SHORT COMMENT FOR THE LANCET DIABETES & ENDOCRINOLOGY

Personalising metformin therapy : a clinician perspective

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Metformin is the first-line pharmacological therapy for the management of hyperglycaemia in type 2 diabetes mellitus[1]. In case of failure of lifestyle, metformin is recommended to be prescribed first in every patient with type 2 diabetes, if there are no contraindications (renal impairment and/or hypoxic conditions). However, the glucose-lowering response to metformin may vary greatly from patient to patient, suggesting that some persons are rather poor responders to the biguanide. Because of the well known physician therapeutic inertia, insufficient glucose control may persist for a long time before therapy adjustment is made in such poor responders to metformin monotherapy. Furthermore, intensifying therapy generally consists of adding a second eventually followed by a third glucose-lowering medication, to be chosen among various options, while metformin is maintained in the long run[1]. A more logical attitude might be to stop metformin if poor responders to this glucose-lowering agent are clearly identified, instead of pile up medications.

Therefore, instead of prescribing metformin to every person with type 2 diabetes, a valuable alternative might be to select the more appropriate patients for this pharmacological approach. For a long time, the physician selects metformin upon simple clinical criteria (body weight, age, absence of comorbidities), which may influence both efficacy and safety, although most of them have been challenged[2]. Thus, there are no obvious clinical arguments that could help the physician to decide which patient with type 2 diabetes may benefit at most from metformin. There are many factors that may contribute to the interindividual variability of the metabolic response to metformin therapy (Figure 1). On the one hand, the pharmacological profile of metformin may be affected by pharmacokinetic considerations that can alter the exposure to the drug or by pharmacodynamic particularities that may directly influence its glucose-lowering action. On the other hand, patient's characteristics due to its genetic background or to its environment may also impact the metformin-induced HbA1c reduction.

The pharmacogenetics of type 2 diabetes raised increasing interest in recent years[3]. By analysing the data of the GoDARTS ("Genetics of Diabetes Audit and Research in Tayside Scotland") study and using the remarkable GWAS (Genome-Wide Association Study) approach, Zhou and colleagues conclude that genetic variants contribute to the variation in HbA1c reduction with metformin within the first 18 months after initiation of treatment, with the heritability of metformin glycaemic response estimated at up to 34%, a level almost similar to heritability estimates for schizophrenia and Alzheimer's disease[4]. The dual influence of the patient's disease pathophysiology and the metformin intrinsic effect (Figure 1) is supported by the fact that heritability concerns both pre-treatment baseline and on-treatment HbA1c levels. Although the variants are likely to have a small-to-moderate effect and be scattered across the genome, these original data suggest that future genetic analysis might enable physicians to make better predictions for the glucose-lowering response to metformin and thereby for stratified therapy [4]. This would be an important step in a better individualized management, which is of special interest in a heterogeneous and complex disease such as type 2 diabetes[5].

However, this study of Zhou and colleagues has some limitations[4]. First, it has a rather small size and there is a need of GWAS analyses with larger samples to find more genetic variants that could enable better predictions to be made for personalised medicine. Second, the HbA1c reduction was simply evaluated by the difference between one baseline HbA1c level and the lowest HbA1c value within the 18 months after the initiation of metformin. This crude approach may overestimate the real efficacy of metformin therapy and may explain why a surprisingly high HbA1c reduction relative to the average low dose of metformin used

was observed, both for metformin monotherapy (from 8.7±1.3 to 7.0±1.0 % with a mean dose of 1.26±0.47 g/day) and for addition of metformin to sulfonylureas (from 9.2±1.3 to 7.4±1.1 % with a mean dose of 1.29±0.51 g/day). In a systematic review of clinical trials, metformin monotherapy versus placebo lowered HbA1c by 1.12% (95% CI 0.92-1.32) and metformin versus placebo added to oral therapy lowered HbA1c by 0.95% (0.77-1.13), with a significantly greater reduction in HbA1c using higher doses (≥ 1.7 g/day) than lower doses of metformin (≤ 1.5 g/day)[6].

Third, in absence of measurements of plasma concentrations of metformin, it is not possible to decide whether the heritability mainly affects the pharmacodynamics or the pharmacokinetics of the drug. Recent data suggest that the oral absorption, hepatic uptake and renal excretion of metformin are largely mediated by organic cation transporters (OCTs) [7]. An intron variant of OCT1 (single nucleotide polymorphism [SNP] rs622342) has been associated with a decreased effect of metformin on blood glucose. In a large cohort of patients with type 2 diabetes, an 80-fold variability in trough steady-state metformin plasma concentration has been found[8]; OCT1 activity affects metformin steady-state pharmacokinetics, and OCT1 genotype influences HbA1c response to metformin treatment[8]. However, overall, the effect of structural variants of OCTs[8] and other cation transporters (multidrug and toxin extrusion transporters or MATE)[9] on the pharmacokinetics of metformin appears rather small and the subsequent effects on HbA1c reduction are also limited [7].

In conclusion, when considering the reduction in HbA1c level with metformin therapy in patients with type 2 diabetes, the likely multifactorial nature of metformin response may mask the effects of genetic variants. Despite the demonstration of a rather high heritability of the glucose-lowering response to metformin, further genetic studies are required to propose a truly stratified approach to metformin treatment in type 2 diabetes.

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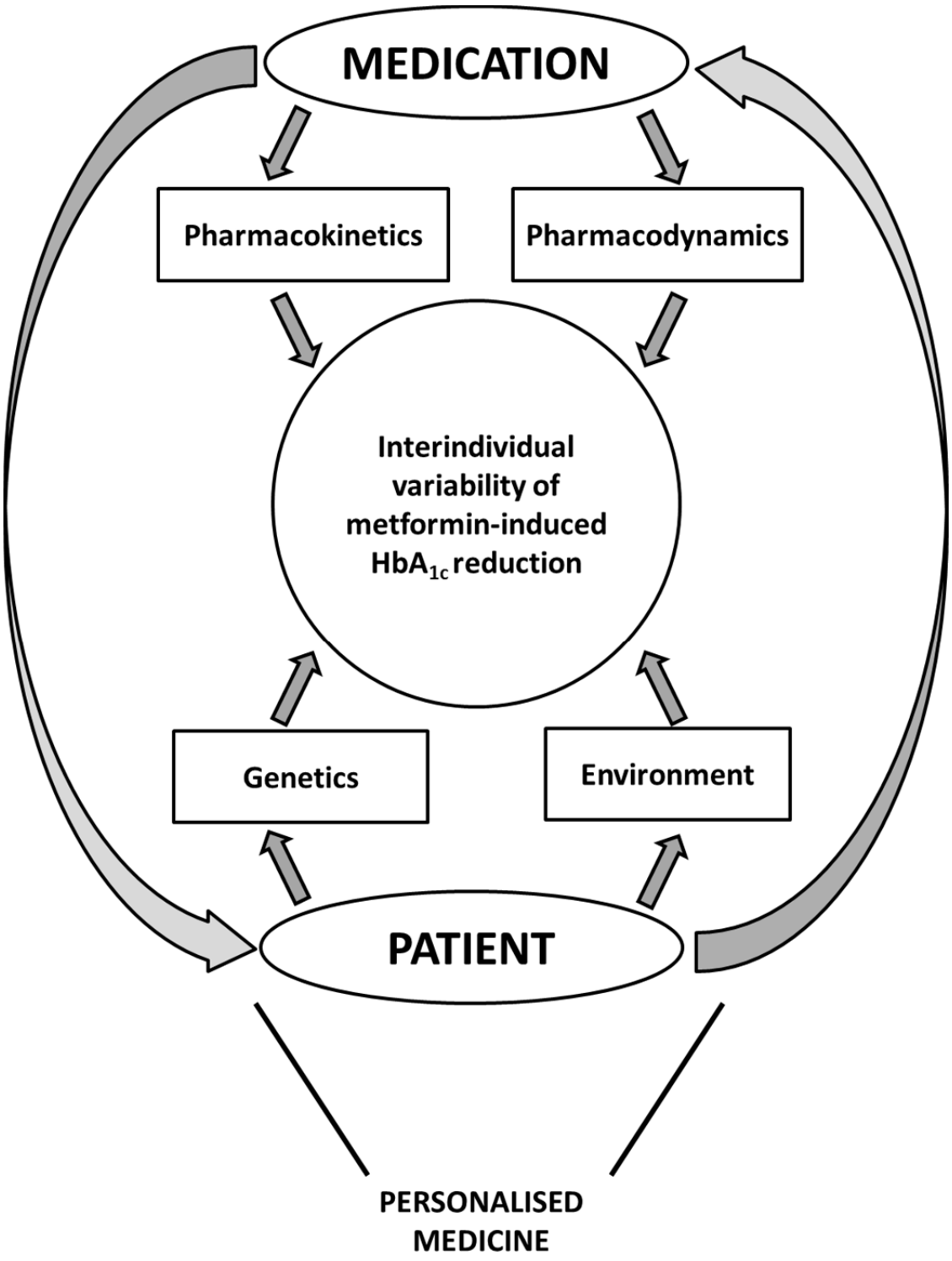
Figure 1 : Interactions between medication-related and patient-related factors contributing to the interindividual variability of metformin-induced HbA1c reduction in patients with type 2 diabetes, beyond daily drug dosage and patient's compliance.



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