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Pharmacogenetics of Glucose-Lowering Drug Treatment

A Systematic Review

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Abstract

Intensive blood glucose lowering can significantly reduce the risk of micro- and macrovascular complications in patients with diabetes mellitus. However, 30% of all treated patients do not achieve optimal blood glucose levels. Genetic factors may influence the response to glucose-lowering medication.

A search of MEDLINE-indexed literature published between January 1966 and July 2007 revealed 37 studies reporting data on genetic polymorphisms and response to glucose-lowering drugs.

Most studies involving cytochrome P450 (CYP) genes had small sample sizes (21 studies <50 subjects) and were among healthy volunteers. Multiple studies indicated that the *CYP2C9* *3 allele (Ile359Leu polymorphism) was associated with decreased clearance of sulfonylurea drugs. Supporting this, one study reported an increased insulin secretion in *CYP2C9**3 allele carriers when using the sulfonylurea agent glyburide. The *CYP2C9**3 allele

was also associated with a decreased clearance of meglitinides, whereas the *CYP2C8**3 (Arg139Lys; Lys399Arg) variant increased the clearance of meglitinides.

Polymorphisms in genes encoding the inwardly rectifying potassium channel Kir6.2 (*KCNJ11*) and the insulin receptor substrate-1 (*IRS1*) were reported to be associated with an increased risk of (secondary) failure to respond to sulfonylurea therapy. A significant decrease in fasting plasma glucose and hemoglobin A_{1c} (HbA_{1c}) in response to rosiglitazone was seen in subjects carrying the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-γ (*PPARG*) gene. Conversely, carriers of this polymorphism also had a higher conversion to diabetes mellitus when treated with acarbose; this effect was also seen in adiponectin (*ADIPOQ*) gene polymorphism carriers.

Future studies with adequate sample sizes in which several SNPs in multiple candidate genes are genotyped in patients with diabetes should provide reliable information on genetic variants and response to glucose-lowering drugs.

Diabetes mellitus is a growing global health burden. Up to 80% of patients with type 2 diabetes die from macrovascular cardiovascular disease.[1] Several trials have demonstrated that achieving near normal glycemic control in patients with type 1 and type 2 diabetes reduces the risk of microvascular complications.[1,2] Intensive control of blood glucose can significantly reduce and retard the microvascular complications of retinopathy, nephropathy, and neuropathy.[3] According to previous research, 30% of patients in general practice do not achieve the targets for good glycemic control.[4] Interindividual variation in response to glucose-lowering drugs is common, and there is no single agent that leads to optimal blood glucose in all treated patients.[5] Factors such as obesity, the level of physical activity, diet, and genetic risk factors[6] are thought to play a role in the interindividual variation in response to diabetic medication. A pharmacogenetic approach may help to elucidate the role of genetics in variable response to glucose-lowering drugs.[7]

Pharmacogenetics aims to study the role of genetic variation in interindividual differences in drug response.[8] The information gathered from pharmacogenetic research may be used to optimize treatment regimens that reduce the risk of adverse drug reactions and improve treatment efficacy in susceptible persons. Genetic variability can influence response to medication through several pathways: variation in genes involved in pharmacokinetics, pharmacodynamics, and in genes that are in the causal pathway of the disease.[8,9]

The aim of this review is to summarize what is known about genetic variants that have been studied in relation to the response to glucose-lowering drug therapy.

1. Published Pharmacogenetic Studies

A literature search in MEDLINE of publications between January 1966 and July 2007 was conducted to identify studies containing information on the pharmacogenetics of diabetes. Keywords of the search were 'gene', 'genotype', 'polymorphism', 'genetics', 'diabetes', 'pharmacogenetics', 'SNP', and 'variant', in combination with the names of specific oral antidiabetic drugs. The references of all identified articles were checked. All clinical studies reporting data on pharmacokinetic and pharmacodynamic response to antidiabetic drugs and genetic polymorphisms were included. Response was not further defined.

The literature search identified 42 articles, of which 5 were case reports; the case reports were excluded.[6,10-13] The details and main findings of all included studies are summarized in table I. Table II shows the frequency of the most common polymorphisms studied.

2. Candidate Genes Affecting Pharmacokinetics

2.1 Cytochrome P450 (CYP) 2C9 Polymorphisms and Response to Sulfonylureas

The pharmacokinetics of oral hypoglycemic agents can be altered through polymorphisms involved in drug metabolism (cytochrome P450 [CYP] 2 genes, e.g. *CYP3A5*) and transport (organic anion transporters [OATs] and organic cation transporters [OCTs]). CYP2C9, CYP2C8, and CYP2D6 are major CYP enzymes that are involved in the metabolic clearance of a wide variety of therapeutic agents.[69] CYP3A5 is a principal catalyst of the biotransformation of repaglinide.[70] Important drug transporters include the OATs (e.g. SLCO1B1), and the OCTs (e.g. SLC22A1), which are involved in the uptake of many hydrophilic organic cations.[71]

Most of the studies involving the CYP genes have a very small sample size and/or were performed in healthy subjects. Healthy carriers of the Ile359Leu polymorphism of the *CYP2C9* gene, also referred to as *CYP2C9**3, showed decreased clearance of tolbutamide,[15-18] glyburide,[19-21] glimepiride,[19,22] and chlor-

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Table I. The influence of genetic polymorphisms on the effect of glucose-lowering medicine

Drug	Gene and allele[a]	Study population	Result [95% CI]	Reference
Sulfonylureas (SU)/cytochrome P450 (CYP) genes				
Tolbutamide	*CYP2C9*2, *3	172 DM	Significantly lower increase in prescribed daily dose between first and tenth prescription for *3 carriers vs *1/*1	14
Tolbutamide	*CYP2C9*2, *3	15 ND	Reduction in clearance in *1/*3: 48%; *1/*2: 29% vs *1/*1 ($p < 0.05$); no association with blood glucose lowering	15
Tolbutamide	*CYP2C9*2, *3	23 ND	Reduction in clearance in *1/*2: 12%; *2/*2: 23%; *1/*3: 42%; *2/*3: 54%; *3/*3: 84% vs *1/*1; no association with blood glucose, plasma insulin levels	16
Tolbutamide	*CYP2C9*2, *3	16 ND	Reduction in 24h formation clearance of tolbutamide metabolites in *1/*2: 32%; *1/*3: 42% vs *1/*1	17
Tolbutamide	*CYP2C9*3	18 ND (Korean)	Reduction in $t_{1/2}$ in *1/*3: 24% vs *1/*1	18
Tolbutamide	*CYP2C19*2, *3	18 ND (Korean)	No effect on pharmacokinetic nor pharmacodynamic parameters	18
Glyburide	*CYP2C9*2, *3	29 ND	$t_{1/2}$ (h) in *1/*1: 1.7[1.5; 1.9]; *1/*3 or *2/*3: 2.6 [2.3; 2.8] ($p \leq 0.05$); no association with blood glucose lowering	19
Glyburide	*CYP2C9*2, *3	21 ND	Reduction in oral clearance in *3: 50% vs *1 ($p \leq 0.001$); significant increase in insulin secretion 12h after administration	20
Glyburide	*CYP2C9*3	18 ND (Chinese)	Increase in $t_{1/2}$ in *1/*3: 71% vs *1/*1 ($p < 0.03$), Δ glucose (2h) 17.85% more decrease in *3, Δ insulin (2h) 161.1% more increase in *3 vs *1*1	21
Glyburide	*CYP2C19*2, *3	18 ND (Chinese)	No effect on pharmacokinetic nor pharmacodynamic parameters	21
Glimepiride	*CYP2C9*2, *3	29 ND	$t_{1/2}$ (h) in *1/*1: 1.9 [1.1; 2.5]; *1/*3 or *2/*3:3.0 [2.5; 4.0] ($p \leq 0.01$); no association with blood glucose lowering	19
Glimepiride	*CYP2C9*3	19 ND (Chinese)	Increase of $t_{1/2}$ in *1/*3: 163% vs *1/*1 ($p < 0.05$); reduction in clearance in *3/*3: 75% vs *1/*1 ($p < 0.05$)	22
Chlorpropamide	*CYP2C9*3	21 ND (Korean)	Nonrenal clearance in *1/*1: 1.8 ± 0.2; *1/*3: 2.4 ± 0.1 mL/h/kg ($p < 0.05$)	23
Chlorpropamide	*CYP2C19*2, *3	21 ND (Korean)	No effect on pharmacokinetic nor pharmacodynamic parameters	23
SU (unspecified)	*CYP2C9*2, *3	20 DM	*3 associated with higher risk of severe hypoglycemia	24
Meglitinides/CYP genes				
Nateglinide	*CYP2C9*2, *3	24 ND	2-fold increased median AUC in *3/*3 vs *1/*1	25
Nateglinide	*CYP2D6*4, *5	24 ND	No effect on pharmacokinetic nor pharmacodynamic parameters	25
Repaglinide	*CYP2C8*3, *4	28 ND	Decreased mean AUC in *1/*3: 45% vs *1/*1 ($p < 0.05$); no association with blood glucose lowering	26
Repaglinide	*CYP2C8*3, *4	56 ND	C_{max} 44% lower in *3 carriers vs *1; no effect on blood glucose levels	27
Repaglinide	*CYP3A5* +6986G/A	56 ND	No effect on pharmacokinetics	27
Thiazolidinediones/CYP genes				
Rosiglitazone	*CYP2C8*3	31 ND	Decreased mean AUC in *3: 36% vs *1/*1; no effect on blood glucose	28
Meglitinides/organic anion transporter (OAT) genes				
Repaglinide	*SLCO1B* −11187G/A	56 ND	−11187A allele associated with an increased glucose-lowering effect; maximum decrease 1.8 ± 0.9 mmol/L ($p < 0.05$)	27

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Table I. Contd

Drug	Gene and allele[a]	Study population	Result [95% CI]	Reference
Nateglinide	*SLCO1B1* +521T/C	31 ND	Increase of $t_{1/2}$ by 78% in CC vs TT genotype; increase in AUC by 82% in TC and 108% in CC vs TT	29
Thiazolidinediones/OAT genes				
Rosiglitazone, pioglitazone	*SLCO1B1* +521T/C	16 ND	No effect on pharmacokinetic parameters	30
SU/receptor and channel genes				
SU (unspecified)	*SUR1* 16–3T/C	70 T2DM	–3T allele associated with significant decrease in plasma (triglycerides) [p = 0.026]; no association with plasma insulin and glucose	31
SU or combination	*SUR1* 16–3T/C	68 T2DM	No significant differences in allele distribution in T2DM patients with early treatment failure compared with T2DM patients responding to SU	32
Tolbutamide	*SUR1 C/T* exon 18; 16–3T/C	449 T2DM	Significant reduction insulin response (19–22 min) in carriers of combined genotype exon18/exon16 (nt-3): 124 ± 27 vs 231 ± 10 min × pmol/L; p = 0.045	33
Tolbutamide	*SUR1* –437A/T	233 ND	No difference in tolbutamide-stimulated insulin response between carriers and noncarriers of the –437T allele	34
Tolbutamide	*SUR1–/–*	24 HI	*SUR1–/–* no acute insulin response to tolbutamide compared with heterozygote and normal subjects	35
SU (unspecified)	*IRS1* Gly972Arg	477 T2DM	Arg972 associated with SU treatment failure	36
SU (unspecified)	*KCNJ11* Glu23Lys	525 T2DM	Lys23 variant associated with secondary failure to SU (relative risk carriers of Lys23 allele vs Glu23 homozygotes; 1.45; p = 0.04)	37
Thiazolidinediones/ receptor genes				
Pioglitazone	*PPARG* Pro12Ala	131 T2DM	No association with blood glucose lowering	38
Troglitazone	*PPARG* Pro12Ala	3548 impaired glucose tolerance	No association with incidence of T2DM	39
Troglitazone	*PPARG* Pro12Ala	93 GD	No association with blood glucose lowering	40
Rosiglitazone	*PPARG* Pro12Ala	198 T2DM (Korean)	Ala12 allele associated with FPG level (50.6 ± 27.8 mg/dL vs 24.3 ± 41.9 mg/dL [noncarriers]; p = 0.026) and decrease in HbA_{1c} level (1.41% ± 1.47% vs 0.57% ± 1.16% [noncarriers], p = 0.015)	41
Other combinations				
Rosiglitazone	*ADIPOQ* +45T/G, +276G/T	166 T2DM (Korean)	GG in both SNPs associated with lower reduction in FPG and HbA_{1c}	42
Pioglitazone	*LPL* Ser447X	113 DM (Chinese)	Significant decrease in FPG in X allele carriers treated with rosiglitazone	43
Metformin	*IRS1* Gly972Arg	60 PCOS	Reduced efficacy in lowering fasting insulin level and insulin resistance in Arg972 carriers vs noncarriers (p < 0.001)	44
Metformin	*KCNJ11* Glu23Lys	3234 IGT	Preventive effect against DM in Glu/Glu homozygotes, HR: 0.55 (0.54–1.67); Glu/Lys HR: 0.89 (0.66–1.19); and Lys/Lys HR: 0.95 (0.54–1.67) vs placebo	45
Metformin	*HNF1A*[b]	36 T2DM MODY	No difference in response	46

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Table I. Contd

Drug	Gene and allele[a]	Study population	Result [95% CI]	Reference
Gliclazide	*HNF1A*[b]	36 T2DM MODY	Improved response of fasting glucose to gliclazide; FPG reduction from baseline (mmol/L) T2DM vs *HNF1A* 1.2 [0; 2.4] vs 4.7 [3.3; 6.2]	46
Tolbutamide	*HNF1A*[b]	7 MODY	Normal response to tolbutamide	47
SU (unspecified)	*TCF7L2* Rs12255372G/T, Rs7903146	4469 T2DM	Higher rate of SU treatment failure in Rs12255372 TT vs GG: OR (95% CI): 1.95 (1.23, 3.06)	48
Metformin	*TCF7L2* Rs12255372G/T, Rs7903146	4469 T2DM	No association between polymorphisms and metformin response	48
Acarbose	*PPARG* Pro12Ala	356 IGT	2.9-times higher conversion to T2DM in women with Pro/Pro vs Pro/Ala genotype	49
Acarbose	*PPARGC1A* Gly482Ser	356 IGT	Prevention of diabetes among carriers of the Ser482 allele	49
Acarbose	*ADIPOQ* +45T/G, +276G/T	356 IGT	TT genotype of SNP+276 associated with higher conversion to T2DM than in GG genotype carriers OR 2.83 (95% CI 1.26, 6.36; p = 0.012) Combination of the +45 G-allele and +276 TT genotype further increases risk OR 3.05 (95% CI 1.34, 6.96; p = 0.008)	50

a *CYP2C9**2 = Arg144Cys; *CYP2C9**3 = Ile359Leu; *CYP2C8**3 = Arg139Lys, Lys399Arg (416G/A, 1196A/G); and *CYP2C8**4 = Ile264Met (792C/G).

b Several mutations; not mentioned in article.

ADIPOQ = adiponectin (ACDC); **AUC** = area under the concentration-time curve; $\mathbf{C_{max}}$ = maximum drug concentration; **DM** = diabetes mellitus; **EM** = extensive metabolizer; **FPG** = fasting plasma glucose; **GD** = gestational diabetes; $\mathbf{HbA_{1c}}$ = hemoglobin A_{1c}; **HI** = hyperinsulinemic; ***HNF1A*** = hepatocyte nuclear factor-1α; **HR** = hazard ratio; **IGT** = impaired glucose tolerance; ***IRS1*** = insulin receptor substrate-1; ***KCNJ11*** = inwardly rectifying potassium channel Kir6.2; **MODY** = maturity onset diabetes of the young; **ND** = nondiabetic; **OR** = odds ratio; **PCOS** = polycystic ovarian syndrome; **PM** = poor metabolizer; ***PPARG*** = peroxisome proliferator-activated receptor-γ2; ***PPARGC1A*** = PPARγ coactivator 1α (PCG1α); ***SLCO1B1*** = solute carrier OAT family, member 1B1; **SNP** = single nucleotide polymorphism; ***SUR1*** = sulfonylurea receptor; $\mathbf{t_{1/2}}$ = half-life; **T2DM** = type 2 diabetes mellitus.

propamide.[23] These findings did not differ substantially between Caucasians,[15-17,19,20] Korean,[18,23] or Chinese[21,22] populations. Blood glucose response was not influenced by the *CYP2C9* polymorphisms among Caucasians[19,20] although insulin secretion was increased within 12 hours of ingestion.[20] Among Chinese, 2-hour blood glucose response and 2-hour insulin response was reduced to a greater extent in *CYP2C9**3 carriers.[21]

The *CYP2C9**3/*3 and the *2/*3 genotypes were more common in diabetic patients admitted to the emergency department with severe hypoglycemia during sulfonylurea drug treatment compared with a control group of patients with type 2 diabetes but without a history of severe hypoglycemia.[24] Diabetic patients carrying the *CYP2C9**3 polymorphism require lower doses of tolbutamide to regulate serum glucose than do carriers of the wild-type genotype.[14]

No differences related to *CYP2C19* polymorphism, tolbutamide,[18] glyburide,[21] or chlorpropamide[23] use were found.

2.2 *CYP2C9, CYP2C8, CYP3A5, SLCO1B1,* and *CYP2D6* Polymorphisms and Response to Meglitinides

The pharmacokinetics of meglitinides was altered in healthy carriers of the *CYP2C9**3,[25] *CYP2C8**3,[26,27] and *SLCO1B1* 521T/C.[29] The *CYP2D6**4/*5[25] and *CYP3A5**3[27] polymorphisms did not change the response of meglitinides. While no statistically significant changes were seen in blood glucose response to meglitinides with regard to *SLCO1B1* 521T/C and *CYP2C9**3, the *SLCO1B1* −11187G>A[27] single nucleotide polymorphism (SNP) was significantly associated with an increased glucose-lowering effect.

2.3 *CYP2C8* and *SLCO1B1* Polymorphisms and Response to Thiazolidinediones

The *CYP2C8**3[28] and *SLCO1B1* 521T/C[30] polymorphisms did not affect the pharmacokinetics of thiazolidinediones in healthy volunteers.

2.4 Organic Cation Transporter (OCT) Polymorphisms and Response to Biguanides

Eleven *OCT1* (*SLC22A1*) and two *OCT2* (*SLC22A2*) polymorphisms did not change the response to metformin.[63]

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Table II. Allele frequencies for studied candidate genes

Gene and allele	Frequency (%)	Population	References
*CYP2C9**2	10.7–15.0	Caucasians	51-55
	0	Korean, Chinese	56-58
*CYP2C9**3	7.4–9.8	Caucasians	51-54
	1.1	Korean	56
	1.7–4.9	Chinese	57,58
CYP2C19 PM	12.6	Korean	59
	11.1–17.65	Chinese	60
*CYP2C8**3	13	Caucasians	61
SLCO1B1 −11187A	14.3–17.7	Finnish	27,62
OCT1 Val408	0.19–0.28	Japanese/T2DM	63
SUR1 16−3T/C (T allele)	47	Caucasians/T2DM	64
SUR1 C/T exon 18 (T allele)	3	Caucasians/T2DM	64
SUR1 combined alleles	4	Caucasians/T2DM	64
IRS1 ARG972	9.8–22.6	Caucasians/T2DM	65
PPARG Ala12	10	Caucasians/T2DM	66
PPARGC1A Ser482	35.6	Danish/metabolic syndrome	67
ADIPOQ +45G	31.3	Korean/T2DM	42
	19.4	Caucasian/IGT	50
ADIPOQ +276T	28.3	Korean/T2DM	42
	50.8	Caucasian/IGT	50
KCNJ11 Lys23	61.5	Caucasian/T2DM	37
HNF1A	5.2	Caucasian/MODY3	68

ADIPOQ = adiponectin; **CYP** = cytochrome P450; ***HNF1A*** = hepatocyte nuclear factor-1α; **IGT** = impaired glucose tolerance; ***IRS1*** = insulin receptor substrate-1; **MODY3** = maturity onset diabetes of the young – type 3; ***OCT*** = organic cation transporter; **PM** = poor metabolizer; ***PPARG*** = peroxisome proliferator-activated receptor-γ 2; ***PPARGC1A*** = PPARγ coactivator 1α; ***SUR1*** = sulfonylurea receptor 1; **T2DM** = type 2 diabetes mellitus.

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3. Candidate Genes Affecting Pharmacodynamics

3.1 *SUR1* Polymorphisms and Response to Sulfonylureas

Sulfonylurea receptor 1 (SUR1; also known as ABCC8 [ATP-binding cassette, subfamily c, member 8]) is a subunit of the pancreatic β-cell K (ATP) channel and plays a key role in the regulation of glucose-induced insulin secretion.[72] SUR1 polymorphisms may bind sulfonylureas with different affinity, which might explain the difference in response.

An influence of the *SUR1* intron 16−3T/C polymorphism and the impact of sulfonylurea therapy on plasma insulin, glucose, and triglyceride concentrations could not be detected in subjects with type 2 diabetes.[31,32] However, there was a significant reduction of insulin response in diabetic subjects carrying the combined genotype, silent exon 18 Thr775Thr (ACC→ACT) and intron 16−3T/C of the *SUR1* gene,[33] after tolbutamide administration. Carriers of the *SUR1* −437A/T polymorphism did not differ from noncarriers in glucose- or tolbutamide-stimulated insulin response during a glucose tolerance test with intravenous tolbutamide injections;[34] children with diffuse SUR1−/− hyperinsulinism, characterized by two abnormal *SUR1* alleles, showed no acute insulin response to tolbutamide.[35]

3.2 Insulin Receptor Substrate-1 (*IRS1*) Polymorphisms and Response to Sulfonylureas and Biguanides

Insulin receptor substrate-1 (IRS1), a member of the IRS protein substrate family, is considered to play a role in the insulin signaling pathway.[73] This receptor substrate can be activated by several sulfonylureas.

The Arg972 allele of the *IRS1* Gly972Arg polymorphism was associated with an increased risk of nonresponse to sulfonylurea therapy.[36] This polymorphism also modified the response to metformin. In subjects without the variant allele, metformin lowered fasting insulin levels and insulin resistance more effectively and significantly than in carriers of the Arg972 allele.[44]

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3.3 Peroxisome Proliferator-Activated Receptor-γ Polymorphisms and Response to Thiazolidinediones and Acarbose

Peroxisome proliferator-activated receptor-γ (PPARγ) receptors are found in key target tissues for insulin action, such as adipose tissue, skeletal muscle, and liver. Studies indicate that these receptors are important regulators of adipocyte differentiation, lipid homeostasis, and insulin action.[74] This receptor is the target receptor for thiazolidinediones compounds, which are a class of insulin-sensitizing drugs used in the treatment of type 2 diabetes.[5] The PPARγ coactivator 1α (PGC-1α) activates PPARγ and regulates the determination of muscle fiber type,[75] controls insulin sensitive glucose transporter expression in muscle cell,[76] and phosphoenolpyruvate carboxykinase and glucose-6-phosphatase in the liver.[77] The Gly482Ser polymorphism in the *PPARG* gene has been reported to be associated with type 2 diabetes.[78]

The response to pioglitazone[38] and troglitazone[40] was not modified by the presence of the *PPARG* Pro12Ala polymorphism. In contrast, patients with impaired glucose tolerance who also had the homozygous wild-type (Pro/Pro) genotype showed a higher conversion to type 2 diabetes compared with other genotypes while treated with troglitazone[39] or acarbose.[49] Acarbose also prevented the development of diabetes among carriers of the Ser482 allele of the Gly482Ser polymorphism of the PPARγ coactivator 1α (*PPARGC1A*) gene. Treatment with rosiglitazone significantly decreased hemoglobin A_{1c} (HbA_{1c}) levels in Korean subjects with the *PPARG* Ala12 allele, compared those without this allele.[41]

3.4 Adiponectin Polymorphisms and Response to Thiazolidinediones and Acarbose

Adiponectin (ACDC; ADIPOQ) is a protein secreted by adipocytes and is known to be a potent insulin sensitizer. A low fasting adiponectin concentration is associated with low insulin-stimulated skeletal muscle insulin receptor tyrosine phosphorylation. Although *ADIPOQ* gene expression in adipose tissue is associated with obesity, insulin resistance, and type 2 diabetes, hypoadiponectinemia is more strongly related to the degree of insulin resistance than the degree of adiposity or glucose intolerance.[79] Genetic polymorphisms may be involved in the regulation of adiponectin.[80]

Carriers of the GG genotype for *ADIPOQ* +45T/G polymorphism showed smaller reductions in fasting plasma glucose level and HbA_{1c} value after rosiglitazone treatment than heterozygotes and those without the polymorphism.[42] No association was found between the *ADIPOQ* +45T/G polymorphism and conversion to type 2 diabetes among acarbose-treated patients with impaired glucose tolerance.[50] However, the TT genotype of the *ADIPOQ* +276G/T polymorphism was associated with a higher risk of type 2 diabetes than the GG genotype in all subjects treated with acarbose.

3.5 *KCNJ11* Polymorphisms and Response to Sulfonylurea and Biguanides

The K_{ATP} channel is comprised of four pore-forming inwardly rectifying potassium channel (Kir channel) 6.2 subunits and four regulatory sulfonylurea receptor (SUR) subunits. Kir6.2 is found in the pancreatic β-cell, cardiac and skeletal muscle, and nonvascular smooth muscle. *KCNJ11*, encoding Kir6.2, has been shown to be associated with both type 2 diabetes and cardiovascular disease in several populations.[81]

Carriers of the Lys23 variant allele of the *KCNJ11* Glu23Lys polymorphism more often showed secondary failure to sulfonylurea[37] (secondary failure is defined as requiring insulin due to uncontrolled hyperglycemia after adding metformin to the therapy of patients whose plasma glucose rose to >300 mg/dL after 3 months of SU treatment). Lys23 allele carriers had a tendency toward a shorter duration of therapy with oral agents before sulfonylurea failure compared with subjects who were homozygous for the wild-type Glu23 allele. Those who were homozygous for the Lys23 variant allele responded less well to the protective effect of metformin than Glu23 homozygotes.[45]

3.6 Transcription Factor-7-Like 2 (*TCF7L2*) Polymorphisms and Response to Sulfonylureas and Biguanides

Transcription factor-7-like 2 (*TCF7L2*) is one of the most important type 2 diabetes susceptibility genes.[82] Genetic variants in the gene encoding *TCF7L2* have been associated with type 2 diabetes and impaired β-cell function, but the mechanisms remains unknown. It has been suggested that risk alleles, such as Rs12255372T and Rs7903146T, increase *TCF7L2* expression in the pancreatic β cell, reducing insulin secretion and predisposing the individual to diabetes.[82,83]

Carriers of a risk allele have been found to respond less to sulfonylurea treatment and had a higher risk for failure to sulfonylurea. The response to metformin was not found to be modified by this polymorphism.[48]

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4. Candidate Genes in the Causal Pathway

4.1 Hepatocyte Nuclear Factor-1α (HNF-1α) Polymorphisms and Response to Sulfonylureas and Biguanides

Hepatocyte nuclear factor-1α (HNF-1α) constitutes part of a network of transcription factors controlling organ-specific gene expression during embryonic development and in adult tissues. HNF-1α is expressed in the pancreatic β-cell, and mutations in this gene lead to β-cell dysfunction and maturity onset diabetes of the young – type 3 (MODY3). MODY3 diabetes is the most common form of MODY in many countries.[84] The presence of two defective *HNF1A* alleles is assumed to be lethal in humans. Heterozygous carriers may be more sensitive to sulfonylureas.

The plasma insulin responses to glucose and tolbutamide in *HNF1A* mutation carriers was decreased.[47] Normoglycemic as well as recently diagnosed diabetic *HNF1A* mutation carriers showed a normal response to sulfonylureas.

The response of fasting glucose and fructosamine to treatment with gliclazide was better in diabetes associated with several mutations in the *HNF1A* gene than in patients with type 2 diabetes.[46] The fall in fasting plasma glucose in response to gliclazide was 3.9-fold larger in *HNF1A* diabetic patients than in type 2 diabetic patients. No difference was found in the glucose-lowering response to metformin between *HNF1A* diabetes patients and type 2 diabetic patients.[46]

4.2 Lipoprotein Lipase Polymorphism and Response to Thiazolidinediones

Lipoprotein lipase (LPL) is an enzyme that plays a central role in lipid metabolism. LPL catalyzes the hydrolysis of triglycerides, providing free fatty acids for cells and affecting the maturation of circulating lipoproteins.[43,85] It has been proposed that the enzyme plays a role in the development of obesity and atherosclerosis.[86]

The presence of one defective allele of the *LPL* Ser447X polymorphism was associated with lower response rate to pioglitazone. In contrast, subjects homozygous for the normal Ser447 allele had a more significant decrease in blood pressure after pioglitazone treatment than S447X genotype carriers.[87]

5. Discussion

The published literature suggests that pharmacogenetics could play an important role in the treatment of patients with diabetes. Several studies have indicated a pharmacogenetic interaction between blood glucose-lowering medication and genetic polymorphisms.

The most often studied genes were related to pharmacokinetics, such as the CYP450 complex genes, OCTs and OATs (see table III). Most of these studies reported a decrease in drug clearance when subjects had the variant gene, whereas no effects were seen on insulin secretion and blood glucose levels.

The published studies focused mainly on a small number of SNPs in a small number of genes, so it is not surprising that appropriate genes, SNPs, or haplotypes of major importance have not yet been identified. In many cases it is also unclear in which tissue a given polymorphism exerts its effect to influence the phenotype of interest.

When comparing the study population of the abovementioned studies, questions concerning study power, false-positive findings, and ethnic-specific effects may rise. Since the majority of the pharmacogenetic studies involved very small numbers of participants, it is not surprising that contradictory results with regard to some polymorphisms have been reported. While some studies were not able to show an interaction, others might suffer from false-positive results due to the small numbers of subjects and the potentially small contribution of any given polymorphism to blood glucose lowering. Except for a few studies, most studies were performed among Caucasians. Since the frequency of some polymorphisms is related to ethnicity, the results seen in the studied population should be interpreted with care.

Notably, many pharmacokinetic studies used healthy subjects. One can imagine that certain drugs have different effects in healthy individuals compared with diabetic patients. Also environmental factors and gene-gene interactions were not always taken into account. This is very important since it is known that diabetes is a multifactorial disease and several environmental factors can reveal or facilitate the phenotypic expression of susceptibility genes. These interactions may help to find other possible candidate genes and drug targets.

Unfortunately, it is not yet possible to predict individual patient responses to blood glucose-lowering medicines based on their genetic background. New candidate genes are ready to be investigated and several interactions with other genes and the environment are becoming clearer. However, the magnitude of the genetic effects is still not known, making it difficult to calculate the required number of study participants needed to obtain conclusive results.

Genes involved in pancreatic development and in the control of insulin secretion have been linked to an increased risk to develop diabetes. Several loci have been found which contain genes potentially involved in β-cell development or function, such as those encoding insulin degrading enzyme (*IDE*), hematopoietically expressed homeobox protein (*HHEX*), and kinesin family member 11 (*KIF11*).[88] Genes encoding factors involved in hypertension

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Table III. Gene-drug interactions stratified according to pathway of drug response. Results presented are comparisons between carriers of the variant allele vs wild-type unless stated otherwise

Drug class	Drug	Parameter	Genes		
			pharmacokinetic pathway	pharmacodynamic pathway	causal pathway
Sulfonylurea	Sulfonylurea derivatives	Hypoglycemia	↑ (*CYP2C9**3)		
		Insulin response		↔ (*SUR1*)	
		Secondary failure[a]		↑ (*IRS1*, *KCNJ11*)	
		Early failure[b]		↔ (*SUR1*)	
	Tolbutamide	Clearance	↓ (*CYP2C9**2/*3)		
		Blood glucose	↔ (*CYP2C9**2/*3)		
		Insulin response	↔ (*CYP2C9**2/*3)	↔ ↓ (*SUR1*)	↔ (*HNF1A*)
	Glyburide	Clearance	↓ (*CYP2C9**3)		
		Blood glucose	↔ (*CYP2C9**2) ↓ (*CYP2C9**3)[c]		
		Insulin secretion	↔ (*CYP2C9**2) ↑ (*CYP2C9**3)[c]		
	Glimepiride	Clearance	↓ (*CYP2C9**3)		
		Blood glucose	↔ (*CYP2C9**2/*3)		
	Chlorpropamide	Clearance	↓ (*CYP2C9**3)		
	Gliclazide	Fasting plasma glucose			↓ (*HNF1A*)
Meglitinides	Nateglinide	Clearance	↔ (*CYP2C9**2, *CYP2D6**4/*5) ↓ (*CYP2C9**3)		
	Repaglinide	Clearance	↓ (*CYP2C9**3, *CYP2C8**3)		
	Blood glucose		↔ (*CYP2D6**4/*5, *SLCO1B1*)		
Biguanides	Metformin	Fasting insulin level		↓ Noncarriers (*IRS1*)	
		Insulin resistance		↓ Noncarriers (*IRS1*)	
		Insulin response			↔ (*HNF1A*)
		HbA_{1c}		↔ (*SLC22A1*, *SLC22A2*)	
Thiazolidinediones	Pioglitazone	Blood glucose		↔ (*PPARG*)	
	Troglitazone	Blood glucose		↔ (*PPARG*)	
	Rosiglitazone	Fasting plasma glucose		↓↓ (*PPARG*) Less reduction (*ADIPOQ*)	
		HbA_{1c}		↓↓ (*PPARG*) Less reduction (*ADIPOQ*)	
α-Glucosidase inhibitors	Acarbose	Conversion to diabetes mellitus		↑ (*PPARG*) ↓ (*ADIPOQ*)	

a Secondary failure is defined as requiring insulin due to uncontrolled hyperglycemia after adding metformin in patients whose plasma glucose rose to >300 mg/dL after SU treatment.

b Early failure is defined as receiving insulin treatment in the first 5 years after diabetes diagnosis.

c In a Chinese population.

ADIPOQ = adiponectin; **CYP** = cytochrome P450; **HbA_{1c}** = hemoglobin A_{1c}; ***HNF1A*** = hepatocyte nuclear factor-1α; ***IRS1*** = Insulin receptor substrate-1; ***KCNJ11*** = inwardly rectifying potassium channel Kir6.2; ***PPARG*** = peroxisome proliferator-activated receptor-γ 2; ***SLC22A1***, ***SLC22A2*** = solute carrier family 22 (organic cation transporter), members 1 and 2; ***SLCO1B1*** = solute carrier organic anion transporter family, member 1B1 ***SUR1*** = sulfonylurea receptor 1; ↓ indicates decreased; ↑ indicates increased, ↔ indicates no effect.

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and obesity, including *ADIPOQ*, leptin receptor (*LEPR*), and guanine nucleotide-binding protein β3 (*GNB3*) have also been shown to play a role in the development of diabetes.[89,90] These genes may also play a role in the response to glucose-lowering drugs.

6. Conclusion

The clearest pharmacogenetic associations have been found between the Ileu359Leu variant of the *CYP2C9* gene (*CYP2C9**3) and clearance of sulfonylureas. Polymorphisms in several receptor genes were related to reduced response to treatment with different glucose-lowering drugs, including sulfonylureas (*IRS1*, *KCNJ11*), metformin (*IRS1*), rosiglitazone (*PPARG*, *ADIPOQ*), and acarbose (*PPARG*, *ADIPOQ*).

Future pharmacogenetic studies of glucose-lowering drugs should focus more specifically on patients with diabetes, as the response to oral antidiabetic medications differs between diabetic and nondiabetic individuals. Population structure should also be considered such that false genotype-phenotype associations are avoided. Recently a few solutions have been proposed to deal with this kind of bias, such as genomic control and structured association methods.[91] Population-based genome-wide screening for pharmacogenetic studies has recently become feasible with advances in genome-wide genotyping.[88,92] Currently, studies in which several SNPs are typed in multiple candidate genes are the most feasible to study interactions between oral antidiabetics and genetic polymorphisms. Such methods should contribute greatly to the discovery of the genes that play a role in antidiabetic drug response.

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