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Short Report: Treatment

Organic cation transporter 1 variants and gastrointestinal side effects of metformin in patients with Type 2 diabetes

T. Dujic[1], A. Causevic[1], T. Bego[1], M. Malenica[1], Z. Velija-Asimi[2], E. R. Pearson[3] and S. Semiz[1,4]

[1]Department of Biochemistry and Clinical Analysis, University of Sarajevo, [2]Clinic for Endocrinology, Diabetes and Metabolism Diseases, University Clinical Centre of Sarajevo, Sarajevo, Bosnia and Herzegovina, [3]Division of Cardiovascular & Diabetes Medicine, School of Medicine, University of Dundee, Dundee, UK and [4]Faculty of Engineering and Natural Sciences, International University of Sarajevo, Sarajevo, Bosnia and Herzegovina

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Abstract

Aims Metformin is the most widely used oral anti-diabetes agent and has considerable benefits over other therapies, yet 20–30% of people develop gastrointestinal side effects, and 5% are unable to tolerate metformin due to the severity of these side effects. The mechanism for gastrointestinal side effects and their considerable inter-individual variability is unclear. We have recently shown the association between organic cation transporter 1 (OCT1) variants and severe intolerance to metformin in people with Type 2 diabetes. The aim of this study was to explore the association of OCT1 reduced-function polymorphisms with common metformin-induced gastrointestinal side effects in Type 2 diabetes.

Methods This prospective observational cohort study included 92 patients with newly diagnosed Type 2 diabetes, incident users of metformin. Patients were genotyped for two common loss-of-function variants in the OCT1 gene (*SLC22A1*): R61C (rs12208357) and M420del (rs72552763). The association of OCT1 reduced-function alleles with gastrointestinal side effects was analysed using logistic regression.

Results Forty-three patients (47%) experienced gastrointestinal adverse effects in the first 6 months of metformin treatment. Interestingly, the number of OCT1 reduced-function alleles was significantly associated with over two-fold higher odds of the common metformin-induced gastrointestinal side effects (odds ratio = 2.31, 95% confidence interval 1.07–5.01, $P = 0.034$).

Conclusions In conclusion, we showed for the first time the association between OCT1 variants and common metformin-induced gastrointestinal side effects. These results confirm recent findings related to the role of OCT1 in severe metformin intolerance, and suggest that high inter-individual variability in mild/moderate and severe gastrointestinal intolerance share a common underlying mechanism. These data could contribute to more personalized and safer metformin treatment.

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Introduction

Metformin is the first-line drug for treatment of Type 2 diabetes [1], and the most widely used oral anti-diabetes agent. It has considerable advantages over other Type 2 diabetes therapies, including low risk of hypoglycaemia, weight neutrality, low cost and possible cardiovascular benefits [1]. However, 20–30% of people treated with metformin develop gastrointestinal side effects, and 5% are unable to tolerate metformin due to the severity of these side effects [2]. The mechanism behind gastrointestinal side effects and their considerable inter-individual variability is not known. We recently reported the first study of the genetic and phenotypic determinants of severe intolerance to metformin in a large cohort of people with Type 2 diabetes [3]. Reduced-function alleles of organic cation transporter 1 (OCT1), and the concomitant use of medications known to inhibit OCT1 activity, were identified as risk factors for metformin intolerance [3]. However, in the reported research, a proxy phenotype for metformin gastrointestinal intolerance was established based upon prescribing patterns, namely the discontinuation of metformin and switching to another oral hypoglycaemic agent in the first months of metformin treatment. In this study, we aimed to explore the association between OCT1 reduced-function variants and

Correspondence to: Tanja Dujic. E-mail: tanja.dujic@gmail.com

What's new?

- The mechanism of high inter-individual variability in gastrointestinal side effects associated with metformin treatment is unknown.
- We show for the first time the association between organic cation transporter 1 reduced-function variants and common metformin-induced gastrointestinal side effects.
- These results might contribute to more personalized and safer treatment with metformin.

common metformin gastrointestinal side effects in a prospectively recruited cohort of patients with newly diagnosed Type 2 diabetes, incident users of metformin.

Patients and methods

This prospective observational study included patients with newly diagnosed Type 2 diabetes who were prescribed metformin as their initial hypoglycaemic therapy. Patients were recruited from the Clinic for Endocrinology and Diabetes, University Clinical Centre of Sarajevo. The research was carried out in accordance with the ethics recommendations and practices of the University Clinical Centre of Sarajevo, and complied with ethics principles outlined in the Declaration of Helsinki. The study was approved by Ethics Committee of the International University of Sarajevo, and each patient gave written informed consent.

Ninety-two patients with a Type 2 diabetes diagnosis after the age of 35 years were included in the study. Patients with chronic gastrointestinal diseases, including chronic liver disease, cholelithiasis, chronic pancreatitis, inflammatory bowel disease and gastroduodenal ulcer, chronic kidney disease, endocrine disorders, infection and hormonal therapy were excluded. Patients were monitored during the first 6 months of metformin treatment. The gastrointestinal side effects of metformin were defined as the presence of any of the following symptoms during metformin therapy: bloating, abdominal pain, nausea, diarrhoea, vomiting, and anorexia, in the absence of any acute gastrointestinal disease.

Patients were genotyped afterwards for two common loss-of-function variants in the OCT1 gene (*SLC22A1*): R61C (rs12208357) and M420del (rs72552763), using TaqMan genotyping assays (Applied Biosystems, Foster City, CA, USA). Both variants were in line with the Hardy–Weinberg equilibrium ($P > 0.05$).

Differences in the categorical variables were tested using the χ^2-test, and differences in continuous variables using the *t*-test (variables with normal distribution) or Mann–Whitney *U*–test (variables with non-normal distribution). R61C and M420del variants were analysed together, according to the number of haplotypes carrying reduced-function alleles: 0, 1 or 2 (OCT1 combined genotype). Haplotype analysis was performed using PLINK software (http://pngu.mgh.harvard.edu/purcell/plink/) [4]. The OCT1 combined genotype frequencies between the two groups were compared using the exact Cochran–Armitage trend test (additive model). The association of OCT1 diplotypes with gastrointestinal side effects was analysed using logistic regression, with age, sex, weight and concomitant use of OCT1-inhibiting medications [5] as covariates [3]. Statistical analyses were performed with SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Of a total of 92 patients enrolled in the study, 43 experienced gastrointestinal side effects. Baseline characteristics for the patients are shown in Table 1. Patients with metformin-induced side effects were more commonly women ($P = 0.004$), and accordingly, had lower body weight ($P = 0.007$), higher HDL-cholesterol ($P = 0.002$) and lower creatinine levels ($P = 0.001$) than the group without gastrointestinal symptoms at the beginning of metformin therapy (Table 1).

Haplotype and diplotype frequencies for R61C and M420del variants are shown in Tables S1–S2. The two OCT1 variants occurred only on the wild-type allele of each other ($D' = 1.00$, $r^2 = 0.02$), in line with other studies in Caucasians [3]. As shown in Table S2, the number of reduced-function haplotypes in each patient could be characterized by the total numbers of variant alleles in R61C and M420del (OCT1 combined genotype). The numbers of patients with 0, 1 or 2 reduced-function alleles (the OCT1 combined genotype frequencies) are shown in Table 1. There was a significant difference in the combined genotype frequencies between the two groups ($P = 0.048$).

The results of the logistic regression analysis model are presented in Table 2. Although individual variants were not associated with the occurrence of side effects in the multivariate model (data not shown), the number of OCT1 reduced-function alleles was significantly associated with more than two-fold higher odds of metformin side effects [Table 2, odds ratio (OR) = 2.31, 95% confidence interval (CI) 1.07–5.01, $P = 0.034$]. Female sex and lower weight showed a trend of association with the incidence of gastrointestinal side effects, without reaching statistical significance (Table 2).

Discussion

Metformin is used by over 120 million people worldwide, and considering the high prevalence of metformin-induced gastrointestinal distress, millions of people are suffering from these adverse effects during metformin treatment. These symptoms negatively affect their quality of life and may result in suboptimal drug dosage and non-adherence

Table 1 Baseline characteristics of patients with and without gastrointestinal side effects

	Group without gastrointestinal side effects (n = 49)	Group with gastrointestinal side effects (n = 43)	P
Age (years)	58.8 ± 8.4	57.1 ± 9.5	0.365
Women/men (% women)	22/27 (44.9)	32/11 (74.4)	0.004
Weight (kg)	93.7 ± 15.8	85.2 ± 13.8	0.007
BMI (kg/m^2)	31.7 ± 4.2	30.4 ± 4.3	0.128
Fasting plasma glucose (mmol/l)	8.0 (7.5–9.2)	8.2 (7.5–9.2)	0.573
Fasting plasma insulin (pmol/l)	95.0 (57.0–154.0)	120.5 (70.0–186.0)	0.246
HOMA-IR*	4.4 (2.9–8.1)	6.1 (3.7–8.9)	0.198
HbA_{1c} (mmol/l)	56 (51–63)	58 (53–66)	0.376
HbA_{1c} (%)	7.3 (6.8–7.9)	7.5 (7.0–8.2)	
Total cholesterol (mmol/l)	5.2 ± 1.3	5.3 ± 1.2	0.690
HDL-cholesterol (mmol/l)	1.02 ± 0.23	1.18 ± 0.25	0.002
LDL-cholesterol (mmol/l)	3.27 ± 1.27	3.10 ± 1.09	0.523
Triglycerides (mmol/l)	1.93 (1.53–3.13)	2.22 (1.40–3.18)	0.997
Creatinine (μmol/l)	84.1 ± 17.8	71.9 ± 16.2	0.001
Creatinine clearance (ml/min)†	109.1 ± 28.9	109.0 ± 31.8	0.983
Metformin daily dose (mg)	1000 (821–1500)	1000 (960–1700)	0.492
Use of OCT1 inhibiting drugs‡	6 (14.0%)	8 (16.3%)	0.752
Number of OCT1 reduced-function alleles (0/1/2)§	30/17/2 (61.2%/34.7%/4.1%)	18/20/5 (41.9%/46.5%/11.6%)	0.048¶

Data are presented as means ± SD, medians (interquartile range) or numbers (percentages).
*The homeostasis model assessment insulin resistance index was calculated using the formula: fasting insulin (pmol/l) × fasting glucose (mmol/l)/156.26.
†Creatinine clearance was estimated using the Cockcroft–Gault formula.
‡Number of individuals concomitantly treated with OCT1 inhibiting drugs, including proton pump inhibitors, clopidogrel, doxazosin, verapamil, tramadol and citalopram [3,5].
§Data are presented as numbers of individuals (percentages).
¶Significance of test for comparison of combined genotype frequencies between the two groups under the additive model.

Table 2 Association of OCT1 combined genotype with metformin gastrointestinal side effects – logistic regression model

	OR (95% CI)	P
Age	0.96 (0.91–1.01)	0.121
Sex (Women *vs* Men)	2.49 (0.91–6.82)	0.076
Weight	0.97 (0.94–1.00)	0.074
Use of OCT1-inhibiting drugs	0.93 (0.27–3.19)	0.912
Number of OCT1 reduced-function alleles	2.31 (1.07–5.01)	0.034

OR, odds ratio.

[6]. Although different hypotheses have been suggested, the pathophysiology of metformin-induced gastrointestinal side effects is not clear, and data are lacking to explain the high inter-individual variability [7]. In this prospective study, we found for a first time a significant association between the number of OCT1 reduced-function alleles and common gastrointestinal adverse effects to metformin. These results are in accordance with earlier findings obtained in the large GoDARTS cohort in which severe gastrointestinal intolerance to metformin was investigated [3]. However, in the GoDARTS study, only individuals carrying two deficient OCT1 alleles (recessive model) had higher odds of severe intolerance leading to discontinuation of therapy compared with individuals with one or no deficient alleles. Interestingly, in the current study, the number of deficient alleles (additive model) was associated with common metformin gastrointestinal side effects. Thus, our results suggest that the high inter-individual variability seen in mild/moderate, as well as severe gastrointestinal intolerance shares a common underlying mechanism despite the considerably different intensity and duration of gastrointestinal symptoms.

Furthermore, female sex and lower body weight showed a trend of association with side effects, in accordance with the GoDARTS findings [3]. However, contrary to our earlier study [3], age and the concomitant use of OCT1-inhibiting drugs had no significant effect on the incidence of side effects. A reason for this discrepancy might be difference in the studied phenotypes between the two studies (common vs. severe intolerance), or perhaps the small sample size in the current study.

Our results are in contrast with a previous study [8] demonstrating significant associations of the OCT1 variants M408V and the 8-bp insertion rs36056065 with the presence of common metformin gastrointestinal adverse effects, whereas R61C and M420del or OCT1 haplotypes had no effect. However, M408V does not alter the uptake of metformin *in vitro* [9], and the function of rs36056065 is unknown. Also, contrary to our results, the prevalence of side effects was correlated positively with age [8], in line with the GoDARTS results [3]. However, both previous studies

also included patients with a longer duration of Type 2 diabetes treated with other anti-diabetes drugs in addition to metformin, whereas in the current study, only patients with newly diagnosed Type 2 diabetes and metformin prescribed as their initial Type 2 diabetes therapy were included. This might explain the similar age between patients with and without gastrointestinal adverse effects.

The mechanism behind the association of OCT1 reduced transport with increased metformin side effects is not clear. It has been suggested that gastrointestinal symptoms are due to high local concentrations of metformin in the intestine [10]. Because OCT1 is expressed in the membranes of enterocytes [11,12], a change in its activity might affect local metformin concentrations in the gut, possibly leading to changes in incretins, ghrelin, bile acids or serotonin balance [7].

The main limitation of our study is its limited power. This might be the reason for not detecting the effect of OCT1-inhibiting drugs on common metformin side effects. Future studies in larger cohorts are needed to explore these possible interactions and to confirm our findings.

In conclusion, we showed for the first time the association between OCT1 reduced-function alleles and the incidence of common metformin-induced gastrointestinal side effects in patients with Type 2 diabetes. Importantly, this study confirms recent findings related to the role of OCT1 in severe metformin intolerance, further supporting the role of OCT1 variants in gastrointestinal side effects following metformin treatment.

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Competing interests

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Haplotype analysis of R61C and M420del variants.
Table S2. OCT1 diplotypes for R61C and M420del variants.