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Abstract

BACKGROUND: A substantial minority of type 2 diabetes mellitus (T2DM) patients treated with metformin develop severe gastrointestinal (GI) symptoms leading to drug discontinuation, depriving them of the potentially cardioprotective pleiotropic effects of this first-line oral agent. At present, it is unclear whether treating diabetes without being able to ever use metformin alters cardiovascular outcomes. PATIENTS AND METHODS: From a population of 773 consecutive T2DM outpatients, the cardiometabolic phenotypes of 83 patients who discontinued metformin due to GI intolerance (Met-Intol cases) were compared with those of 332 age- and gender-matched metformin-tolerant (Met-Tol) controls, amounting to a case: control ratio of 1:4. RESULTS: Mean age (SD) was 70 (13) (male:female: 46:54). Metformin intolerance was associated with a reduced prevalence of macroangiopathy (P=0.0486), mainly due to a lower prevalence of CAD (-34%; P=0.0374). Met-Intol cases more often belonged to blood group A ...

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Original article

What is the phenotype of patients with gastrointestinal intolerance to metformin?

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Abstract

Background. – A substantial minority of type 2 diabetes mellitus (T2DM) patients treated with metformin develop severe gastrointestinal (GI) symptoms leading to drug discontinuation, depriving them of the potentially cardioprotective pleiotropic effects of this first-line oral agent. At present, it is unclear whether treating diabetes without being able to ever use metformin alters cardiovascular outcomes.

Patients and methods. – From a population of 773 consecutive T2DM outpatients, the cardiometabolic phenotypes of 83 patients who discontinued metformin due to GI intolerance (Met-Intol cases) were compared with those of 332 age- and gender-matched metformin-tolerant (Met-Tol) controls, amounting to a case: control ratio of 1:4.

Results. – Mean age (SD) was 70 (13) (male:female: 46:54). Metformin intolerance was associated with a reduced prevalence of macroangiopathy ($P = 0.0486$), mainly due to a lower prevalence of CAD (−34%; $P = 0.0374$). Met-Intol cases more often belonged to blood group A and subgroup A Rh+, with 50% and 66% relative increases ($P = 0.0039$ and $P = 0.0005$), respectively. There were twice as many non-right-handers among the Met-Intol (18% vs. 9%; $P = 0.0262$), and this group also had significantly higher serum ferritin and LDL cholesterol levels. Statins/fibrates were used by 66%/19% of Met-Tol vs. 48%/18% of Met-Intol ($P = 0.0051$ for statins). On the other hand, there were no differences between groups as regards smoking, diabetes duration, HbA_{1c}, BMI, blood pressure, waist size, fat mass, visceral fat, liver steatosis, the metabolic syndrome, eGFR, albuminuria, erectile dysfunction and microangiopathy.

Conclusion. – Intolerance to metformin represents an unforeseen phenotype in T2DM patients characterized by a low rate of ischaemic heart disease, left-handedness, ABO group imbalance and an iron load.

Keywords: Metformin; T2DM; GI side-effects; CAD; Handedness; ABO blood groups; Ferritin

Résumé

Quel est le phénotype des patients avec intolérance gastro-intestinale à la metformine ?.

Introduction. – Une minorité appréciable de patients diabétiques de type 2 (DT2) traités par metformine souffrent d'effets secondaires gastro-intestinaux (GI) marqués, conduisant à l'arrêt précoce du médicament, et les privant ainsi d'effets pléiotropes potentiellement cardioprotecteurs. On ignore si un traitement glycémique au long cours excluant d'emblée la metformine altère le devenir cardiovasculaire de ces patients, et si ces derniers présentent un phénotype particulier.

Patients et méthodes. – Analyse du phénotype cardiométabolique de 773 DT2 consécutifs, parmi lesquels 83 patients qui ont dû arrêter définitivement toute prise de metformine en raison d'intolérance GI (groupe [Met-INTOL]) ont été comparés à 332 patients DT2 contrôles, tolérant la metformine, et appariés pour l'âge et le sexe (groupe [Met-Tol]), représentant un rapport cas-témoin de 1:4.

Résultats. – L'âge moyen (DS) était de 70 (13) ans et le rapport hommes:femmes 46:54. L'intolérance GI à la metformine était associée à une nette réduction de prévalence de macroangiopathie (*P* 0,0486), principalement due à une prévalence moindre de cardiopathie ischémique (−34 % ; *P* 0,0374). Les [Met-Intol] appartenaient plus souvent au groupe sanguin A, sous-groupe ARh+ : +50 % et +66 % (*P* 0,0039 et 0,0005). Il y

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avait deux fois plus de non-droitiers chez les [Met-Intol] (18 % vs 9 % ; $P = 0{,}0262$). Les statines/fibrates étaient prescrites chez 66 %/19 % des [Met-Tol] vs 48 %/18 % des [Met-Intol] (P 0,0051 pour les statines). Les taux moyens de LDL-C et de ferritine étaient significativement plus élevés chez les [Met-Intol]. Aucune différence n'était observée entre les groupes concernant : tabagisme ; durée du diabète ; HbA_{1c} ; IMC ; pression artérielle ; périmètre abdominal ; masse grasse totale et viscérale ; stéatose hépatique ; syndrome métabolique ; filtration glomérulaire ; albuminurie ; dysfonction érectile ; et microangiopathies.

Conclusion. – L'intolérance gastro-intestinale à la metformine représente un phénotype méconnu du DT2, caractérisé par un très faible taux de cardiopathie ischémique, une présence accrue de gauchers, un déséquilibre ABO et une surcharge en fer.

Mots clés : Metformine ; Diabète de type 2 ; Effets secondaires ; Gastro-intestinal ; Cardiopathie ischémique ; Gaucher ; Groupes ABO ; Ferritine

1. Introduction

Metformin is currently recommended as a first-line oral glucose-lowering agent for type 2 diabetes mellitus (T2DM) patients because of:

- its favorable cost-effectiveness ratio;
- a mechanism of action that is a logical approach for targeting the major T2DM determinant of hepatic glucose overproduction, driven by insulin resistance and/or portal hypoinsulinaemia;
- its neutral or beneficial effects on weight;
- a rarity of serious drug-related adverse events;
- the mild and reversible nature of its more frequent side-effects.

On the other hand, by far the most common disadvantage concerns the gastrointestinal (GI) system, as abdominal cramps and/or changes in intestinal motility, leading to loose stools and overt diarrhoea, sometimes uncontrollable [1–9].

For the majority of metformin-treated patients, GI symptoms are absent or only temporarily seen to a moderate degree during the initial titration period [6,7,10,11]. However, patients who are unable to tolerate metformin are doubly disadvantaged due to, first, the limited management of their diabetes and, second, their high-risk phenotype [12]. They are missing out from the start on a major therapeutic option and so are doomed to requiring earlier insulin therapy. They also cannot take advantage of the potentially beneficial effects of metformin on cardiometabolic risk (CMR) conferred by the cellular and molecular mechanisms of action of this AMP-activated protein kinase (AMPK) activator [7,9].

For these reasons, it is logical to surmise that the T2DM patients not able to benefit from metformin treatment because of permanent discontinuation of the drug due to adverse GI effects most likely have cardiovascular (CV) and metabolic characteristics that are worse over time than those of T2DM patients treated continuously by metformin. However, there are at present no data on the phenotype of T2DM patients prematurely weaned from metformin due to GI intolerance. The present study was therefore designed to assess, without prerequisites, the cardiometabolic characteristics of T2DM patients according to GI (in)tolerance to metformin. The analyzed variables selected for the study, either belong to the definition, are major determinants, are frequent comorbidities of the metabolic syndrome (MetS) or T2DM, and/or are major CMR factors.

2. Patients and methods

This cross-sectional study included 773 T2DM patients [North-Caucasian (81%), North-African (8%) and Sub-Saharan African (8%) ancestry] followed at St-Luc Hospital. Metformin intolerance ranging from intermittent/moderate to severe/persistent was defined as the presence of diarrhoea and/or GI dysmotility concomitant with medication intake that persisted after uptitration beyond the first few weeks of drug initiation in metformin-naïve patients. Intolerance was considered severe when, in addition, GI side-effects persisted even with a substantially reduced dose ($\geq 50\%$), the intensity of GI side-effects led to metformin withdrawal, and withdrawal led to rapid and complete disappearance of the GI symptoms [7,10].

Intolerance was documented in 182 T2DM patients (24%). Among these cases, severe metformin intolerance resulting in lifelong drug discontinuation was present in 83 (11%) patients (Met-Intol). The remaining 591 (76%) with no GI intolerance even at the highest dose (2550 mg/day) represented the control population. Of these metformin-tolerant (Met-Tol) patients, 14% had the drug subsequently interrupted for reasons unrelated to GI intolerance (such as a progressive decrease in glomerular filtration rate or congestive heart failure) and were considered controls. For every Met-Intol case ($n = 83$), four age- and gender-matched Met-Tol controls ($n = 332$) were identified.

All cases and controls were evaluated according to age, gender, diabetes duration, glycated haemoglobin (HbA_{1c}), socioeducational level (dichotomized as below high school vs. otherwise), family history of early-onset coronary heart disease (CHD) [13], smoking habit, alcohol intake, handedness, glucose-lowering/CV medications, body mass index (BMI), waist circumference, fat mass, visceral fat and skeletal muscle mass as measured by a body composition monitor (Omron BF500, Omron Healthcare Europe B.V., Hoofddorp, The Netherlands). The MetS was diagnosed according to the joint interim report of Alberti et al. [14]. Insulin sensitivity and β-cell function were measured according to the updated homoeostasis model assessment (HOMA2; http://www.dtu.ox.ac.uk) [15].

Hypertension was defined as a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or treatment with antihypertensive drugs. Diabetic retinopathy was confirmed by fluorescein angiography. Peripheral neuropathy was diagnosed using knee/ankle reflexes, the

Table 1
Patients' characteristics.

		Met tolerant	Met intolerant	*P*
n		332	83	∼
Age	Years	70 (13)	70 (13)	∼
Diabetes duration	Years	17 (10)	17 (9)	NS
HbA_{1c}	%	7.9 (1.5)	7.9 (1.4)	NS
	$mmol.mol^{-1}$	62 (12)	63 (11)	NS
Family history of premature CHD	%	10	13	NS
Men	%	46	46	∼
Right-: non-right-handedness	%	91:9	82:18	0.0262
Former smokers	%	35	30	NS
Current smokers	%	11	5	NS
Body mass index	$kg.m^{-2}$	30.3 (5.8)	30.3 (6.7)	NS
Waist circumference	cm	104 (14)	105 (15)	NS
Fat mass	%	35.2 (9.4)	35.1 (9.2)	NS
Visceral fat	0–30 score	13 (4)	12 (5)	NS
Insulin sensitivity (HOMA)	%	56 (38)	44 (23)	0.0062
Metabolic syndrome	%	86	86	NS
Hypertension	%	91	90	NS
Systolic blood pressure	mmHg	141 (19)	142 (21)	NS
Diastolic blood pressure	mmHg	79 (10)	80 (12)	NS
ACE-I	%	43	35	NS
ARB	%	29	22	NS
CCB	%	28	25	NS
BB	%	33	35	NS
Diuretic	%	41	37	NS
Statin	%	66	48	0.0051
Fibrate	%	19	18	NS
eGFR	$mL.min^{-1}.1.73\,m^2$	77 (27)	78 (27)	NS
Albuminuria	$\mu g.mg\ creatinine^{-1}$	66 (128)	78 (166)	NS
Microangiopathy	%	58	53	NS
DRP – PNP – erectile dysfunction	%	27 – 28 – 52	23 – 28 – 47	NS

Results are expressed as means (SD) or proportions (%). ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BB: beta-blocker; CCB: calcium-channel blocker; CHD: coronary heart disease; DRP: diabetic retinopathy; eGFR: estimated glomerular filtration rate; HbA_{1c}: glycated haemoglobin; HOMA: homeostatis model assessment; Met: metformin; PNP: peripheral neuropathy; NS: non-significant.

Semmes–Weinstein monofilament test and/or electromyography. Erectile dysfunction was diagnosed according to the present authors' previous reports [16,17]. Albuminuria was defined as albumin excretion $\geq 30\,\mu g.mg\ creatinine^{-1}.1.73\,m^2$ in the first morning sample. Glomerular filtration rate was estimated (eGFR) using the modification of diet in renal disease (MDRD) study formula [18].

Coronary artery disease (CAD) was diagnosed as defined in the present authors' previous report [13] and by Gerber et al. [19]. Stroke was defined according to the UK Prospective Diabetes Study (UKPDS) criteria [20]. The presence of peripheral arterial disease (PAD) was described as applied elsewhere [13].

ABO/Rhesus (Rh) blood group, fasting lipids [high-density lipoprotein cholesterol (HDL-C)], triglycerides (TG), apolipoprotein B_{100} (apoB), high-sensitivity C-reactive protein (hsCRP), fibrinogen, uric acid, white blood cells, iron, transferrin, ferritin, folates and homocysteine were all determined. Low-density lipoprotein cholesterol (LDL-C) was computed using Friedewald's formula. Atherogenic dyslipidaemia (AD) prevalence and severity were defined as reported elsewhere [12,21,22]. Each study participant gave their written informed consent; the study was performed in agreement with the declaration of Helsinki and principles of good clinical practices, and the local ethics Institutional Review Board.

2.1. Statistical methods

Results are presented as means and standard deviation (SD) or as proportions (%). The significance of differences between means was assessed by two-tailed Student's *t* test or Welch's test and by Fisher's exact test for differences in proportions, with modified Bonferroni adjustments to minimize type 1 errors as a result of multiple testing. Results were considered significant at $P < 0.05$.

3. Results

Patients' characteristics are described in Table 1. Ethnogeographical extraction, diabetes duration and HbA_{1c} were similar in both Met-Tol and Met-Intol groups. In insulin-treated patients, treatment duration before insulin was 11 (7) years in the Met-Tol vs. 7 (6) years in the Met-Intol patients ($P < 0.0001$).

In addition, 47% of patients had completed tertiary/university degrees; the socioeducational levels were 58%/42% in the Met-Tol vs. 53%/47% in the Met-Intol [not significant (NS)], proportions reflecting the fact that St-Luc Hospital is located

Table 2
Glucose-lowering therapy.

		Met tolerant	Met intolerant	*P*
n		332	83	∼
Metformin	%	85	0	∼
Metformin dose	$g.day^{-1}$	1.95 (0.54)	∼	∼
ß-cell stimulant	%	51	55	NS
Thiazolidinedione	%	5	6	NS
Incretin-based therapies[a]	%	9	4	NS
Insulin	%	45	60	0.0193
Insulin dose	$IU.day^{-1}.kg^{-1}$	0.66 (0.46)	0.76 (0.82)	NS
Oral monotherapy	%	20	19	NS
Oral bitherapy	%	32	10	<0.001
Oral tritherapy	%	1	0	NS
Oral therapy & insulin	%	37	26	NS
Insulin monotherapy	%	8	34	<0.001

Results are expressed as means (SD) or proportions (%). Met: metformin. NS: non-significant.
[a] DPP4-I (dipeptidyl peptidase type 4 inhibitor) or GLP1-RA (glucagon-like peptide 1 receptor agonist) drugs.

in a prosperous district of Brussels and thus attended by generally well-educated/high-income patients. Current/past smoking prevalences did not differ between groups, and alcohol intakes were 12 (22) units/week in the Met-Tol vs. 12 (21) units/week in the Met-Intol (NS). Leisure-time physical activity was also not different between groups.

In all patients ($n=773$), non-right-handedness (left-handedness and ambidexterity) was found in 12%. However, there were twice as many non-right-handers among the Met-Intol (18%) than Met-Tol (9%) patients ($P=0.0262$), with left-handedness found in nearly one-fifth of the Met-Intol (100% mean relative increase).

BMI, waist circumference, fat mass and visceral fat did not differ between groups. Muscle mass was 29% (5) in both Met-Tol and Met-Intol patients (NS), whereas insulin sensitivity was lower (−12%) in the Met-Intol ($P=0.0062$). The MetS was highly prevalent (86%) in both groups, with a MetS score of 3.9 (1.1) in Met-Tol vs. 3.7 (1.1) in Met-Intol patients (NS). Hypertension prevalence was similar between groups, as were systolic/diastolic blood pressure (BP) levels and the use of BP-lowering agents. Non-alcoholic liver steatosis was detected radiologically in 69% of Met-Tol vs. 80% of Met-Intol patients (NS; Table 1).

Lipid-lowering drugs were used by 77% of Met-Tol vs. 58% of Met-Intol ($P=0.0008$), while statins, fibrates and/or ezetimibe were used by 66%, 19% and 5% of Met-Tol vs. 48%, 18% and 4% of Met-Intol, respectively ($P=0.0051$, NS and NS, respectively). Statin monotherapy, fibrate monotherapy and statin plus fibrate bitherapy were used by 54%, 10% and 8% of Met-Tol vs. 36%, 10% and 8% of Met-Intol, respectively ($P=0.0183$, NS and NS, respectively). The greater use of statins in the Met-Tol was related to higher CAD prevalence (data not shown). There were no differences in eGFR, albuminuria, erectile dysfunction, overall microangiopathy and organ-specific microangiopathy between groups (Table 1).

Altogether, 85% of the Met-Tol were taking metformin at a mean daily dose of 1.95 (0.54) g/day as monotherapy (18%) or combined with a sulphonylurea (with or without insulin; 38%). There were no differences between groups in the use of drugs with putative cardioprotective/cardiotoxic effects, including β-cell stimulants, thiazolidinediones and incretin-based therapies. However, Met-Intol patients were more often treated with insulin [as monotherapy or with an oral antidiabetic drug (OAD)]. Insulin dosages were non-significantly higher in the Met-Intol, who were also more often receiving insulin monotherapy (Table 2).

LDL-C and apoB were also higher in the Met-Intol (Table 3). Otherwise, there were no significant differences between groups in HDL-C, TG, AD prevalence/severity and estimated LDL size. The Met-Intol had lower leucocyte counts (relative −8%) with higher iron indices, including greater iron, transferrin saturation and ferritin levels (relative +12%, +17% and +64%, respectively). There were no differences in hsCRP, fibrinogen, urate and homocysteine levels between groups, although folates were lower (mean −36%) in the Met-Intol.

ABO/Rh blood group distributions were: A (39.6%); B (14.0%); AB (3.2%); and O (43.3%). Rates by subgroups were: A Rh+ (34.3%); A Rh− (5.3%); B Rh+ (12.8%); B Rh− (1.2%); AB Rh+ (2.8%); AB Rh− (0.4%); O Rh+ (37.5%); and O Rh− (5.8%). Overall, the Rh+ frequency was 87.4%. In the case–control comparison, the Met-Intol more often belonged to group A and subgroup A Rh+, with 50% and 66% relative increases, respectively ($P=0.0039$ and $P=0.0005$, respectively). Group O and subgroup O Rh+ were each significantly underrepresented in the Met-Intol by a relative 41% ($P=0.0027$ and $P=0.0049$, respectively; Fig. 1).

In the entire cohort, overall macroangiopathy was 32%, comprising CAD (22%), PAD (8%) and/or transient ischaemic attack (TIA)/stroke (9%). The Met-Intol had a markedly lower prevalence of macrovascular disease ($P=0.0486$), with the reduction mostly related to CAD (−34%; $P=0.0374$) and PAD (−44%; NS; Fig. 2). Differences in CHD were seen in both groups irrespective of ferritin levels and ABO grouping. However, after Bonferroni adjustments, the differences between groups were no longer significant for insulin use, apoB, leucocytes, and serum iron and folates (data not shown).

Table 3
Laboratory values.

		Met tolerant	Met intolerant	*P*
n		332	83	
LDL-C	$mg.dL^{-1}$	92 (36)	102 (32)	0.0213
HDL-C	$mg.dL^{-1}$	49 (15)	49 (15)	NS
Apolipoprotein B_{100}	$mg.dL^{-1}$	87 (27)	95 (27)	0.0162
Triglycerides	$mg.dL^{-1}$	178 (123)	168 (92)	NS
Atherogenic dyslipidemia	%	42	31	NS
Log(TG)/HDL-C		0.050 (0.020)	0.049 (0.018)	NS
LDL-C/apolipoprotein B_{100}		1.01 (0.30)	1.08 (0.26)	NS
hsCRP	$mg.dL^{-1}$	0.39 (0.60)	0.38 (0.49)	NS
Fibrinogen	$mg.dL^{-1}$	330 (77)	342 (79)	NS
White blood cells	$10^3.mm^{-3}$	7.39 (1.92)	6.82 (1.75)	0.0143
Neutrophiles	%	58 (9)	57 (9)	NS
Lymphocytes	%	30 (9)	31 (8)	NS
Iron	$\mu g.dL^{-1}$	85 (31)	95 (34)	0.0103
Transferrin	$mg.dL^{-1}$	282 (48)	265 (44)	0.0035
Transferrin saturation	%	22.0 (9.9)	25.8 (9.3)	0.0017
Ferritin	$\mu g.L^{-1}$	124 (137)	203 (176)	<0.001
Folic acid	$ng.mL^{-1}$	9.4 (12.9)	6.0 (3.4)	0.0178

Results are expressed as means (SD) or proportions (%). LDL-C/HDL-C: low-density lipoprotein/high-density lipoprotein cholesterol; hsCRP: high-sensitivity C-reactive protein; Met: metformin; TG: triglycerides (triacylglycerols); NS: non-significant.

4. Discussion

It is still not known whether treating diabetes without the use of metformin leads to altered CV outcomes. However, the main findings of our present study were fourfold: metformin GI intolerance was associated with a lower prevalence of CAD; and there were also an ABO blood group imbalance, higher ferritin levels and brain function lateralization leaning towards left-handedness.

There is still some debate over whether AMPK activation by metformin improves vascular outcomes beyond the beneficial effects of glucose-lowering on small vessels [5,8,9]. In fact, in our Met-Intol patients, lifelong drug discontinuation did not result in the emergence of a negative CMR phenotype, but was instead related to a lower prevalence of all-cause macroangiopathy and ischaemic heart disease. Indeed, it cannot be ruled out from a transverse study that some as yet unidentified cardioprotective determinants are either mechanistically or incidentally related to GI intolerance, nor can a survival bias be excluded. Unrecognized cardiotoxic factors may be related to long-term metformin use, or metformin may prove to be not as beneficial as is generally thought. This confounding effect (lower CHD prevalence among Met-Intol patients) could thus far have been hindering the unambiguous detection of long-term cardioprotection with metformin.

There were no differences between groups regarding the use of glucose-lowering drugs purporting to have cardioprotective properties (thiazolidinediones, incretin-based therapies) or cardiotoxic side-effects (sulphonylureas, thiazolidinediones), yet almost 40% of metformin-treated T2DM patients also received sulphonylureas, a combination that is widely recommended despite concerns that it might increase the risk of CHD [6,23–28]. Met-Intol patients were less often treated with lipid-lowering drugs, most likely as a result of lower CAD prevalence. The Met-Intol also had significantly lower leucocyte counts, which was in agreement with previous reports linking raised white cell counts with CAD risk [29].

There is a growing body of evidence in the literature, albeit disparate, concerning CHD risk and ABO blood groups [30–34]. The present study sheds some light on a previously unreported interaction between ABO grouping and CHD prevalence in T2DM, albeit with no grounds on which to base a mechanistic hypothesis. As regards the GI tract, a correlation between ABO blood group and relative proportions of healthy GI microbiota was recently reported [35].

Although the underlying cause(s) of GI symptoms due to metformin is still unclear, digestive intolerance remains a major limiting factor for optimizing glucose-lowering therapy, particularly when starting treatment and during uptitration [7]. In addition, it cannot be excluded that metformin may alter the intestinal flora especially by inducing mild sugar malabsorption with carbohydrate displacement to distal parts of the GI tract, resulting in local/systemic changes in incretins, serotonin, ghrelin and bile salt handling, all considered to be CV risk modulators [36]. Metformin-induced GI malabsorption of macro-/micronutrients has also been reported with sugars, folates and vitamin B12, occasionally leading to hyperhomocysteinaemia [11,37].

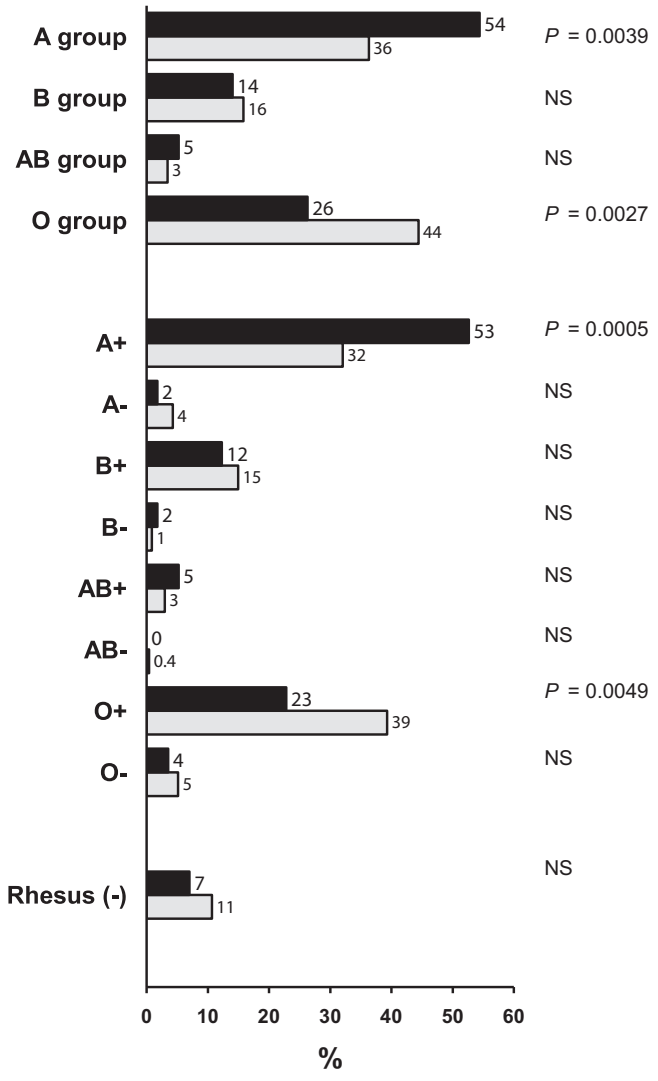

Fig. 1. Frequency of ABO and Rhesus blood groups in metformin-tolerant (gray; $n = 332$) and metformin-intolerant (black; $n = 83$) type 2 diabetes patients. NS: not significant.

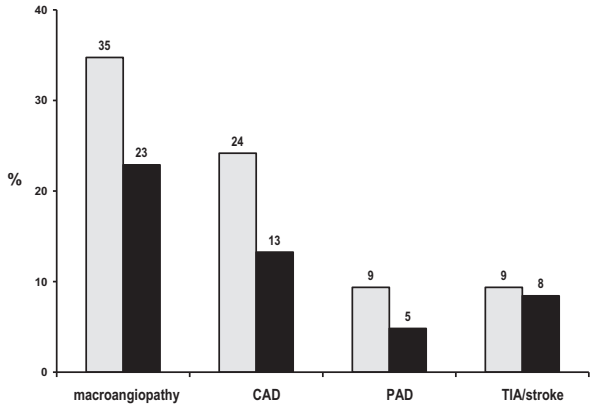

Fig. 2. Prevalence of macroangiopathy in metformin-tolerant (gray; $n = 332$) and metformin-intolerant (black; $n = 83$) type 2 diabetes patients. CAD: coronary artery disease; PAD: peripheral artery disease; TIA: transient ischaemic attack; NS: not significant. $P = 0.0486$ (macroangiopathy); $P = 0.0374$ (CAD); NS (PAD and TIA/stroke).

Hyperferritinaemia in T2DM is linked to a decreased CHD prevalence despite more severe insulin resistance (IR) and markers of non-alcoholic steatohepatitis, suggesting that higher ferritin levels and/or steatosis may paradoxically be conferring a lower risk of CV in T2DM patients [38–40]. Metformin can lower ferritin through different mechanisms either directly or indirectly through less hyperinsulinaemia and liver fat deposition. A link between metformin and ferritin was recently described in cardiomyocytes [41]. However, to our knowledge, no association between GI tolerability, iron absorption/load and metformin on the one hand, and lower iron-related indices on the other hand, has been reported. As ferritin is a natural antioxidant, it may be speculated that such differences could unexpectedly confer vascular benefit to Met-Intol patients.

It has previously been reported that non-right-handedness can modulate the cardiometabolic phenotype of T2DM in Caucasians [42]. Fujiwara et al. [43] reported a negative association between left-handedness and satiation, raising the possibility that brain lateralization might affect the incidence and expression of GI symptoms. This observation is all the more challenging as our group has observed a higher prevalence of left-handers in Met-Intol patients than in the general or T2DM population [42]. Although the separate components of the intolerance phenotype may appear to be mutually unrelated, each has previously been described as modulating CMR. Their joint presence fostered by metformin intolerance may be contributing to a lower CVD prevalence. At the cellular level, an association between genetic variations in organic cation transporters [such as OCT1, OCT2, and multidrug and toxin extrusion protein 1 (MATE1)] genes and metformin GI side effects has also been reported in T2DM [44].

One clear limitation of our present study, which mostly included Caucasians, lies in its cross-sectional design, which should be extended to include diabetics of other ethnicities. Another limitation is the lack of data for accumulated metformin exposure in our two patient groups. In Met-Tol patients, the mean duration of use was most likely similar to their known diabetes duration, as metformin is almost invariably introduced as the first oral treatment once therapeutic lifestyle changes fails. Its early implementation is decided on the basis of its:

- low cost, general safety and the fact that all recommendations advocate its use as the first-line OAD;
- hitherto alleged beneficial effects on CMR;
- virtual inability to cause hypoglycaemia when used on its own;
- frequent, albeit modest, slimming effects that are apparently related to mild appetite loss.

In the present study, those patients with low-to-moderate GI tolerance to metformin who continued to take the medication at a reduced/normal dose despite experiencing GI side-effects were excluded. In these cases, intolerance was either:

- weak in intensity;
- acceptable in view of the achieved HbA_{1c} reduction;
- offset by a consensual decision to keep using the drug, but at a reduced dose.

The study design thus allowed comparison of two distinct groups—tolerant patients with long-term exposure to metformin at the recommended dose vs. patients with the most severe form of GI intolerance (early in onset and at every dosage) who had insignificant drug exposure in terms of duration or cumulative dose.

In conclusion, highlighting metformin intolerance in T2DM patients has revealed a phenotype as unexpected as it is complex, and characterized by a lower rate of ischaemic heart disease, left-handedness, blood group A and iron loading. Uncovering how GI intolerance to metformin is associated with a lower CAD prevalence and how the seemingly heterogeneous parts of the phenotype interconnect could help to further characterize CMR in T2DM. Prospective studies are now required to confirm our observations.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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