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SLCO1B1 c.521T>C gene polymorphism decreases hypoglycemia risk in sulfonylurea-treated type 2 diabetic patients

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Abstract

Objectives: Pharmacogenomics can explain some of the heterogeneity of sulfonylurea (SU)-related hypoglycemia risk. Recently, a role of OATP1B1, encoded by *SLCO1B1* gene, on SU liver transport prior of metabolism has been uncovered. The aim of the present study was to explore the potential association of *SLCO1B1* c.521T>C polymorphism, leading to reduced OATP1B1 function, with SU-related hypoglycemia risk.

Methods: Study cohort consists of 176 type 2 diabetes patients treated with the SUs glimepiride or gliclazide. 92 patients reported SU-related hypoglycemia, while 84 patients had never experienced a hypoglycemic event. Patients were previously genotyped for *CYP2C9* *2 and *3 variant alleles that lead to decreased enzyme activity of the SU metabolizing enzyme CYP2C9 and have been associated with increased SU-related hypoglycemia risk. *SLCO1B1* c.521T>C polymorphism was genotyped by use of PCR-RFLP analysis.

Results: *SLCO1B1* c.521TC genotype frequency was significantly lower in hypoglycemic cases than non-hypoglycemic controls (15.2% vs. 32.1%, p=0.008). In an adjusted model, c.521TC genotype significantly reduced the risk of hypoglycemia (OR 0.371; 95% C.I. 0.167–0.822; p=0.015). In CYP2C9 intermediate metabolizers (n=54) c.521TC genotype frequency was significantly decreased in cases compared to controls (3 out of 36 cases, 8.3% vs. 7 out of 18 controls, 38.9%, p=0.012). A similar albeit not significant difference of *SLCO1B1* c.521TC genotype was present in CYP2C9 extensive metabolizers (n=120) (18.2% in cases vs. 30.8% in controls, p=0.113).

Conclusions: We have found a protective effect of *SLCO1B1* c.521C variant on SU-related hypoglycemia risk both independently and in interaction with CYP2C9 phenotypes. Our results suggest a possible linkage of *SLCO1B1* c.521T>C polymorphism with variants in other genes impairing OATPs expressed in pancreatic islets that could interfere with SU tissue distribution.

Keywords: *CYP2C9*; gliclazide; glimepiride; hypoglycemia; pharmacogenomics; *SLCO1B1*; sulfonylureas.

Introduction

Sulfonylureas (SUs) were the mainstay of type 2 diabetes mellitus (T2DM) treatment since 1950s. Nowadays, in the presence of newer classes of antidiabetic drugs, SUs are still included in international guidelines, however, they are classified in the range of second-line options for add-on to metformin [1–3]. Despite their glucose lowering potency, the choice of SUs highly depends on individualized risk for hypoglycemia and weight gain. Towards SU therapy individualization, pharmacogenomics can explain some of the heterogeneity of SU-related hypoglycemia risk [4]. We and others have shown that in SU-treated T2DM patients impaired drug metabolism due to *CYP2C9* gene polymorphisms increases the risk of experiencing hypoglycemic events [5–10]. Identifying additional gene polymorphisms associated with SU-related hypoglycemia holds promise to improve T2DM patient therapy with these agents.

Hepatic metabolism of SUs is indeed a major factor of drug response variability since impaired SU metabolism prolongs drug action and leads to hypoglycemic events. During last decade, evidence emerged that OATP1B1 encoded by *SLCO1B1* gene can transport into liver a wide variety of drugs, including some oral antidiabetics, such as the meglitinides repaglinide and nateglinide and the SUs gliclazide and glimepiride. *SLCO1B1* is a well characterized

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gene comprised of variations with actionable pharmacogenomic modifications. Among *SLCO1B1* identified polymorphisms, c.521T>C (rs4149056, p.Val174Ala), found in *SLCO1B1**5 and *15 haplotypes, leads to significantly impaired transport activity toward several OATP1B1 substrates [11, 12] and is highly associated with statin induced myopathy [13, 14].

The field of *SLCO1B1* antidiabetic pharmacogenomics is in its infancy; only a few studies exist on *SLCO1B1* c.521T>C impact on meglitinide (repaglinide and nateglinide) pharmacokinetics [15–17] and thiazolidinedione response [18–20], whereas the potential effect of *SLCO1B1* c.521T>C polymorphism on SU disposition is even less studied. During the last 5 years, it was shown that gliclazide and glimepiride are substrates of OATP1B1 [21] and their transport by OATP1B1 is affected *in vitro* by *SLCO1B1* genotypes [22]. In HEK293T cells OATP1B1*5 and OATP1B1*15 mutants present with significantly decreased transport capacity of gliclazide and glimepiride compared with the OATP1B1*1a normal function allele [22]. Additionally, for glimepiride pharmacokinetics, an effect of *SLCO1B1* c.521TC genotype towards higher maximum plasma concentration and area under the plasma concentration-time curve was found in healthy volunteers when glimepiride was co-prescribed with rosuvastatin, a known OATP1B1 inhibitor [23]. More recently, in T2DM patients treated with SUs, including gliclazide and glimepiride, rs10770791, a *SLCO1B1* reduced function intronic variant, was associated with increased HbA1c reduction [24]. These results indicate that OATP1B1 has affinity for the SUs gliclazide and glimepiride and *SLCO1B1* c.521T>C polymorphism is potentially implicated in SU response.

Triggered by these findings, in the present study we aimed to assess the effect of *SLCO1B1* c.521T>C polymorphism on SU response. We have hypothesized that reduced SU transport into the liver due to *SLCO1B1* c.521C allele potentially leads to increased drug plasma concentration available at the site of action (pancreas) and this could lead to an increased pharmacological response and, thus, increased SU-related hypoglycemia risk. We have tested our hypothesis in a well characterized patient cohort of T2DM patients treated with the SUs gliclazide and glimepiride who were classified as having experienced or not any SU-associated hypoglycemic event.

Materials and methods

The study group has been described in detail in previous pharmacogenomic-association studies from our laboratory [6, 25–27]. In brief, it consists of 176 T2DM patients (61 male/115 female) treated with the SUs gliclazide (n=22) or glimepiride (n=154). 92 patients had reported drug-associated hypoglycemia and were classified as cases, while 84 had never experienced a hypoglycemic event and were the control group. All patients participated after being informed about the study by their clinician and giving informed consent. The study protocol was approved by the Scientific Council and the Ethics Committee of the Academic General Hospital of Alexandroupolis and was conducted according to Declaration of Helsinki.

SLCO1B1 c.521T>C genotype determination was performed using a PCR-RFLP method as described elsewhere [28]. All PCR amplifications were carried out in Nexus Mastercycler (Eppendorf, Germany).

Relative frequencies of genotypes and alleles were calculated for each group and a χ^2 test was used to compare their distribution between hypoglycemic and non-hypoglycemic T2DM patients. Comparisons for categorical data between two groups were performed by using χ^2 test. To estimate the risk of hypoglycemia associated with *SLCO1B1* c.521T>C, odds ratio (OR) was calculated using logistic regression analysis after adjustment for other factors known to affect this condition including patient genotypes for *CYP2C9*. A p value of less than 0.05 or less after Bonferroni correction for multiple comparisons, where applicable, was considered statistically significant. *Post-hoc* power calculation with a preset level of significance (p=0.05) was performed. Analyses were carried out with the use of SPSS software package (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp).

Results

Characteristics of patient cohort both in total as well as after stratifying patients in cases and controls have been extensively described in previous work published by our group [6, 25–27]. In brief, cases and controls were age- and gender-matched and did not differ in other variables such as body mass index (BMI), duration of T2DM, HbA1c, renal impairment or SU mean daily dose.

In the entire cohort of T2DM patients, 135 patients (76.7%) carried c.521TT genotype, 41 patients (23.3%) were c.521TC heterozygous, whereas c.521CC homozygous genotype was not present in the studied population (Table 1). *SLCO1B1* genotypes were in Hardy-Weinberg equilibrium (χ^2 3.059, p=0.217). Between hypoglycemic cases and non-hypoglycemic controls, *SLCO1B1* c.521TC genotype frequency was significantly lower in cases than controls (15.2% vs. 32.1%, p=0.008) (Table 1). Patient cohort was further divided according to their CYP2C9 genotype-derived phenotype into extensive (EMs), intermediate (IMs) and poor metabolizers (PMs). In CYP2C9 EMs, *SLCO1B1* c.521TC genotype frequency was decreased in cases compared to controls (10 out of 55 cases, 18.2% vs. 20 out of 65 controls, 30.8%), however this difference did not reach statistical significance (p=0.113) (Table 2). In CYP2C9 IMs c.521TC genotype frequency was significantly decreased in cases compared to controls (3 out of 36 cases,

8.3% vs. 7 out of 18 controls, 38.9%, p=0.012 after Bonferroni correction) (Table 2). Our study detected a statistically significant difference of 30.6% in the frequency of *SLCO1B1* TC genotype between hypoglycemic cases and non-hypoglycemic controls in CYP2C9 IMs with 75.7% power. Due to low sample size of CYP2C9 PMs (n=9) frequency of c.521T>C genotypes was not analyzed between two groups.

Logistic regression analysis with hypoglycemia status as the dependent variable and *SLCO1B1* c.521T>C genotypes as contributing variable estimated that *SLCO1B1* c.521TC genotype reduces significantly the risk of hypoglycemia in a model adjusted for age, sex, BMI, T2DM duration and renal impairment (OR 0.371; 95% C.I. 0.167–0.822; p=0.015). When further adjusting the regression model for CYP2C9 genotype-derived phenotypes, a similar association with decreased hypoglycemia risk derived (OR 0.366; 95% C.I. 0.164–0.818; p=0.014). When analysis was restricted in CYP2C9 IMs, *SLCO1B1* c.521TC genotype reduced significantly the risk of hypoglycemia (OR 0.106; 95% C.I. 0.017–0.670; p=0.017).

Discussion

In the present study, we investigated the potential association of *SLCO1B1* c.521T>C polymorphism with SU-related hypoglycemia. We have initially hypothesized that reduced OATP1B1 SU transfer into liver could be associated with increased drug concentration and increased risk for SU-related hypoglycemia. Surprisingly, we have found a significant association of *SLCO1B1* c.521TC genotype with reduced hypoglycemia risk both independently as well as in interaction with CYP2C9 genotype-derived impaired phenotypes. Moreover, the hypoglycemia protective effect exerted by c.521TC genotype could discriminate CYP2C9 IMs who did not report any hypoglycemic event.

OATP1B1 is a genetically polymorphic influx transporter almost exclusively expressed in liver and it mediates the hepatic uptake of many endogenous compounds and xenobiotics [12]. *SLCO1B1* c.521T>C polymorphism is a well characterized pharmacogenomic marker associated with statin-induced myopathy [12, 14]. However, the potential impact of *SLCO1B1* c.521T>C polymorphism on oral antidiabetic response is far less studied.

For SUs, it appears that the affinity of different OATPs varies according to substrate. Results from *in vitro* studies assessing the affinity of OATP1B1 to SUs support that gliclazide and glimepiride, the drugs administered in our patient cohort, are substrates of OATP1B1 [21, 22]. For these two drugs, an effect of *SLCO1B1* c.521C reduced function allele towards reduced gliclazide and glimepiride clearance has been shown *in vitro* [22]. Currently, there is a sole study published on the effect of *SLCO1B1* polymorphisms on glycemic response to SUs in T2DM patients treated with the SUs gliclazide, glipizide, glyburide (glibenclamide), glimepiride, tolazamide and tolbutamide [24]. Results showed

Table 1: Frequencies of *SLCO1B1* c.521T>C genotypes in T2DM patients having experienced or not at least one hypoglycemic event.

SLCO1B1 genotype	Sulfonylurea treated diabetic patients (n=176)	C.I. (95%)	Sulfonylurea treated diabetic patients with hypoglycemia (n=92)	C.I. (95%)	Sulfonylurea treated diabetic patients without hypoglycemia (n=84)	C.I. (95%)	p-Value
TT	135 (76.71%)	70.06–82.48	78 (84.78%)	76.42–91.00	57 (67.86%)	57.40–77.11	0.008
TC	41 (23.29%)	17.52–29.94	14 (15.22%)	9.00–23.58	27 (32.14%)	22.89–42.60	
C Allele, MAF	41 (11.65%)	8.61–15.31	14 (7.61%)	4.43–12.11	27 (16.07%)	11.12–22.18	0.013

M, minor allele frequency.

Table 2: Frequencies of *SLCO1B1* c.521T>C genotypes in T2DM patients having experienced or not at least one hypoglycemic event in different CYP2C9 genotype based metabolic status.

CYP2C9 genotype-derived phenotype	*SLCO1B1* c.521T>C genotype	Sulfonylurea treated diabetic patients with hypoglycemia	C.I. (95%)	Sulfonylurea treated diabetic patients without hypoglycemia	C.I. (95%)	p-Value
EM (n=120)	TT	45 (81.8%)	70.1–90.3	45 (69.2%)	57.4–79.4	0.113
	TC	10 (18.2%)	9.8–29.9	20 (30.8%)	20.6–42.6	
IM (n=54)	TT	33 (91.7%)	79.4–97.6	11 (61.1%)	38.3–80.6	0.012[a]
	TC	3 (8.3%)	2.4–20.6	7 (38.9%)	19.4–61.7	

[a]After Bonferroni correction for multiple comparisons.

that an intronic *SLCO1B1* polymorphism, rs10770791T>C, leading to reduced expression of SLCO1B1 mRNA in the liver, was associated with greater reduction in HbA1c [24]. In the same study, *SLCO1B1* rs10770791T>C polymorphism was found to be in partial linkage disequilibrium (LD) with c.521T>C variation. When authors performed conditional analysis, *SLCO1B1* c.521T>C polymorphism was not associated with SU response whereas SU-related hypoglycemia was not studied [24].

For other antidiabetics, currently, three studies have been published on *SLCO1B1* c.521T>C polymorphism association on meglitinide pharmacokinetics, showing that *SLCO1B1* c.521C allele carriage leads to increased Cmax or AUC of repaglinide and nateglinide [15–17]. All studies, however, included heathy volunteers who were given a single oral dose of meglitinides. More recently, in a published report describing the case of a patient experiencing severe hypoglycemia while on an extremely low dose of repaglinide, the authors conclude that delayed elimination of repaglinide might have derived, among other factors, from reduced hepatocyte uptake due to inhibitory effects of nilotinib on OATP1B1 [29].

To the best of our knowledge this is the seminal study assessing the effect of *SLCO1B1* c.521T>C polymorphism with SU-related hypoglycemia in T2DM patients. Our results do not confirm the hypothesis that implicates impaired OATP1B1 function with increased SU plasma levels that could substantially lead to hypoglycemia. Interestingly, according to our results, not only *SLCO1B1* c.521C allele protects the whole cohort from SU-related hypoglycemia, but, additionally, it discriminates CYP2C9 IMs who did not report any hypoglycemic event. The design of our study focuses on hypoglycemia incidence and other response endpoints have not been assessed.

It is challenging to explain these findings, especially since similar studies have not yet been performed. *SLCO1B1* c.521T>C polymorphism is a well characterized variant and its role on reduced OATP1B1 transport potency cannot be disputed. Our results, indicate that carriers of 521C allele may present with reduced insulin secretion despite potential increased drug plasma levels, however, OATP1B1 is considered to be solely expressed in liver. The potential association of OATPs with SU response potentially lies on their pancreatic tissue expression. Given the fact that OATP1B3 is expressed in pancreas [30], the SU target organ, and it mediates and enhances SU insulinotropic effect [31], we suggest that linked polymorphisms in *SLCO1B3* gene encoding for OATP1B3 transporter could be a hint in SU distribution in pancreas. Several variants have been identified in *SLCO1B3* gene that are associated with altered OATP1B3 function *in vitro* [32]. Evidence from *in vivo* studies suggests that *SLCO1B3* c.334T>G/c.699G>A haplotype leads to reduced uptake of OATP1B3 substrate mycophenolic acid [33, 34]. Functional significance of different *SLCO1B3* variants and haplotypes, as well as their potential linkage with *SLCO1B1* polymorphisms merits further investigation to clarify their impact on SU metabolism and distribution in pancreatic tissue. High transcript levels of OATP2B1 and OATP1A2, have also been observed in isolated human adult islets [30]. The pharmacological relevance of these transporters on SU therapy is unknown. Additionally, several OATPs, including OATP1B1, are overexpressed in pancreatic cancer [35, 36]. It cannot be excluded that OATP differential expression is present in diabetic pancreatic cells resembling that of pancreatic cancer since T2DM and cancer are linked through different biological mechanisms. According to the American Diabetes Association and the American Cancer Society consensus report, T2DM is associated with increased risk for some cancers, including pancreatic cancer, whereas hyperinsulinemia, hyperglycemia and inflammation are considered to be direct links between diabetes and cancer [37]. Thus, the possible linkage of *SLCO1B1* c.521T>C polymorphism with *SLCO1B3* variants reducing OATP1B3 function or expression in pancreatic β cells and the expression of different OATPs in diabetic islets should be further explored.

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