Erythrocyte metformin levels in patients with type 2 diabetes and varying severity of chronic kidney disease

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Introduction

On the basis on a novel metformin assay, Frid et al. published clinical recommendations on use of the drug in patients with type 2 diabetes and varying severity of chronic kidney disease (CKD). The researchers stated that a threshold of 20 μmol/L (2.8 mg/L) was a ‘preliminary upper therapeutic limit’ [1]. However, the latter work can be questioned for several reasons: (i) the patients with an estimated glomerular filtration rate (eGFR) >60 mL/min/1.73m² were not given the full therapeutic dose (median: 1500 mg/day); (ii) 22% of the patient population had an eGFR <60 mL/min/1.73m²; (iii) the study reported median metformin concentrations rather than individual values and (iv) lastly, and most importantly, the metformin concentration was measured in plasma, although the erythrocyte level may provide a better estimation of the risk of accumulation [2]. Indeed, metformin has a longer half-life in erythrocytes than it does in plasma (23.4 ± 1.9 versus 2.7 ± 1.2 h [3]); this makes the interpretation of a single concentration time point less critical if the time of the last metformin intake is not known.

Here, we report on the distribution of erythrocyte metformin levels measured in a larger population with a wider range of eGFRs. We sought to test two hypotheses. Firstly, our previous work suggesting that metformin accumulation is not dangerous per se [4] (since metformin-associated lactic acidosis is related to the severity of concomitant pathologies (for a review, see [4])) may have prompted the physicians in our centre to continue metformin administration beyond the limit stated in the current guidelines. Secondly, this particular situation offered an opportunity to study the extent to which CKD may lead to significant elevation of the metformin level. Given that metformin clears four to five times more quickly than creatinine [5], we did not expect this phenomenon to be significant.

Materials and methods

Selection of study subjects

We systematically reviewed all erythrocyte metformin assay data recorded by our university medical center’s pharmacokinetics laboratory in 2008 and 2009. In general, the metformin assays had been requested in order to adjust the dose to the patient’s renal status or to screen for metformin accumulation.

We then selected all such patients for whom data on renal function and the metformin dose were available. Only one value is shown per patient; if several values were present in our database, we used the earliest one only. We excluded patients with lactic acidosis (arterial lactate >5 mmol/L and blood pH <7.35) in a context of acute renal injury or metformin overdose.

Estimation of the glomerular filtration rate

The glomerular filtration rate (GFR) was estimated with the abbreviated Modification of the Diet in Renal Disease (MDRD) equation, including gender, race, age and serum creatinine parameters. The MDRD equation has four variables:

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\text{GFR} (\text{mL/min/1.73m²}) = 175 \times \frac{\text{serum creatinine}}{0.742}\times \text{(age)}^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American)} \times (\text{conventional units}) [6].
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Patients were then divided into five CKD stages: >90 mL/min/1.73m² (Stage 1), from 90 to 60 mL/min/1.73m² (Stage 2), from 60 to 30 mL/min/1.73m² (Stage 3), from 30 to 15 mL/min/1.73m² (Stage 4) and <15 mL/min/1.73m² (Stage 5).

Analytical methods

Creatinine levels were measured in a colorimetric assay. Measurements of metformin levels were made in duplicate in the same laboratory using reverse-phase high-performance liquid chromatography with diode-array
detection, according to the method described by Lacroix et al. [7]. The erythrocyte level measurement technique has been described in detail elsewhere [2]. Results are expressed as basic metformin. Detection limit was 0.03 mg/L for erythrocytes.

Statistical analysis

Individual patient metformin levels are presented for each CKD stage. These data were studied with respect to the 95th percentile of the metformin level range observed for the study population as a whole. All statistical analyses were performed with GraphPad Prism 5 software (GraphPad Software, La Jolla, CA).

Results

We identified erythrocyte metformin assay results for 260 patients. We excluded 20 patients because of a lack of information on renal function or the metformin dose. In the remaining 240 patients (males: 64%), the median (range) values for key parameters were as follows: age 65 (38–88) years; body mass index 32 (20–77) kg/m²; glycated haemoglobin 8.1 (5.4–15.9) %; eGFR 47 (6.8–120) mL/min/1.73m²; metformin daily dose 2000 (500–4000) mg and metformin level 1.06 (0.12–3.11) mg/L.

Table 1 presents these parameters with respect to the different stages of CKD. Around two-thirds of the patients (68.5%) had an eGFR <60 mL/min/1.73m². When compared with Stage 1 patients, patients with lower eGFR were older and had a lower glycated haemoglobin value (the more severe the CKD, the lower the glycated haemoglobin value, to be more precise), a lower daily dose of metformin and higher metformin levels. However, Stage 5 patients constituted a specific group: they were not obese (and not even overweight), they had a normal glycated haemoglobin value, and higher metformin levels. However, Stage 5 patients did not appear to depend on eGFR for Stages 2–5 patients.

For each stage, the distribution of metformin levels and the percentage of levels above the 95th percentile are shown in Figure 1. The 95th percentile was 2.86 mg/L. None of the Stage 1 patients had a metformin level above this value. In Stages 2–4, the proportion of patients with metformin levels above the 95th percentile was relatively small and ranged from 1.7 to 10.5%; the proportion was higher in the small group of Stage 5 patients. Considering individual values, the distribution of metformin levels did not appear to depend on eGFR for Stages 2–5 patients.

For comparative purposes, the upper limit for a reference group without kidney failure was 1.6 mg/L [2] and the highest ever metformin value reported in the literature was 61 mg/L [8].

Discussion

Here, we report all the individual metformin levels available in our hospital (with the exception of patients with lactic acidosis). The fact that the metformin level was higher on average in patients with CKD is not especially important; the key thing is to be sure that none of the patients had an inappropriate level. A statistically significant difference in mean metformin levels between patients with and without CKD does not necessarily imply that levels of the drug are always elevated in all patients with CKD. Reciprocally, a normal mean level in patients with CKD does not rule out high values in some of these individuals.

Although our non-selective retrospective study had some disadvantages, it nevertheless reflects ‘real-life’ use of a drug. In this respect, our first hypothesis (i.e. whereby a high proportion of patients with CKD was still being treated with metformin) was confirmed. Indeed, 68.5% of the patients had an eGFR <60 mL/min/1.73m² and 18.2% even had an eGFR <30 mL/min/1.73m². This high proportion of patients with a low eGFR is not a source of bias per se; metformin assays are requested by physicians because of uncertainty about the existence, extent or stability of CKD and thus the potential for continuing metformin therapy or not. This particular situation offered an opportunity to study the extent to which CKD may lead to significant elevation of the metformin level.

Our second hypothesis (i.e. a low proportion of elevated metformin levels in patients with a low eGFR) was also confirmed. Indeed, given that non-modified metformin is eliminated solely by the kidneys [2], it is striking that there was no significant difference in the distribution of metformin levels between patients in Stage 1 of CKD (i.e. eGFR >90 mL/min/1.73m²) and those with a lower eGFR. However, this can be explained by the fact that median metformin doses were lower in patients with a low eGFR. Compared with Stage 1 patients, the median metformin dose was one-third lower in Stages 2–3, two-thirds lower in Stage 4 patients and one half lower in Stage 5.

In view of the above findings, one should not hastily blame the many physicians who apparently did not comply with the standard contraindications for metformin (i.e. CKD). In fact, common sense dictates that metformin therapy can be continued in kidney failure as long as the metformin dose is adjusted to fit the patient’s renal status and thus to prevent a premature switch to other drugs with their own disadvantages.

The above reasoning implies that metformin therapy can be continued in cases of stable CKD. Unfortunately,
our study did not include data on the change over time in our patients’ renal function. We can nevertheless speculate that Stage 2–4 patients had chronic disease (compared with Stage 1 patients) because they were older (by at least 10 years) and the metformin dose had been reduced proportionately with the severity of kidney disease. In contrast to Stage 1–4 patients, those at Stage 5 (i.e. eGFR <15 mL/min/1.73m²) constituted a particular group: they were younger, not obese (and not even overweight) and had a normal glycated haemoglobin value. Furthermore, the metformin dose reduction in Stage 5 patients was smaller than Stage 4 patients. Hence, we can speculate that kidney failure was progressing more rapidly in Stage 5 patients than in Stages 2–4 patients with a more conventional profile of long-standing diabetic nephropathy; this would explain why an appropriate median metformin dose reduction was not applied rapidly enough. In light of this reasoning, it is noteworthy that acute kidney injury appeared to be about three times more frequent than CKD in the largest series of metformin-treated patients with lactic acidosis reported on to date [9].

**Conclusion**

By applying what was probably a pragmatic metformin dose reduction in our centre’s low eGFR patients, elevated values were rare and true metformin accumulation was not encountered. Prospective studies are now required to establish whether or not it is possible to continue metformin therapy in CKD, provided that the dose is reduced appropriately. Whereas current guidelines focus on searching for a single ‘stop/go’ eGFR threshold for metformin therapy (amounting to ‘the usual dose or not at all’) [10–13]; for a review, see [13]; we suggest building a nomogram in which the adjusted metformin dose is plotted against eGFR.

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**Conflict of interest statement.** None declared.

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