk of hypoglycaemic episodes [39].

Thus, treatment-resistant diabetes encompasses multiple mechanisms that need to be assessed before considering any intensification of pharmacological therapy in the face of a T2D patient with PPDM (Fig. 1) [36]. Numerous therapies that combine medications with different and complementary glucose-lowering actions are now available, and may help both patients and physicians overcome PPDM and treatment-resistant diabetes [9].

In conclusion, a large number of T2D patients have poor glycaemic control despite oral therapy combining metformin, SU and another glucose-lowering agent. Such patients may be defined as treatment-resistant and should be proposed alternative pharmacological strategies. Better knowledge of the possible causes of treatment-resistant diabetes should help in the search for appropriate solutions to overcome inherent difficulties [14]. Nevertheless, before intensifying any pharmacotherapy in

Fig. 1. Schematic illustration of the three major components comprising 'treatment-resistant diabetes'.

treatment-resistant T2D patients [9], physicians should first consider evaluating patient compliance/adherence and discuss patient preferences in a shared care approach.

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