The Genetics of Adverse Drug Outcomes in Type 2 Diabetes: A Systematic Review

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Background: Adverse drug reactions (ADR) are a major clinical problem accounting for significant hospital admission rates, morbidity, mortality, and health care costs. One-third of people with diabetes experience at least one ADR. However, there is notable interindividual heterogeneity resulting in patient harm and unnecessary medical costs. Genomics is at the forefront of research to understand interindividual variability, and there are many genotype-drug response associations in diabetes with inconsistent findings. Here, we conducted a systematic review to comprehensively examine and synthesize the effect of genetic polymorphisms on the incidence of ADRs of oral glucose-lowering drugs in people with type 2 diabetes.

Methods: A literature search was made to identify articles that included specific results of research on genetic polymorphism and adverse effects associated with oral glucose-lowering drugs. The electronic search was carried out on 3rd October 2020, through Cochrane Library, PubMed, and Web of Science using keywords and MeSH terms.

Result: Eighteen articles consisting of 10,383 subjects were included in this review. Carriers of reduced-function alleles of organic cation transporter 1 (OCT 1, encoded by SLC22A1) or reduced expression alleles of plasma membrane monoamine transporter (PMAT, encoded by SLC29A4) or serotonin transporter (SERT, encoded by SLC6A4) were associated with increased incidence of metformin-related gastrointestinal (GI) adverse effects. These effects were shown to exacerbate by concomitant treatment with gut transporter inhibiting drugs. The CYP2C9 alleles, *2 (rs1799853C>T) and *3 (rs1057910A>C) that are predictive of low enzyme activity were more common in subjects who experienced hypoglycemia after treatment with sulfonylureas. However, there was no significant association between sulfonylurea-related hypoglycemia and genetic variants in the ATP-binding cassette transporter sub-family C member 8 (ABCC8)/Potassium Inwardly Rectifying Channel Subfamily J Member 11 (KCNJ11). Compared to the wild type, the low enzyme activity C allele at CYP2C8*3 (rs1057910A>C) was associated with less weight gain whereas the C allele at rs6123045 in the NFATC2 gene was significantly associated with edema from rosiglitazone treatment.
INTRODUCTION

Diabetes mellitus refers to a group of metabolic disorders characterized by hyperglycemia resulting from insufficient production and/or ineffective response of cells to insulin. It is one of the major contributors to morbidity and mortality globally, and its prevalence continues to rise. By 2019, an estimated 463 million adults aged 20–79 years were living with diabetes which accounts 9.3% of the global population in this age group (International Diabetes Federation, 2019). This figure is expected to surge to 578 million (10.2%) by 2030 and to 700 million (10.9%) by 2045, most of this in the form of type 2 diabetes (T2D) (International Diabetes Federation, 2019). Poorly controlled diabetes progressively leads to chronic microvascular, macrovascular and neuropathic complications which manifest as renal failure, blindness, lower limb amputation, and accelerated vascular disease.

Several drugs are available for the management of T2D, referred to as glucose lowering agents. These include: biguanides (metformin), insulin secretagogues (sulfonylureas, meglitinides), thiazolidinediones, alpha glucosidase inhibitors (acarbose), incretin mimetics (GLP-1RAs, DPP-4is), amylin antagonists, sodium-glucose co-transporter-2 inhibitors (SGLT-2i), and insulin. These classes of drugs are either prescribed as monotherapy or given in combination.

The management of T2D is guided by national and international evidence-based guidelines (Buse et al., 2020), but there is noticeable inter-individual variability in treatment response as defined by glycemic reduction and adverse drug reactions. This variation is the net effect of several environmental and clinical factors including age, sex, adherence, concomitant therapy, drug interactions, and disease severity. In addition to these, a patient’s genotype can affect interindividual differences in drug response.

Adverse drug reactions are major clinical and public health problems world-wide. In the UK, around 6.5% of hospital admissions are due to adverse drug reactions (Pirmohamed et al., 2004), and that almost 15% of patients experience an ADR during their admission (Davies et al., 2009, 2010). The projected annual cost of such admissions to the NHS was £466m (Davies et al., 2009). Glucose lowering agents are one of the drugs of great concern for ADRs (Ducoffe et al., 2016). They have a well-described set of ADRs that are detrimental to individuals’ health and quality of life (Table 1). In the US, from 2010 to 2013, there were 600,991 ADRs associated with glucose-lowering agents with an average hospital marginal cost of $4,312 resulting in an annual hospital cost of $2.59 billion (Spector et al., 2017). Optimizing drug therapy through the avoidance of ADRs will dramatically improve patient health while generating millions of dollars by saving unnecessary medical costs.

However, there is inter-individual variability in the type and severity of ADRs experienced by individuals taking glucose-lowering drugs. While clinical and environmental factors influence this, genomic factors are also important. Here, we aim to undertake a systematic review of pharmacogenomic studies of ADRs related to oral glucose-lowering drugs.

METHODS

This systematic review is reported according to the Preferred Reporting Items for the Systematic Reviews and Meta-analysis Protocols (PRISMA-P) 2015 Checklist (Shamseer et al., 2015).

Type of Participants

Participants included in eligible studies must be diagnosed with T2D and treated with oral glucose-lowering drugs.

Type of Exposure

We included studies in which participants genotype were investigated in relation to ADRs of oral glucose-lowering agents.

Outcomes

The primary outcome was the incidence of any of the adverse effects of glucose-lowering drugs (Table 1). For metformin, GI adverse effects were considered - hypoglycemia and weight gain for sulfonylureas and weight gain and edema for thiazolidinediones.

Eligibility Criteria

Inclusion Criteria

Studies assessing the effect of genetic variations on the incidence of adverse effects of oral glucose-lowering drugs in people with T2D, published up to 3rd October 2020 in English language without any geographical restriction were included in this review.

Exclusion Criteria

We did not consider news, qualitative studies, case reports, reviews, editorials, and comments; and all non-published studies and published in non-English languages. Studies in which relevant data on genetic polymorphisms and/or ADRs associated
### Table 1: List of adverse drug reactions related to glucose-lowering drugs in type 2 diabetes.

| Drug                      | Side effects                                                                 | Comments                                                                                      |
|---------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Metformin                 | GI side effects (10%–25%): nausea, indigestion, abdominal cramp or bloating, or combination of these (Bailey and Turner, 1996; Goodman, 2017). Decrease in vitamin B12 concentration (5 to 10%) (Bell, 2010; de Jager et al., 2010; Aroda et al., 2016; Donnelly et al., 2020) Lactic acidosis (Misbin, 2004). | Symptoms are usually mild, transient, and reversible after dose reduction. When severe requires drug switch in about 5% of the population. Patient may develop anemia and/or peripheral neuropathy (Bell, 2010). Rare but serious |
| Thiazolidinediones        | Increased risk of overweight, congestion, heart failure, fractures, bladder cancer (pioglitazone) and myocardial infarction (rosiglitazone) (Jearath et al., 2016). | An average of 2 to 4 kg weight gain in the first year of treatment (Yni-Järvinen, 2004; Winkelmayer et al., 2008). Higher risk of adverse cardiovascular events with rosiglitazone (Winkelmayer et al., 2008; Juurlink et al., 2009; Graham et al., 2010). |
| Sulfonylurea and meglitinides | Hypoglycemia including coma (Schopman et al., 2014). Weight gain of 1–3 kg (Meneilly, 2011; Guardado-Mendoza et al., 2013). | Could be mediated through neural activation of specific CNS neurons due to peripheral dosing of peptide (Madsbad et al., 2011). |
| GLP-1 analogs             | Nausea and vomiting, injection site reactions                                |                                                                                              |
| DPP-4 inhibitors          | Headache, nasopharyngitis, and urinary tract infections (sitagliptin) (Katzung et al., 2019). Have no effects on body weight or risk of hypoglycemia (Salvo et al., 2016). |                                                                                              |
| SGLT2 inhibitors          | Genital and urinary tract infections. IV volume depression and hypotension can result from osmotic diuresis (Katzung et al., 2019). |                                                                                              |

Data Extraction and Management

Two review authors (AMB and AYD) independently extracted data from the articles reviewed. A data extraction form for this purpose was designed. Data was collected on the first author’s name, year of publication, geographical location (country where the study was performed), sample size, population characteristics, relevant genetic polymorphism, primary outcome measurements (incidence of adverse events after treatment with oral glucose-lowering agents). Any disagreements between the two review authors were resolved through discussion and consensus.

Selection of Studies for Inclusion in the Review

Two review authors (AMB and AYD) independently identified articles and then screened their titles and abstracts for eligibility. Thereafter, full texts of articles considered to be eligible were retrieved. Furthermore, the review authors independently assessed the eligibility for inclusion in the review based on the inclusion and exclusion criteria. Disagreements between the two authors was resolved by consensus. A PRISMA flow diagram (Shamseer et al., 2015) was employed to document the process of literature selection and the reasons for exclusion of articles were stated.

Search Strategy for Identifying Relevant Studies

A literature search was made to identify articles that included specific results of research on genetic polymorphisms and adverse effects associated with oral glucose-lowering agents. The electronic search was carried out on 3rd October 2020, through Cochrane Library, PubMed, and Web of Science using keywords and MeSH terms with no restriction for time of publication. The search strategy conducted in MEDLINE via PubMed, Cochrane, and Web of Science is shown in Supplementary Material. We also manually searched reference lists from relevant studies and contact experts in the field in order to identify additional eligible studies.

RESULT

Study Selection

Of the 362 studies identified, 66 were included for review of the full text. Of these studies, 18 studies met the inclusion criteria (Figure 1).

Characteristics of Included Studies

Eighteen articles comprised of 10,383 subjects were included in this review (Table 2). Among these, two studies were multinational (Bailey et al., 2010; Dawed et al., 2019). While 12 studies were conducted in Europe (Holstein et al., 2005, 2011, 2012; Ragia et al., 2009, 2012, 2014; Tarasova et al., 2012; Dujic et al., 2015, 2016a,b, 2018; Dawed et al., 2016), three were in Asia...
Metformin

Metformin is the first-line therapy for T2D. Around 30% of metformin treated subjects experience gastrointestinal (GI) side effects manifested as nausea, indigestion, abdominal cramps, bloating, diarrhea, or combination of these (Table 1) (Garber et al., 1997; Hirst J. A. et al., 2012). Metformin is an organic cation, and carrier proteins mediate its oral absorption, hepatic uptake, and renal elimination. Several solute carrier transporters, expressed in the membranes of the enterocytes, could be involved in the absorption of metformin from the intestinal lumen, including organic cation transporter (OCT) 1, plasma membrane monoamine transporter (PMAT), carnitine/cation transporter 1, OCT3 (encoded by \textit{SLC22A3}), and serotonin reuptake transporter (SERT) (Han et al., 2015). Genetic variants in genes encoding these transporters have been reported in five articles (Table 3) (Tarasova et al., 2012; Dujic et al., 2015, 2016a,b; Dawed et al., 2019).

Association between genetic variants in \textit{SLC22A1} (a gene encoding OCT1), and GI intolerance related to metformin therapy have been reported in three studies (Tarasova et al., 2012; Dujic et al., 2015, 2016a). A study conducted using the GoDARTS cohort (Hébert et al., 2018), in 251 metformin-intolerant and 1,915 metformin-tolerant individuals showed that the presence of two or more reduced-function alleles at R61C, C88R, G401S, M420del, or G465R increased the odds of GI side effects of metformin by more than 2-fold (Dujic et al., 2015). This effect was over 4-fold with concomitant use of OCT1-inhibiting drugs. The findings were replicated in another prospective observational cohort study from Bosnia and Herzegovina that included 92...
| References            | Country                  | Study drug                  | Study period                                  | Parent study  | Population                                                                 | Gene              | Comparators                  | N   |
|----------------------|--------------------------|-----------------------------|-----------------------------------------------|---------------|----------------------------------------------------------------------------|-------------------|-------------------------------|-----|
| Dawed et al. (2019)  | Multinational (Europe)   | Metformin                   | IMI DIRECT                                    | White Europeans aged between 18 and 90 years | SLC29A4         | Metformin-intolerant, Metformin-tolerant | 286, 1,128 |
| Dujic et al. (2015)  | Scotland, UK             | Metformin                   | 1 January 1994–1 June 2011.                   | GoDARTS       | White Europeans                                                           | SLC22A1           | metformin-intolerant, Metformin-tolerant | 251, 1,915 |
| Dujic et al. (2016b)| Scotland, UK             | Metformin                   | 1 January 1994–1 June 2011.                   | GoDARTS       | White Europeans                                                           | SLC6A4, SLC22A1   | Metformin-intolerant, Metformin-tolerant | 1,356, 164 |
| Dujic et al. (2016a)| Bosnia and Herzegovina   | Metformin                   | T2D diagnosis after the age of 35 years       |                |                                                                            | SLC22A1           | Metformin-intolerant, Metformin-tolerant | 49, 43  |
| Tarasova et al. (2012)| Latvia                 | Metformin                   | from 2003 to 2010                             | LGDB          | Subjects with T2D older than 18 years                                      | SLC22A1, SLC22A2, SLC47A1 | Metformin-tolerant, Metformin-tolerant | 193 |
| Gökalp et al. (2011)| Turkey                   | Glimepiride, Gliclazide, Glipizide | 2003 and 2005                                | None          | Subjects with T2D treated with SU for at least 3 months.                   | CYP2C9, CYP2C19, CYP2C8 | Without hypoglycemia, With hypoglycemia | 93, 15 |
| Dujic et al. (2018)| Scotland                 | Glibenclamide, Gliclazide, Glimepiride | 1994–2010                                     | GoDARTS       | Subjects with T2D who were incident users of SU                           | POR, CYP2C9       | Without hypoglycemia, With hypoglycemia | 311, 69 |
| Holstein et al. (2011)| Germany              | Glimepiride, Glibenclamide, Gliclizide | 1 January 2000 and 31 December 2009            | None          | Subjects with T2D treated with SU                                         | CYP2C9           | Without severe hypoglycemia, With severe hypoglycemia | 101, 102 |
| Holstein et al. (2005)| Germany              | Glibenclamide, Glimepiride | January 2000 and 31 December 2003            | None          | Subjects with T2D treated with SU                                         | CYP2C9           | Without severe hypoglycemia, With severe hypoglycemia | 337, 20 |
| Holstein et al. (2012)| Germany              | Glimepiride, Glibenclamide, Gliclizide | January 2000–31 December 2010                | None          | Subjects with T2D admitted to the emergency department                    | ABCC8            | Without hypoglycemia, With hypoglycemia | 100, 111 |

(Continued)
| References       | Country       | Study drug                  | Study period                          | Parent study | Population                                      | Gene         | Comparators                      | N    |
|------------------|---------------|-----------------------------|---------------------------------------|--------------|------------------------------------------------|--------------|-----------------------------------|------|
| Sato et al. (2010) | Japan         | Glimepiride/Glibenclamide   | January 2005 and October 2009         | None         | Subjects with T2D treated with Sulfonylureas    | ABCG2        | Without hypoglycemia               | 32   |
|                  |               |                             |                                       |              |                                                |              | With hypoglycemia                 | 125  |
| Ragia et al. (2012) | Greece        | Glimepiride/Gliclazide      | February 2007–September 2008          | None         | Subjects with T2D treated with Sulfonylureas    | KCNJ11       | Without hypoglycemia               | 84   |
|                  |               |                             |                                       |              |                                                |              | With hypoglycemia                 | 92   |
| Ragia et al. (2014) | Greece        | Glimepiride/Gliclazide      | February 2007–September 2008          | None         | Subjects with T2D treated with Sulfonylureas    | CYP2C9       | Without hypoglycemia               | 84   |
|                  |               |                             |                                       |              |                                                |              | With hypoglycemia                 | 92   |
| Ragia et al. (2009) | Greece        | Glimepiride/Gliclazide      | February 2007–September 2008          | None         | Subjects with T2D treated with Sulfonylureas    | CYP2C9       | Without hypoglycemia               | 84   |
|                  |               |                             |                                       |              |                                                |              | With hypoglycemia                 | 92   |
| Ruaño et al. (2009) | USA           | Rosiglitazone/Pioglitazone  | Between February and June 2007         | None         | Subjects with T2D treated with Rosiglitazones or Pioglitazones for ≥4 months | For BMI: ADORA1, PKM2, ADIPOR2, UCP2, APOH, IRS1, LIPA, RARB, and CHRM3  For Edema: NPY, GYS1, CCL2, OLR1, GHRH, ADRB1, ACACB, SCARB2, HRH3 and ACE | 87   |
| Kang et al. (2006)  | South Korea   | Rosiglitazone               |                                       | None         | Subjects with T2D aged between 35 and 80 years  | PLIN         |                                   | 160  |
| Dawed et al. (2016) | Scotland, UK  | Rosiglitazone/Pioglitazone  |                                       | None         | Subjects with T2D treated with TZD              | CYP2C8       |                                   | 833  |
| Bailey et al. (2010) | Multinational | Rosiglitazone/Placebo       |                                       | None         | Subjects with T2D ≥30 years of age              | NFATC2       | Rosiglitazone                      | 965  |
|                  | (21 countries)|                             |                                       |              |                                                |              | Placebo                           | 956  |
TABLE 3 | Association between metformin and selected SNPs for the incidence of GI adverse outcomes.

| References                  | Outcome measure                  | Drug | Tolerant | Intolerant | Drug | Tolerant | Intolerant | Gene     | SNP/genotype | Conclusion                                                                 |
|-----------------------------|----------------------------------|------|----------|------------|------|----------|------------|----------|--------------|----------------------------------------------------------------------------|
| Dawed et al. (2019)         | Incidence of GI adverse effects  | Metformin | 1,128    | 286        | Metformin | 1,128    | 286        | SLC29A4  | rs3889348G>A  | The G allele at rs3889348 (SLC29A4) was associated with higher odds of gastrointestinal intolerance (OR 1.34 [1.09–1.65], P = 0.005). |
| Dujic et al. (2015)         | Incidence of GI adverse effects  | Metformin | 1,915    | 251        | Metformin | 1,915    | 251        | SLC22A1  | R61C          | Compared to carriers of one or no deficient allele, carriers of two reduced-function OCT1 alleles had higher odds of intolerance (OR 2.41 [1.48-3.93], P < 0.001). |
| Dujic et al. (2016b)        | Incidence of GI adverse effects  | Metformin | 1,356    | 164        | Metformin | 1,356    | 164        | SLC6A4   | L”*S”          | Each S” allele was associated with higher odds of metformin intolerance (OR = 1.28 [1.01–1.63], P = 0.04). Multiplicative interaction between SLC6A4 and SLC22A1 (P = 0.003) |
| Dujic et al. (2016a)        | Incidence of GI adverse effects  | Metformin | 49       | 43         | Metformin | 49       | 43         | SLC22A1  | R61C          | Each OCT1 reduced-function allele was associated with higher odds of GI side effects (OR = 2.31 [1.07–5.01], P = 0.034). |
| Tarasova et al. (2012)      | Incidence of GI side effects     | Metformin | 193      | 53         | Metformin | 193      | 53         | rs12208357A>G | Each A allele at rs628031 was associated with lower odds of intolerance (OR = 0.39 [0.19–0.82], P = 0.01) Each 8 bp insertion at rs36056065 was associated with lower odds of intolerance (OR = 0.41 [0.23–0.72], P = 0.01) |

newly diagnosed subjects in the first 6 months of metformin treatment (Dujic et al., 2016a). Likewise, Tarasova et al. showed significant associations between a SNP (rs628031) and an 8 bp insertion (rs36056065) in the SLC22A1, with GI side effects of metformin (Tarasova et al., 2012).

Dawed et al. reported association between rs3889348, a variant that alters intestinal expression of the SLC9A4 (a gene encoding PMAT), with metformin related GI intolerance in 286 severe intolerant and 1,128 tolerant subjects. The G allele that reduces expression of SLC29A4 was associated with 34% higher odds of intolerance. Concomitant administration of metformin transporter inhibiting drugs exacerbate GI intolerance by more than 3-folds (Dawed et al., 2019).

Considering involvement of serotonin reuptake transporter (SERT) in metformin intestinal absorption, Dujic et al. investigated association between the low-expressing S” allele derived from a composite SERT (SLC6A4)-5-HTTLPR/rs25531 genotypes and metformin intolerance. In this study, each S” allele was associated with 30% higher odds of intolerance. Interestingly, a multiplicative interaction between OCT1 and SERT genotypes was observed (Dujic et al., 2016b). Carriers of reduced function alleles in OCT1 at the background of the wild type SERT (L”*L”*) genotype had greater odds of intolerance (OR 9.25 [3.18–27.0]) compared to carriers of the S” allele.

Sulfonylureas
Sulfonylureas were the first oral glucose-lowering therapy introduced into clinical practice and along with metformin, are the most prescribed drugs for the management of T2D (Inzucchi et al., 2015). SU are transported into the liver by OATP1B1 (encoded by SLCO1B1) and metabolized mainly by the polymorphic CYP2C9 enzyme and to a lesser extent by CYP2C19 enzyme (Becker et al., 2008). CYP2C9*2 (R144C, rs1799853) and CYP2C9*3 (I359L, rs1057910) are the two most common variants that have been associated with poor metabolism of SU (Semiz et al., 2010). Sulfonylureas induce glucose-independent
insulin release from the pancreatic β-cells by binding to the ATP-sensitive potassium (KATP) channels, SUR1 and Kir6.2, that are encoded by the ABCC8 and KCNJ11 genes, respectively. Hypoglycemia is the most common adverse effect of SU. In a systematic review consisting of 22 randomized controlled trials, 10.1 and 5.9% of SU treated subjects experienced hypoglycemia as defined by blood glucose levels of <3.1 or <2.8 mmol/L, respectively (Schopman et al., 2014). Severe hypoglycemia with SU therapy is less common, with reported incidence of 0.8%. SU treatment also results in weight gain of 1–3 kg (Schopman et al., 2014).

### TABLE 4 | Association between sulfonylureas and selected SNPs for the incidence of hypoglycemia.

| References                  | Outcome measure       | Sulfonylurea drug (%) | Gene          | Genotypes | Conclusion |
|-----------------------------|-----------------------|-----------------------|---------------|-----------|------------|
| Gökalp et al. (2011)        | Incidence of mild hypoglycemia | Glimepiride 44 (47%)  Gliclazide 41 (44%)  Glipizide 8 (9%)  | CYP2C9       | CYP2C9’2  | In the gliclazide group a significant association between CYP2C9 genotypes and hypoglycemic attacks were observed (P = 0.035). |
|                            |                       |                       |               | CYP2C9’3  |            |
| Dujic et al. (2018)         | Incidence of SU-induced hypoglycemia | Glibenclamide 5 (1.6%)  Gliclazide 254 (81.7%)  Glimepiride 3 (1.0%)  | POR          | POR’28    | The number of CYP2C9 deficient alleles increased the odds of hypoglycemia nearly 3-fold (OR, 2.81; 95% CI, 1.30-6.09; P = 0.009) only at the POR’1/1 genotype background. |
|                            |                       |                       |               | CYP2C9’2  |            |
|                            |                       |                       |               | CYP2C9’3  |            |
| Holstein et al. (2011)      | Severe hypoglycemia   | Glimepiride 81 (80.2%)  Glibenclamide 76 (74.5%)  Gliclazide 25 (24.5%)  | CYP2C9       | CYP2C9’1  | There was no overrepresentation of the CYP2C9 *2/*2, *2/*3, and *3/*3 variants in the SH group (2%) compared with the control group (5%). |
|                            |                       |                       |               | CYP2C9’2  |            |
|                            |                       |                       |               | CYP2C9’3  |            |
| Holstein et al. (2011)      | Severe hypoglycemia   | Glimepiride 337 20     Glibenclamide 337 20     | CYP2C9       | CYP2C9’1  | The CYP2C9 genotypes *3/*3 and *2/*3 that are predictive of low enzyme activity were more common in the hypoglycemic group than in the comparison groups (10 vs. <2%, OR 5.2; 95% CI, 1.01, 27). |
|                            |                       |                       |               | CYP2C9’2  |            |
|                            |                       |                       |               | CYP2C9’3  |            |
| Holstein J. D. et al. (2012)| Severe hypoglycemia   | Glimepiride 80 28      Glibenclamide 18 28      | ABCC8        | Ser1369Ala | Ser1369Ala variant in ABCC8 does not affect the response to sulfonylurea treatment and so, is not a major player in the etiology of severe hypoglycemia. |
|                            |                       |                       |               |          |            |
| Sato et al. (2010)          | Severe hypoglycemia   | Glimepiride 32 125     Glibenclamide 32 125     | ABCC8        | Ser1369Ala | No significant differences in the distribution of the Ser1369Ala genotype between patients with or without severe hypoglycemia (p = 0.26). |
| Ragia et al. (2012)         | Mild hypoglycemia     | Glimepiride 4 80       Gliclazide 10 12        | KCNJ11       | E23K      | KCNJ11 E23K polymorphism did not affect hypoglycemia risk. |
| Ragia et al. (2014)         | Mild hypoglycemia     | Glimepiride 74 80      Gliclazide 10 12        | CYP2C9       | POR’28    | POR’28 allele was not associated with severe hypoglycemia. CYP2C9’2 allele increased the risk of hypoglycemia by more than 3 times (OR: 3.218, p = 0.031). POR’28 allele is masking the association of CYP2C9’2 allele with severe hypoglycemia. |
| Ragia et al. (2009)         | Mild hypoglycemia     | Glimepiride 74 80      Gliclazide 10 12        | CYP2C9       | CYP2C9’1  | The presence of CYP2C9’2 allele puts subjects with T2D at higher risk of hypoglycemia when receiving the SU |
TABLE 5 | Association between thiazolidinediones and selected SNPs for the incidence of weight gain and edema.

| References          | Outcome measure | Drug            | Sample size | Gene      | SNP/genotype | Conclusion                                                                 |
|---------------------|-----------------|-----------------|-------------|-----------|--------------|----------------------------------------------------------------------------|
| Dawed et al. (2016) | Weight gain     | Rosiglitazone   | 519         | CYP2C8    | rs660339     | The CYP2C8*3 variant was associated with less weight gain (P = 0.02).       |
|                     |                  | Pioglitazone    | 273         | SLCO1B1   | rs10509681   |                                                                            |
| Bailey et al. (2010)| Edema           | Rosiglitazone   | 966         | GWAS      | GWAS         | rs6123045 an intronic SNP in the NFATC2 was significantly associated with      |
|                     |                  |                 |             |           |              | edema (OR 1.89 [95% CI 1.47–2.42]; P = 5.32 x 10^{-1}).                     |
| Ruaño et al. (2009)| BMI              | Rosiglitazone   | 87          | ADORA1    | rs903361     | ADORA1-rs903361 was significantly associated with weight gain (P < 0.0003) |
|                     |                  | Pioglitazone    |             | PKM2      | rs2856929    |                                                                            |
|                     |                  |                 |             | ADIPOR2   | rs7975375    |                                                                            |
|                     |                  |                 |             | UCP2      | rs660339     |                                                                            |
|                     |                  |                 |             | APOH      | rs8178847    |                                                                            |
| Kang et al. (2006) | Weight gain     | Rosiglitazone   | 160         | PLIN      | 6200T>C       | The A allele at 11482G>A was associated with less weight gain (GG, 1.33 ±   |
|                     |                  |                 |             |           | 11482G>A     | 1.59 kg; GA, 0.85 ± 1.89 kg; and AA, 0.03 ± 1.46 kg; P = 0.010)             |
|                     |                  |                 |             |           | 14995A>T     |                                                                            |

2014). Risk of hypoglycemia and weight gain may vary with age, gender, renal function, disease progression, drug exposure, and genetic constitution.

In this systematic review, we have included studies that investigated association between genetic variants in genes, CYP2C9 and ABCC8/KCNJ11, that encode CYP2C9 and SUR1/Kir6.2 with risk of hypoglycemia (Holstein et al., 2005, 2011, 2012; Ragia et al., 2009, 2012, 2014; Gökalp et al., 2011) (Table 4). An association between reduced function CYP2C9*2 and CYP2C9*3 alleles with higher risk of SU related hypoglycemia was reported confirming earlier functional and pharmacokinetic data (Ragia et al., 2009; Gökalp et al., 2011). However, another study could not confirm the findings (Holstein et al., 2011). In the later study subjects within the control arm that carry slow metabolizing alleles were found to be treated with significantly lower doses than carriers of the wild type, whereas in the group with severe hypoglycemia, the dose was the same for all genotype groups. Another small study suggested a possible interaction between P450 oxidoreductase (POR) and CYP2C9 genotypes (Ragia et al., 2014), where POR*28 allele could mask the effect of CYP2C9*2 allele on sulfonylurea-induced hypoglycemia. Indeed, a bigger study from the GoDARTS cohort confirmed this and therefore it is worth considering CYP2C9 and POR genotypes jointly in studies involving the pharmacogenetics of SU (Dujic et al., 2018).

Three other studies investigated association between two strongly linked non-synonymous polymorphisms, S1369A (rs757110) and E23K (rs5219), in the ABCC8 and KCNJ11 genes, respectively with hypoglycemia (Sato et al., 2010; Holstein et al., 2012; Ragia et al., 2012). None of these studies showed statistically significant association between SU treatment and risk of hypoglycemia suggesting these polymorphisms may not play a major role in the etiology of hypoglycemia.

Thiazolidinediones

Thiazolidinediones are insulin sensitizers that act by increasing the transactivation activity of Peroxisome Proliferators Activated Receptors (PPARs). The clinically used TZDs, rosiglitazone and pioglitazone, suffer from serious side effects. Concerns about the cardiovascular safety of rosiglitazone due to fluid retention led suspension in the European market and several restrictions in the US (Woodcock et al., 2010; Shukla and Kalra, 2011). Unlike rosiglitazone, pioglitazone did not show any risk of cardiovascular side effects. However, concerns were raised on the apparent risk of bladder cancer with pioglitazone and hence it is not recommended in people with active or prior history of bladder cancer (Shukla and Kalra, 2011). TZDs are associated with an average of 2–4 kg weight gain in the first year of management (Yki-Järvinen, 2004). In addition, these agents result in peripheral edema in 4–6% (Graham et al., 2010).

This systematic review identified four articles that assessed association between genetic variants in candidate genes and weight gain and/or oedema after treatment with TZDs (Kang et al., 2006; Ruaño et al., 2009; Bailey et al., 2010; Dawed et al., 2016) (Table 5). A post-hoc analysis from the DREAM (Diabetes REDuction Assessment with ramipril and rosiglitazone Medication) trial that consist of 4,197 participants showed higher rate of roziglitazone-induced edema (OR = 1.89 [95% CI = 1.47–2.42], P = 0.017) in subjects homozygous for the C allele at rs6123045, a variant at the Nuclear Factor of Activated T-cells, Cytoplasmic, Calcineurin-Dependent 2 (NFATC2) locus (Bailey et al., 2010). We have previously showed association between the CYP2C8*3 variant with less weight gain compared to the wild
discussions. In addition, next generation sequencing that allows the analysis of rare variants that have been postulated to contribute to ADRs in diabetes. Older people, women, and concomitant use of gut metformin transporter inhibiting drugs were previously shown to increase the likelihood of GI side effects of metformin (Dujic et al., 2015; Dawed et al., 2019). In addition, longer diabetes duration, impaired renal function, lower body mass index, lower triglyceride levels and old age were identified as major risk factors for hypoglycemia in people with type 2 diabetes (Schloot et al., 2016).

Even though this review is comprehensive, it is subjected to limitations. First, the studies included were heterogeneous in design with regards to treatment, adverse effect outcomes, definitions, and population (ethnicity). The timing to measure primary endpoint (adverse effects of oral glucose-lowering agents) is also not uniform.

Poor adherence to treatment is a well-known phenomenon in patients with diabetes and is associated with inadequate glycaemic control leading to rapid disease progression and complications (Polonsky and Henry, 2016). Moderate and severe ADRs such as hypoglycemia and GI intolerance are previously shown to be key contributors of poor adherence in diabetes.

In conclusion, there are few pharmacogenomic studies of ADRs in type 2 diabetes that have been undertaken. Most of the studies have not been externally replicated, except OCT1 and metformin induced GI intolerance, CYP2C9 and SU-induced hypoglycemia. In the future, well-powered pharmacogenomic studies in T2D should collect standardized ADR data in multi-ethnic populations.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

AMB and AYD conceived and designed this research, executed the analysis procedure, and analyzed the results. AMB, MKS, and AYD contributed to the writing of the manuscript. All authors reviewed the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2021.675053/full#supplementary-material
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