Genetic polymorphisms of organic cation transporter 1 (OCT1) and responses to metformin therapy in individuals with type 2 diabetes

A systematic review

Edith Pascale Mofo Mato, MSca, Magellan Guewo-Fokeng, PhDb,c, M. Faadiel Essop, PhDb, Peter Mark Oroma Owira, PhDb

Abstract

Background: Metformin is one of the most commonly used drugs for the treatment of type 2 diabetes mellitus (T2DM). Despite its widespread use, there are considerable interindividual variations in metformin response, with about 35% of patients failing to achieve initial glycemic control. These variabilities that reflect phenotypic differences in drug disposition and action may indeed be due to polymorphisms in genes that regulate pharmacokinetics and pharmacodynamics of metformin. Moreover, interethnic differences in drug responses in some cases correspond to substantial differences in the frequencies of the associated pharmacogenomics risk allele.

Aim: This study aims to highlight and summarize the overall effects of organic cation transporter 1 (OCT1) polymorphisms on therapeutic responses to metformin and to evaluate the potential role of such polymorphisms in interethnic differences in metformin therapy.

Methods: We conducted a systematic review according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. We searched for PubMed/MEDLINE, Embase, and CINAHL, relevant studies reporting the effects of OCT1 polymorphisms on metformin therapy in T2DM individuals. Data were extracted on study design, population characteristics, relevant polymorphisms, measure of genetic association, and outcomes. The presence of gastrointestinal side effects, glycated hemoglobin A1 (HbA1c) levels, fasting plasma glucose (FPG), and postprandial plasma glucose (PPG) concentrations after treatment with metformin were chosen as measures of the metformin responses. This systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO).

Results: According to the data extracted, a total of 34 OCT1 polymorphisms were identified in 10 ethnic groups. Significant differences in the frequencies of common alleles were observed among these groups. Met408Val (rs628031) variant was the most extensively explored with metformin responses. Although some genotypes and alleles have been associated with deleterious effects on metformin response, others indeed, exhibited positive effects.

Conclusion: Genetic effects of OCT1 polymorphisms on metformin responses were population specific. Further investigations in other populations are required to set ethnicity-specific reference for metformin responses and to obtain a solid basis to design personalized therapeutic approaches for T2DM treatment.

Abbreviations: AMPK = adenosine monophosphate activated protein kinase, BMI = body mass index, FPG = fasting plasma glucose, HbA1c = glycosylated hemoglobin, LKB1 = liver kinase B1, OCT1 = organic cation transporter 1, OCTs = organic cation transporters, OR = odds ratio, PPG = postprandial plasma glucose, SLC22A1 = solute carrier family 22 member 1, SNP = single nucleotide polymorphism, T2DM = type 2 diabetes mellitus, WHO = World Health Organization.

Keywords: genetic polymorphisms, glycemic response, metformin, OCT1, type 2 diabetes mellitus
1. Introduction

Metformin is the first-choice oral anti-hyperglycemic drug for use as monotherapy in individuals with newly diagnosed type 2 diabetes mellitus (T2DM).\cite{1,2} It has several beneficial effects on cardiovascular risk factors, cancer, and polycystic ovary syndrome.\cite{3,4} Moreover, metformin specifically reduces hepatic gluconeogenesis without increasing insulin secretion, inducing weight gain or risk of hypoglycemia.\cite{1,5} The precise molecular mechanisms of metformin action are not well understood. It was initially suggested that a key action of metformin was to activate AMP-activated protein kinase (AMPK) through a decrease in hepatic energy status (i.e., increasing AMP: ADP and/or ADP/ATP concentration ratio) or through an upstream modulator, liver kinase B1 (LKB1), thereby leading to a reduction in gluconeogenic gene transcription.\cite{6} However, recent investigations in conditional AMPK knockout mice demonstrated that metformin inhibits hepatic gluconeogenesis in an LKB1- and AMPK-independent manner via a decrease in the hepatic energy state.\cite{7} Emerging evidence also indicates that inhibition of mitochondrial glycerophosphate dehydrogenase (mGPD), a critical enzyme in the glycerophosphate shuttle, could be the primary mechanism of metformin-induced inhibition of gluconeogenesis.\cite{8} This preferential action of metformin in hepatocytes is due to the predominant expression of organic cation transporters 1 (OCT1) that are responsible of hepatic uptake of metformin. OCT1 belongs to the Solute Carrier family (SLC22A) and is localized in the sinusoidal membrane of rat and human hepatocytes.\cite{9} Other reported locations of human OCT1 include the lateral membrane of intestinal epithelial cells,\cite{10} the luminal (apical) membrane of ciliated cells in the lung, and of tubule epithelial cells in the kidney.\cite{11} The human SLC22A1 gene encoding OCT1 consists of 11 exons, has been mapped to chromosome 6q26 and spans about 37 kb. OCT1 is highly polymorphic in ethnically diverse populations and mediate differences in transporter function.\cite{12} This helps provide a possible mechanism to account for interindividual variations in the metformin responses.\cite{13} Moreover, carriers with loss of function OCT1 polymorphisms displayed decreased hepatic metformin exposure after intravenous injection of $^{13}$C metformin.\cite{14} Many studies have identified genetic polymorphisms in the SLC22A1 gene among different populations but there are still contradictory reports on the effects of OCT1 polymorphisms on metformin-related therapeutic responses.\cite{15} In light of this, it is crucial to obtain a greater understanding of the influence of OCT1 polymorphisms in the context of variable responses elicited by metformin treatment. This systematic review therefore summarizes the overall effects of OCT1 polymorphisms on metformin-related therapeutic responses and also evaluates its potential role in terms of interethnic differences in this instance.

2. Methods

2.1. Literature search strategy

We searched the following electronic databases PubMed/MEDLINE, Embase, and CINAHL from January 1990 to July 2017, to identify studies reporting on the effects of OCT1 variants on metformin responses in T2DM individuals. The search strategy based on the combination of relevant terms was designed by a librarian. The main search strategy conducted in PubMed/Medline was as follows: “(((Diabetes [MeSH Terms]) OR type 2 diabetes)) AND ((((((Genetic [MeSH Terms]) OR genetic markers) OR genetic polymorphism) OR Single nucleotide polymorphism) OR Polymorphism) OR variant) OR gene) OR allele)) AND (((carrier family 22 organic cation transporter, member 1 [MeSH Terms]) OR Organic Cation Transporter 1) OR OCT 1)”. This search strategy was adapted when searching other databases. The search was performed independently by 2 investigators (EPMM and MGF) who identified articles in sequential fashion (titles, abstracts, and then full texts). In addition, references cited in the selected articles and published reviews were manually searched in order to identify any additional relevant studies.

2.2. Study selection

We included genetic association studies that reported data on the genetic effects of OCT1 polymorphisms on levels of HbA1c, fasting plasma glucose (FPG) and post-prandial plasma glucose (PPG), and also on gastrointestinal side effects in T2DM individuals. Two review authors (EPMM and MGF) independently assessed eligibility for inclusion in the review based on the inclusion and exclusion criteria. Any disagreements between the 2 review authors were resolved by consensus or consulting a third review author if necessary. Here we excluded animal studies, review articles, meta-analyses, case reports, editorials, and comments. In addition, 2 articles written in Russian were also excluded. A PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow diagram was used to document the process of literature selection and reasons for exclusion (Fig. 1).

2.3. Data extraction, assessment, and synthesis

Two reviewers (EPMM and MGF) independently extracted data using a preconceived data extraction sheet. Data were collected on the first author name, year of publication, geographical location (population where the study was performed), study design, sample size, participants’ characteristics (mean or median age, age range, and proportion of males), duration of treatment with metformin monotherapy, relevant OCT1 polymorphisms, minor allelic frequencies in each population with Hardy Weinberg equilibrium if available, and primary outcome measurements (measure of metformin response after treatment with metformin). Disagreements were settled by consensus among the authors. The STREGA (Strengthening the Reporting of Genetic Association Studies) statement was used to assess the reporting quality of included studies.\cite{16} Briefly, we assessed the reporting quality of all included studies in accordance with the following criteria: title and abstract, study design, selection criteria and basic characteristics of study participants, duration of metformin treatment, genotyping methods and its reliability, statistical method, accuracy and the outcome data on association between gene variants and the metformin responses. As the metrics used for assessment of genetic effects of OCT1 polymorphisms and study designs in the metformin response were not sufficiently similar, a narrative synthesis of the findings from the included studies was provided. This study is based on published data; therefore, ethical approval is not a requirement. This systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on the December 7, 2017. Trial registration number: CRD42017079978.

3. Results

3.1. Study characteristics

Our initial search identified 4186 records: 1719 from PubMed/MEDLINE, 1907 from Embase, 546 from CINAHL, and 14 from
manually searching the reference list of other articles. After screening of the titles and abstracts, 45 studies were found potentially eligible and their full texts were downloaded for further screenings. Of these 45 studies, we excluded 28 articles and the remaining 17 articles were included in the review (Fig. 1). The majority of included studies were concentrated in Asia (47%), followed by Europe (29.4%). There were no study reported for the African continent. Of these eligible studies, 3 were conducted for each of the Caucasian and Indian population, 2 were conducted for each of the Chinese, Japanese and Scottish populations, while only 1 study was conducted for each of the Latvian, Danish, and Iranian populations. In 2 studies, the population was not specified. Most studies, but not all, reported sufficient details about selection criteria and basic characteristics for participants. The number of participants ranged from 33 to 2216, the proportion of men from 13.6% to 62.7% and the age of participants was above 29 years. Study participants were diagnosed with T2DM and treated with metformin monotherapy for at least 3 months and here the diagnosis was based on World Health Organization (WHO) criteria, HbA1c levels, FBG, and PPG. The response to metformin in individuals diagnosed with T2DM was categorized as responders and nonresponders, respectively. Nonresponders constituted patients whose HbA1c levels declined by <1% after 3 months treatment or who experienced gastrointestinal side effects, while responders were cases where HbA1c levels decreased by more than 1%. Measures of association were used to assess the effects of OCT1 polymorphisms in terms of the metformin response and included: differences in HbA1c, FPG, PPG levels among the various genotyping groups before and after metformin therapy, and odds ratios that were often adjusted for age, gender, and use of co-medications.

Figure 1. PRISMA flow diagram, describing the process of literature selection and reasons for exclusion. A total of 4186 records have been identified: 1719 from PubMed/MEDLINE, 1907 from Embase, 546 from CINAHL, and 14 from manually searching the reference list of other articles. After screening of the titles and abstracts, 45 studies were found potentially eligible and their full texts were downloaded for further screenings. Of these 45 studies, we excluded 28 articles and the remaining 17 articles were included in the review.
3.2. Genetic effects of OCT1 polymorphisms

Over 34 polymorphisms were investigated in 10 different populations with a minimum of 1 and a maximum of 12 per study. Significant differences in the frequencies of common variants have been observed among ethnic groups (Table 1).

3.2.1. rs628031 (1222A>G). The polymorphism rs628031 (1222A>G) was the most genotyped and its frequency has been found to range from 15% to 80% (median, 36%). Japanese population has the highest frequency (80%) while; rs628031 is present only in 40% in Caucasians. Association of rs628031 with the glycemic response to metformin was assessed in 7 studies. Here a study investigating rs628031 in 277 Han Chinese participants found a significant reduction in HbA1c levels (P < .02) in individuals carrying the A/A genotype compared to those with the heterozygous genotype (A/G). However, the A allele of A/A genotype was significantly associated with metformin side effects in a study conducted with 246 Latvian participants (P = .02). By contrast, investigation of rs628031 in Iranian, Indian, Caucasian, and Japanese populations showed that there were no association between this polymorphism and metformin responses.

3.2.2. rs122083571 (181C>T) and rs72552763 (1258_1260delATG). Polymorphisms rs122083571 (181C>T) and rs72552763 (1258_1260del ATG) were assessed in 6 studies and their frequencies varying from 67% to 89% and 18% to 28%, respectively. In 1 study with 92 participants, from unspecific population, the rs122083571 and rs72552763 polymorphisms were significantly associated with gastrointestinal side effects (OR = 2.31, 95% CI [1.07–5.01], P = .034). In addition, the investigation of rs122083571 and rs72552763 in 2216 participants from the GoDART Study found that such individuals (and receiving treatment with known OCT1 inhibitors) were over 4 times more likely to develop intolerance to metformin (OR = 4.13, 95% CI 2.09–8.16, P < .001). However, there was no association for such polymorphisms and metformin responses in Latvian and Danish populations.

3.2.3. rs622342 (1386A>C). The association of rs622342 (1386A>C) with metformin responses was investigated in 5 studies that involved 3 populations (South Indian, Danish, and Caucasian) with the frequency ranging from 5% to 37%. A study conducted in a Caucasian population found a positive significant association between rs622342 and HbA1c levels (P = .005). This translated to an average of 0.28% lower decrease in HbA1c levels for each minor C allele. By contrast, the major allele A of rs622342 displayed a 5.6% greater chance of responding to metformin treatment in a South Indian population. There was no significant relationship with HbA1c levels in a Danish population and also for 2 other studies involving a Caucasian population.

3.2.4. rs2297374 (+43C>T). The polymorphism rs2297374 (+43C>T) and metformin response showed no significant association in Indian populations. However, Han Chinese Shanghai individuals with the rs2297374 GT genotype exhibited significantly greater reductions in their FPG (P = .002) and HbA1c (P = .039) levels following metformin treatment versus homozygous rs2297374 genotypes (CC) and (TT). The frequency of rs2297374 in these populations is close to 40%.

3.2.5. rs4646272 (−43T>G). The rs4646272 (−43T>G) polymorphism was assessed in 3 studies with a frequency ranging from 20% to 67%. Here the one conducted with 66 Japanese subjects showed that rs4646272 is a negative predictor of metformin efficacy. However, the other studies showed no association.

3.2.6. rs34130495 (17857 G>A). Two studies assessed the association between rs34130495 (17857 G>A) and metformin responses. Here a study investigating rs34130495 in 371 Danish subjects found a significant association with absolute decreases in Hb1Ac levels.

3.2.7. rs2282143 (1022C>T). rs2282143 (1022C>T) has been assessed in Indian population with a frequency of 20%. It has been demonstrated to impair OCT1 function in this population.

3.2.8. rs1867351 (156T>C). The effect of rs1867351 (156T>C) on the glycemic response to metformin was investigated in Han Chinese and Indian populations with a frequency of 50% and 27%, respectively. No significant effect of the minor C allele has been shown while, the TT genotype of rs1867351 exhibited a greater reduction in FPG and HbA1c levels (P = .020) in Han Chinese population.

3.2.9. rs594709 (597 A>G). The rs594709 (597 A>G) polymorphism was associated with the metformin treatment response in the Chinese population. Here GG genotype displayed a higher increase in FINS (P = .015) and a greater decrease in HOMA-IR (P ≤ .001) and QUICKI (P = .002) than A allele carriers.

3.2.10. rs200684404 (350C>T). rs200684404 (350C>T) polymorphisms were investigated in the Japanese population and revealed a significant reduction in metformin uptake.

3.2.11. Others polymorphisms. The association of other OCT1 polymorphisms, including rs34104736, rs2297373, rs622591, rs2197296, rs4709400, rs461473, rs1443844, rs9457843, and rs6937722 was also investigated. However, no significant relationships were found between such variants and the metformin response.

4. Discussion

Metformin is the most widely used first-line pharmacotherapy for T2DM. However, the interindividual variations in metformin efficacy ranging from improvement in HbA1c levels (by up to 4%) to a worse outcome with, estimates of ~33% failure rate with treatment clearly suggest that this treatment modality is affected by individual genetic imprints. Although several studies have now identified a plethora of OCT1 genetic variants that underlie such interindividual differences, no systematic review has thus far been conducted (as far as we are aware) to assess its impact. Most studies investigating the effects of OCT1 polymorphisms in the context of therapeutic responses to metformin for T2DM, essentially focused on European, Asian and Caucasian populations without consideration for other population group. Of note, Seitz et al[37] performed a global scale population analysis of OCT1 variants and identified 85 variants in 52 worldwide population groups that included sub-Saharan Africa, the Middle East and North Africa, Central Asia, East Asia and Oceania, Europe, and America. Although OCT1 polymorphisms have also been identified in Africans Americans and African populations such as the Xhosas (South Africa), Luhyas...
| Population     | Reference          | Study design       | Total sample | Age (Mean/ range), years | %Men | Duration of treatment | Polymorphism | MAF: (case/control) or population group | (P) * with HWE (i.a) | Reported outcome                                                                 |
|----------------|--------------------|--------------------|--------------|--------------------------|------|-----------------------|--------------|-----------------------------------------|---------------------|----------------------------------------------------------------------------------|
| Chinese        | Di Xiao et al[32]  | Case control       | 449 (53/214/182) | 29–73                    | 51   | 3 months              | rs 594709    | 0.268                                   | 0.268               | P = .555 Minor allele G is associated with higher increase of FINS (P = .015), decrease in HOMA-IR (P = .001) and QUICKI (P = .002). |
| Iranian        | Shokri et al[19]   | Cross-sectional    | 140 (77/63)    | 35–71                    | 13.75| 6 months              | rs628031     | 0.331                                   | –                    | No significant effect in metformin response (OR = 0.45, [95% CI 0.64–1.76], P = .45). |
| Not specify    | Dujic et al[24]    | Prospective        | 92 (43/49)     | 51.48 ± 8.91             | –    | 6 months              | rs12208357   | 0.317                                   | –                    | Significant association with common metformin induced gastrointestinal side effect, P = .034 |
| GoDARTs Scotland | Dujic et al[25]   | Observational cohort | 2216 (251/1915) | 57.80 ± 10.52           | 56.72| 6 months              | rs12208357   | 0.317                                   | –                    | Significant association with common metformin induced gastrointestinal side effect, P = .034 |
| South Indian   | Umapathysaran et al[27] | Observational cohort | 122 (29/93)    | 31–60                    | 39   | 3 months              | rs 623242    | 0.156                                   | 0.362               | Association of A allele with therapeutic efficacy of metformin and beneficial effects on HbA1c, FPG and PPG. |
| Han Chinese    | Zhou et al[28]     | Single-center      | 277 (153/124)  | 45–68                    | –    | 3 months              | rs1867351    | 0.50                                    | 0.261               | Association of T/T genotype with greater reductions in the HbA1c levels (P = .02), G/G genotype with greater reductions in FPG levels (P = .046). |
| Indian         | D Sur et al[29]    | Cross-sectional    | 50            | 46 ± 12.72               | 48   | –                     | rs 663309    | 0.63                                    | –                    | Unchanged function of OCT1 |
| South Indian Tamalian | Keshy et al[30] | Cross-sectional    | 60            | 35–55                    | –    | –                     | rs122083671  | 0.89                                    | –                    | C allele is associated with poor glycemic control and significantly higher FPG, insulin and blood metformin level (p < .05). |

(continued)
| Population     | Reference            | Study design           | Total sample (Case/Control) | Age (Mean/Range), years | %Men | Duration of treatment | Polymorphism | MAF: (case/control) or population group | (P)∗ with HWE (i.a.) | Reported outcome |
|----------------|----------------------|------------------------|-----------------------------|-------------------------|------|-----------------------|--------------|----------------------------------------|------------------------|------------------|
| Caucasian      | Tkáč et al[30]       | Cross-sectional        | 148                         | 57.5±0.9                | 49   | 6 months              | rs622342     | 0.05                                   | P= .95                 | No significant relationship with HbA1c (P= .96) |
| Latvian        | Tarasova et al[22]   | Case control           | 246 (53/193)                | 50–69                   | 30.1 | ≥3 months             | rs628031     | 0.39                                   | P= .785               | Significant association with gastrointestinal side effects of metformin (OR= 0.389, 95% CI 0.186–0.815, P= .012) |
|                |                      |                        |                             |                         |      |                       | rs 34056508 | 0.04                                   | P= 1                   | Not provided |
|                |                      |                        |                             |                         |      |                       | rs 72552763 | 0.18                                   | P= 1                   | Not provided |
|                |                      |                        |                             |                         |      |                       | rs 36056685 | 0.39                                   | P= .686               | Significant association with side effects of metformin (OR= 0.389, 95% CI 0.186–0.815, P= .012) |
| Danish         | Christensen et al[27]| Randomized controlled trial | 371                         | 52–62                   | 62.7 | 9 months              | rs 122083571 | 0.082                                  | –                      | No significant effect in metformin response |
|                |                      |                        |                             |                         |      |                       | rs 34104736 | 0.0                                    | –                      | No significant effect in metformin response |
|                |                      |                        |                             |                         |      |                       | rs 34130495 | 0.044                                  | –                      | No significant association with absolute decrease in HbA1c |
|                |                      |                        |                             |                         |      |                       | rs 72552763 | 0.175                                  | –                      | No significant effect in metformin response |
|                |                      |                        |                             |                         |      |                       | rs 461473   | 0.114                                  | –                      | No significant association with initial decrease in HbA1c |
| Caucasian      | Becker et al[31]     | Prospective cohort     | 98                          | 70–83                   | 39   | –                     | rs 622342    | 0.38                                   | P= .40                 | No significant effect in metformin response |
| Japanese       | Chen et al[17]       | Cross-sectional        | 66                          | 46–71                   | 48.5 | –                     | rs 4646272   | 0.34                                   | –                      | Negative predictor of efficacy of metformin |
|                |                      |                        |                             |                         |      |                       | rs 20068404 | 0.023                                  | –                      | Significant association with reduced uptake of metformin |
|                |                      |                        |                             |                         |      |                       | 616C>T       | 0.008                                  | –                      | Significant association with reduced uptake of metformin |
|                |                      |                        |                             |                         |      |                       | rs 628031    | 0.15                                   | –                      | No significant effect in metformin response |
|                |                      |                        |                             |                         |      |                       | 289C>A       | 0.017                                  | –                      | Significant Association with reduced uptake of metformin |
| Scottish       | Zhou et al[28]       | Cross-sectional        | 1531                        | 46–68                   | 56.14| At least 6 months    | rs 122083571 | 0.67                                   | P> .05                | No significant reduction in the ability of metformin to lower HbA1c (P= .47) |
|                |                      |                        |                             |                         |      |                       | rs 72552763 | 0.198                                  | P> .05                | No significant reduction in the ability of metformin to lower HbA1c (P= .92) |
| Caucasian      | Becker et al[18]     | Cross-sectional        | 102                         | 70–83                   | 39   | –                     | rs 3708174   | 0.05                                   | P= .56                 | No significant effect in metformin response (P= .49) |
|                |                      |                        |                             |                         |      |                       | rs 0037722   | 0.06                                   | P= .49                 | No significant effect in metformin response (P= .40) |
|                |                      |                        |                             |                         |      |                       | rs 3798168   | 0.02                                   | P= .80                 | No significant effect in metformin response (P= .40) |
|                |                      |                        |                             |                         |      |                       | rs 028031    | 0.40                                   | P= .39                 | No significant effect in metformin response (P= .40) |
|                |                      |                        |                             |                         |      |                       | rs 0457843   | 0.16                                   | P= .63                 | No significant effect in metformin response (P= .40) |
|                |                      |                        |                             |                         |      |                       | rs 3798167   | 0.19                                   | P= .31                 | No significant effect in metformin response (P= .20) |

(continued)
| Population | Reference       | Study design | Total sample (Case/Control) | Age (Mean/ range), years | %Men | Duration of treatment | Polymorphism | MAF: (case/control) or population group | (P)* with HWE (La) | Reported outcome                                                                 |
|------------|----------------|--------------|-----------------------------|--------------------------|------|----------------------|--------------|----------------------------------------|----------------|----------------------------------------------------------------------------------|
| Japanese   | Shikata et al[23] | Cross-sectional | 33 (9/24)                  | 29–73                     | 27.3 | > 1 month            | rs2197206   | 0.26                                   | P= .11 | No significant effect in metformin response                                           |
|            |                |              |                             |                          |      |                      | rs162342     | 0.37                                   | P= .72 | Association with glucose-lowering effect of metformin (P<.05)                        |
|            |                |              |                             |                          |      |                      | rs1443844    | 0.45                                   | P= .60 | No significant effect in metformin response                                           |
|            |                |              |                             |                          |      |                      | rs2297374    | 0.41                                   | P= .90 | No significant effect in metformin response                                           |
|            |                |              |                             |                          |      |                      | rs1564348    | 0.17                                   | P= .55 | No significant effect in metformin response                                           |
|            |                |              |                             |                          |      |                      | rs62591      | 0.18                                   | P= .81 | No significant effect in metformin response                                           |

Reported outcome: genetic effect of polymorphism in the study population
FINS = fasting insulin, FPG = fasting plasma glucose, HWE (i.a) = Hardy-Weinberg Equilibrium if applicable, HOMA IS = homeostatic model assessment of insulin sensitivity, MAF = minor allele frequency, PPG = postprandial plasma glucose, QUICKI = quantitative insulin sensitivity check index. (P)*: P value
The amino acid substitution of glycine to serine at codon 401 (Gly401Ser), resulting from the 17857 G→A polymorphism at rs34130495, causes a strong substrate-independent loss of OCT1 activity. The Gly401Ser variant apparently causes a general impairment of the transport process without affecting OCT1 membrane localization. Surprisingly, in a study conducted in a Danish population, Gly401Ser was associated with a significant, absolute decrease in HbA1c levels. Cys88Arg (rs55918055) in exon 1 is a rare loss of function polymorphism that causes improper membrane localization of OCT1 in the cytoplasmic membrane. It has been associated with intolerance to metformin in a Scottish population. Cys88Arg is located in the large extracellular loop that contains the transporter regulatory and substrate recognition domains. It is generally observed in combination with the Met420del variant. Substitution of Cysteine 88 by arginine destroys a cysteine residue known to build disulfide bonds. Indeed, several cysteine residues within the large extracellular loop between transmembrane helices 1 and 2 are involved in building intramolecular disulfide bonds essential for the oligomerization and targeting of OCT1 to the plasma membrane.

The 1022C>T polymorphism at rs2282143 consisting of the amino acid substitution proline to leucine at codon 341. Pro341Leu, can either elicit no effects or instead decrease OCT1 activity (<50%). The replacement of a rigid proline with leucine (which contains a relatively flexible side chain) could possibly change the local structure of OCT1. This is in agreement with findings of the Indian population in which rs2282143 has been reported to probably damage OCT1 function. Other rare variants known to cause OCT1 loss of function, that is, Pro117Leu (rs200684404), Gly97Lys (289C>G), Arg206Cys (616C>T), and Ser189Leu (rs34104736), were also reported and associated with significantly lowered metformin uptake. [17,21,23,27] For Gly97Lys, the replacement of the polar glutamate with a stronger positively charged lysine at 97 could increase the repulsion of cationic substrates. By contrast, the reduced activity of the Arg206Cys can be explained by decreased export of the OCT1 from the endoplasmic reticulum to the plasma membrane.

This systematic review demonstrated that the potential role of OCT1 polymorphisms in metformin therapeutic responses is population specific and some of them exhibited positive effects on metformin efficacy. The controversial findings related to these polymorphisms may be attributable to differences in the frequency of associated genetic variants and/or population differences that could be genetic or environmental. Indeed, environmental factors like chemicals and radiation exposure, lifestyle factors like diet, drinking, smoking, exercises, and physiological factors like age, sex can also work alone or in combination to influence drug responses. Advancing age for example is characterized by physiological changes affecting different organ systems and their implications for pharmacokinetics and pharmacodynamics of drugs. Although very few data exist in literature about the effect of biguanides particularly metformin in aging patients, no evidence indicated that metformin should be denied “a priori” to aging T2DM patients. However, age-dependent downregulation of OCT1 has been shown in mice brain microvessels of mice.

() and the Yorubas (Nigeria), their effects on metformin responses remain unknown. In light of this, there is a robust need to complete association studies between OCT1 polymorphisms and therapeutic responses to metformin, by evaluating a comprehensive and representative dataset.

The common polymorphism rs628301 (A>G) causes a missense mutation in exon 7 that consists of an amino acid substitution of methionine to valine at position 408 (Met408Val) in the OCT1 protein. Its frequency varies across ethnic population. Met408Val tends to lower OCT1 mRNA expression in enterocytes leading to decreased intestinal metformin uptake and hence its accumulation. Here the local increase of metformin concentrations within intestinal tissues is proposed as a putative mechanism for gastrointestinal side effects. This deleterious effect of Met408Val has been reported in Latvian population. However, Met408Val has been also characterized as a variant that lacks strong effects (did not cause >50% decrease in OCT1 activity). In agreement with this, no significant effects of Met408Val against metformin response have been found in Indian,[19] Caucasian,[18] and Japanese[17,23] populations. Surprisingly, GG and A/A genotypes of Met408Val exhibited significant reduction of FPG and HbA1c in Han Chinese,[18] and have been revealed to be a positive predictor for metformin efficacy in Japanese population.[23]

Numerous studies reported the deleterious effect of rs122083751 polymorphism. The 181C>T polymorphism at rs122083751 consisting of an amino acid substitution (arginine to cysteine at position 61 (Arg61Cys), is known to induce a robust substrate-wide loss of OCT1 activity, leading to decrease in OCT1-mediated uptake by more than 70% for all substrates tested (including metformin). Indeed, the rs122083751 polymorphism is responsible for the retention of OCT1 proteins in the endoplasmic reticulum thus leading decreased sarcolemma protein expression.

The rs7552763 polymorphism constitutes a 3bp deletion at position 420 (Met420del) and is the most common functional OCT1 variant. Met420del does not change OCT1 membrane localization and the exact mechanism how it affects OCT1 function remains unknown. Although it is associated with gastrointestinal side effects in Asian and Caucasian populations, no significant effects were reported for European populations.[22,25,27] Functional modifications by Met420del appear substrate dependent and in combination with other OCT1 variants. For example, Met420del does not affect the uptake of MPP+ (1-methyl-4-phenyl pyridinium). By contrast, it causes a robust decrease in metformin uptake (>60%) together with more than 80% reduction in tropisetron uptake. If the Met420del manifests in combination with Cys88Arg or Gly465Arg, the encoded OCT1 will be inactive regardless of the substrate used.[45,46]

The rs623342 (1386 A>C) variant (in intron between exons 8 and 9) does not elicit strong effects on OCT1 function. The A allele of rs623342 variant has rather been associated beneficial effects on HbA1c in Caucasian population.[131] The study performed by Umamaheswaran et al strengthened this positive effect of A allele on HbA1c in Indian population.

The 32870 G>A polymorphism at rs34059508 consisting of the amino acid substitution glycine to arginine at codon 465 (Gly465Arg), leads to the impairment of OCT1 localization and complete inactivation of OCT1. The exact mechanisms leading to this impairment remain unclear. Dujic et al observed metformin intolerance in carriers of both rs34059508 and another OCT1 reduced function.
Moreover, the way a person responds to a drug (this includes both positive and negative reactions) is a complex trait that is influenced by many different genes. Knowing all of the genes involved in drug response and understanding an individual’s genetic make-up, can help to develop genetic tests that could predict a person’s response to a particular drug and create personalized drugs with greater efficacy and safety.\[14,15\]

All studies included in this systematic review were rigorously assessed for their reporting quality—a key criterion for inclusion for analyses here completed. Different study designs have been used in included studies but, most of them had a cross-sectional design. As such, a causal relationship between genetic variants of OCT1 and responses to metformin cannot be inferred from these studies. For instance, confounding variables such as duration of treatment, metformin dosing might affect metformin responses leading to inconsistent results among studies. In terms of limitations, our investigation was conducted on a relatively small number of primary studies and more research work should help to obtain a wider range of relevant data to generate more conclusive findings. In addition, all studies surveyed did not always report key methodological information, for example, testing of the Hardy Weinberg Equilibrium and the sample size/power calculation. Some studies also reported a relatively small sample size meaning that the study population may not cover the entire spectrum of OCT1 variants. Thus larger sample sizes will enable a firmer correlation between OCT1 genetic variants and metformin responses. For example, we found that 2 studies included more than 1500 participants, 4 studies more than 200 participants, while the rest included less than 200 participants. Discordance of the type of study population and methods used for assessing the genetic effects of OCT1 variants may all have contributed to less powerful conclusions being derived by the current study. Finally, we were not able to pool data collected for a meta-analysis due to the methodological heterogeneity observed.

Great efforts are made to understand the effects of OCT1 genetic polymorphisms on interindividual variability in relation to metformin’s clinical efficacy. However, some questions remain unanswered, e.g. the relationship between OCT1 variants and lactic acidosis. This is a crucial issue as lactic acidosis is a rare but potentially fatal metabolic consequence of metformin therapy.\[16\]

For example, metformin-induced lactic acidosis is associated with an elevation in plasma metformin concentrations in patients with severe renal impairments and is considered as a contraindication of this drug. However, such adverse effects also occur in patients without well-known risk factors.\[17\] Thus a hypothesis emerges that OCT1 polymorphisms that decrease metformin uptake and cause its accumulation in circulation may induce lactic acidosis.\[56\] Thus a hypothesis emerges that OCT1 polymorphisms that decrease metformin uptake and cause its accumulation in circulation may induce lactic acidosis.\[56\]

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**Author contributions**

All authors had full access to the data

**Conceputalization:** Edith Pascale Mofo Mato, Peter Mark Oroma Owira.

**Data curation:** Edith Pascale Mofo Mato, Magellan Guewo-Fokeng.

**Formal analysis:** Edith Pascale Mofo Mato, Magellan Guewo-Fokeng.

**Methodology:** Edith Pascale Mofo Mato, Magellan Guewo-Fokeng.

**Supervision:** M. Faadiel Essop, Peter Mark Oroma Owira.

**Validation:** M. Faadiel Essop, Peter Mark Oroma Owira.

**Writing – original draft:** Edith Pascale Mofo Mato.

**Writing – review & editing:** M. Faadiel Essop, Peter Mark Oroma Owira.

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