fortune Journals

Research Article

FORTUNE JOURNAL OF HEALTH SCIENCES

ISSN: 2644-2906

Genetic Polymorphism of the OCT1 Gene (SLC22A1) and Association with the Development of Gastro-Intestinal Side Effects in Patients with Type 2 Diabetes mellitus on Metformin Therapy at the Baptist Hospital Etoug-Ebe, Yaounde- Cameroon

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Abstract

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. In order to manage diabetes, oral antihyperglycemic drugs are recommended among which, metformin, which is the first-line therapy for the treatment of Type 2 Diabetes mellitus (T2DM) worldwide. Evidence has demonstrated that 20–30% of patients treated with metformin could develop gastrointestinal (GI) side-effects, which could be attributed to genetic polymorphism in the gene (SLC22A1) coding for the protein responsible for metformin transport (Organic cation transporter 1). This study aimed at investigating the association between the OCT1 gene polymorphism M420del (rs72552763) and the development of gastro-intestinal side effects in T2DM patients on metformin therapy in Yaoundé, Cameroon. A case-control study was carried out on 210 participants from the Etoug-Ebe Baptist hospital from whom informed consent was gotten. DNA was extracted from dried blood spots (DBS) on Whartman N^{0}3 filter paper using the Chelex 100 method. Genotyping of the OCT1 gene (M420del) was done using the PCR-RFLP. The Chi squared test (X^2) was used to establish associations and a p-value of <0.05 was considered statistically significant. The most predominant genotype was the homozygous mutant aa genotype (85.71%, 180/210) with respect to the heterozygous Aa genotype (14.29%, 30/210). No homozygous wild type (AA) observed amongst the study participants. Individuals possessing the aa genotype were 3 times more susceptible to development gastro-intestinal side effects (OR= 3.143, P=0.005). In conclusion, an association was found between the OCT1 gene polymorphism M420del and the development of GI side effects.

Keywords: OCT1, Gene polymorphism, T2DM, Metformin, Gastro-Intestinal Side Effects

Introduction

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. WHO guidelines classify diabetes in three main groups namely: Type 1 diabetes

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Received: October 07, 2024
Accepted: October 15, 2024
Published: October 29, 2024

which is as a result of the body's failure to produce enough insulin and requires daily administration of insulin, Type 2 Diabetes is the most common type of diabetes which is as a result of the body's ineffective use of insulin, and gestational diabetes is hyperglycemia, which occurs when blood glucose levels are above normal but below those that are indicative of diabetes (1). It is also very important to note that gestational diabetes can develop during pregnancy (2). In 2021, the International Diabetes Federation (IDF), estimated that 537 million people accounting for 10.5% of the global population have diabetes, and this number is projected to reach 643 million by 2030, and 783 million by 2045 (3). Also, according to the IDF, an estimated 24million adults aged 20–79 years were living with diabetes in the African region in 2021 representing a regional prevalence of 4.5%. The prevalence of age-adjusted (20–79 years) diabetes was 5.5% in Cameroon in the year 2021. Type 2 diabetes mellitus is the most common form encountered globally as it accounts for over 90% of all diabetes cases worldwide (3) making this disease one of today's main social and public health problems. In order to halt the rise in diabetes morbidity, the American Diabetes Association (ADA) suggest early diagnosis and treatment options to get the glucose level as close to normal as possible. Apart from healthy diet and regular physical exercise, the ADA recommends groups of anti-diabetic drugs for the treatment of diabetes among which is metformin, which is used as first line therapy for the treatment of T2DM worldwide (4) including Cameroon.

Metformin belongs to a class of medication called biguanides, which can be used as monotherapy or combined with other anti-diabetic medications such as sulfonylureas□-glucosidase inhibitors, DPP-4 inhibitors as well as GLP-1 agonists (5,6). Human insulin such as mixtard, a suspension for injection that contains human insulin can also be used to treat diabetes mellitus. Once these drugs get into the organism, the mechanism of action and different pathways taken can be used to appraise its safety and efficacy and the way it varies among individuals. Metformin is not metabolized but excreted unchanged in urine with a half-life of 5hrs and it is widely distributed into body tissues including intestine, liver and kidney by the organic cation transporters (5). There are three OCTs homologs: OCTs1, 2, and 3 (SLC22A1, 2, and 3) that were cloned and functionally characterized in the early–mid-1990s (7) which are made up of 553,555 and 556 amino acids respectively(8).

The hepatic uptake of metformin is mediated primarily by the organic cation transporter 1 (OCT1) encoded by the Solute Carrier family 22A member 1(SLC22A1) gene which is highly polymorphic and has been proven to cause pharmacokinetic variability and various glycemic response to metformin (4,9). However, some studies have shown four OCT1 variants: R61C (rs12208357), M420del (rs72552763), G401S (rs34130495), and G465R (rs34059508) responsible for the reduced metformin transport in vitro (4,9). Human OCT1 is encoded by the SLC22A1 gene which is located on chromosome 6q26, and consists of 11 exons spanning approximately 37 kb (9,10). Consequently, the reduced transport of metformin by OCT1 could increase metformin concentration in the intestine, resulting in increased risk of gastro intestinal (GI) intolerance and drug discontinuation (11). In a study by Gong *et al,* it was shown that, in OCT1 deficient mice, glucose lowering effects of metformin were completely abolished and it was found that the hepatic metformin concentration in the liver was significantly lower than in the control mice (5)Among these OCT1 gene reduced function variants is the Methionine deletion at codon 420; rs72552763 (M420del) which is one of the most frequent allelic variants associated with loss of function of OCT1. It is a 3-base pair deletion (ATG) at codon 420 of exon 7 (10).

Several studies have shown OCT1 gene (SLC22A1) polymorphism M420del (rs72552763) to be significantly associated with inflammatory diseases and in some, the development of GI side effects (12). The OCT1 gene polymorphism M420del has been found associated with treatment failure of other chronic non communicable diseases such as chronic myeloid leukemia with imatinib as drug and hepatocellular carcinoma (liver cancer) with sorafenib as drug (12). Till date few studies have been carried out to look at unknown associations between OCT1 gene polymorphism M420del (rs72552763) and the development of gastro-intestinal side effects. Thus, this study aimed at investigating the genetic polymorphism of the OCT1 gene and its association with the development of gastro-intestinal side effects in patients with type 2 Diabetes mellitus on metformin therapy at the Baptist Hospital Etoug-Ebe, Yaounde- Cameroon.

Materials and Methods

Study setting and location

This study was carried out at the Etoug-Ebe Baptist Hospital in Yaoundé. Yaoundé is the capital of the Centre Region in Cameroon (3°51′ N 11°29′ E) the second largest city of Cameroon with a population of more than 4 million. It has a surface area of about 180 km² and it lies in the Centre Region of the nation at an elevation of about 800 meters above sea level and surrounded by many hills with an average annual rainfall of 1628.3mm per year. It contains people from all works of life and people from all other 10 regions of the country. The city is located within the Congo-Guinean phytogeographic zone characterized by a typical equatorial climate with two rainy seasons extending from March to June and from September to November (1,13,14).

Study Population and Sampling

A total of 210 diabetic patients living in Yaoundé and

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visiting the Etoug-Ebe Baptist Hospital were conveniently recruited in the study with 90 diabetic patients with gastro-intestinal side effects and 120 without gastro-intestinal side effects as a case control study, after receiving their informed consent. Inclusion criteria involved: Having Type 2 Diabetes mellitus and on Metformin therapy with a confirmed HbA1c >7%. Also, patients must be followed up at the Etoug-Ebe Baptist Hospital. Pregnant women, participants under excessive alcohol and tobacco consumption and Type 2 Diabetes mellitus patients on metformin newly diagnosed for less than three months were not recruited in the study. After obtaining administrative authorization from the hospital, the register was scoured in the presence of the staff in order to have preliminary data of patients to be included in the study. The study was explained to chosen participants by the head of the diabetic unit. Patients were informed about the potential benefits followed by the administration of an informed consent form. The patients were then requested to fast for 8 hours over night prior to their day of appointment. Anthropometric parameters including data regarding GI side effects and fasting plasma glucose levels were gotten. Venus blood samples were also collected from study participants, from which dried blood spots were made using the Whartman N° 3-filter paper, air dried, labelled, sealed in sterile individual zip lock bags and stored at room temperature for further molecular analysis.

DNA Extraction and Genotyping

Human genomic DNA was extracted from dried blood spot on filter papers using Chelex boiling method as previously described (15). Determination of OCT1 gene polymorphism M420del (rs72552763) was performed according to a modified protocol reported by Ningrum *et al* (16). The primers 5'- AGGTTCACGGACTCTGTGCT -3' and 5'-AAGCTGGAGTGTGCGATCT -3' were used to amplify the OCT1 gene. In each PCR reaction tube, 0.25 µl each of forward and reverse primers (0.5µM), 2 µl genomic DNA, 10 µl One Taq® Hot Start 2X Master Mix with standard buffer (New England Biolabs, MA, USA.) and Nuclease free water up to 20 µl were added. The amplification cycle consisted of an initial denaturation and enzyme activation at 93˚C for 3 mins, followed by 35 cycles of denaturation at 93˚C for 45 seconds, annealing at 58˚C for 35 seconds, extension at 72˚C for 35 seconds followed by a final extension at 72˚C for 5 mins. The Amplification of target gene fragments was performed using a T3 Thermocycler (Biometra, UK). The products were enzymatically digested by 1 µl BspHI (10 U/µl) restriction endonuclease (New England Biolabs) at 37˚C overnight, which cuts T-CATGA sequence at the 197th base. The products were then electrophoresed in 1.5% agarose gel containing DNA staining dye (Ethidium bromide) and visualized by ultraviolet light using a transilluminator device. The Wildtype allele (A) presents as a single band at 600 bp. The Mutant allele (a) cuts into two fragments of 197 and 403 bp. Accordingly, a/a subjects exhibit a 600 bp band, A/A exhibit 197 and 403 bands and heterozygote subjects exhibit all three bands (16).

Statistical Analysis

Data from this study were transcribed from laboratory worksheet records unto Microsoft Excel, version 2016. Categorical data are presented as number (percentage) and quantitative data are summarized as the mean ± standard deviation of the mean. Allele frequencies were calculated using the Hardy-Weinberg formula. Data were analysed using the IBM SPSS biostatistics version 20.0 software (SPSS, Chicago, IL). Chi Square test (X^2 test) was used to establish associations between this SNP and Gastro-Intestinal side effects. Where the number of expected observations was less than 5, the Fisher's test was used and the Odds ratio was calculated using a confidence interval of 95% (17). The significance level was considered to be α=0.05 and $p < 0.05$ was considered to indicate a statistically significant difference.

Ethical Considerations

This study received ethical approval from the Regional Ethics Committee for Human Health Research (CRECRHH) under the ethical clearance document number CE N00065/CRECRHC/2018. Institutional approval letter was gotten from the Institutional Review Board of the Cameroon Baptist Health Board, Institutional Review Board document number IRB2022-62. The potential risks and benefits as well as data privacy and confidentiality were explained to all participants. Only those who signed the informed consent form were included in the study.

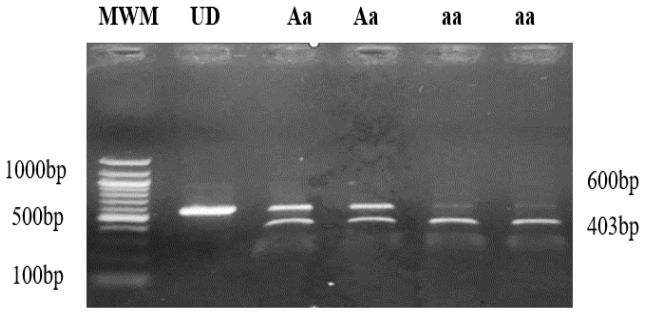

Figure 1: Electrophoresis of OCT1 gene polymorphism M420del (rs72552763) with BspHI enzyme. Aa; heterozygous, aa; homozygote mutant and with no homozygote wildtype AA. DNA size markers (MWM) 100bp and Undigested product UD.

Results

Evaluation of Demographic and clinical characteristics of study Participants

In the current study, a population of 210 diabetic patients was evaluated for OCT1 M420del (rs72552763) SNP,

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DOI:10.26502/fjhs.226

comprising 90 diabetic patients with gastro-intestinal side effects and 120 control patients. The gastro-intestinal side effects group consisted of 22 males and 68 females with a mean age of 59.69±11.34, and the control group included 30 males and 90 females with a mean age of 58.67±8.44. As presented in Table 1, there was no significant difference between the mean age of diabetic patients with gastro-intestinal side effects and that of the controls (P=0.473). Again, no differences were observed between the two groups in terms of sex distribution and fasting blood sugar measurements. Among the Gastro-intestinal side effects, abdominal pain was the most frequent (n=52), followed by nausea (n=38) and diarrhea (n=38). Other GI side effects were vomiting (n=14), constipation (n=8) and bloating (n=24), Figure 2. Diabetic patients with gastro-intestinal side effects exhibited higher diastolic blood pressure (HDBP compared with the controls (81.02±10.49 vs. 78.45±17.32, P=0.184), Table 1.

Genotype and Allele Frequency of OCT1 M420del (rs72552763) SNP

Results from genotyping were as follows: OCT1 M420del (rs72552763) SNP revealed the distribution of Aa (20, 22.22%), and aa (70, 77.78%) in the diabetic patients with GI side effects group and Aa (10, 8.33%), and aa (110, 91.67%) in the controls group. No AA genotype was observed amongst the study participants in both groups. The mutant allele a, was the most predominant in our study population (390, 92.86%) and in both groups (Table 2).

Association between OCT1 gene Polymorphism M420del (rs72552763) and development of Gastro-Intestinal side effects

Results from the association analysis (χ^2 test) showed statistical significance between the GI side effects group and control group. Participants possessing the aa genotype were 3 times at risk of developing Gastro-Intestinal side effects (OR=3.143, P=0.005) where as those possessing the Aa genotype had a reduced risk (OR=0.318, P=0.005). The presence of the wildtype allele A was found not to be a risk factor for the development of Gastro-Intestinal side effects (OR=0.318, P=0.005), as shown on Table 2.

Table 1: Demographic and clinical characteristics of study Participants

Variables		Total Population N=210	Gastrointestinal Side effects N=90	Controls N=120	P-Value
Age (Mean±SD)		59.10±9.78	59.69±11.34	58.67±8.44	0.473
Sex	Male	52(24.76%)	22(24.44%)	30(25.00%)	1
	Female	158(75.24%)	68(75.56%)	90(75.00%)	
FBS(Mean±SD)		176.61±65.14	183.20±25.34	176.92±56.44	0.49
SBP (Mean±SD)		134.50±21.68	135.31±19.19	133.90±23.43	0.642
DBP (Mean±SD)		79.55±14.81	81.02±10.49	78.45±17.32	0.184
BMI (Mean±SD)		25.47±4.86	25.42±4.86	25.49±5.00	0.915
Waist Circumference (Mean±SD)		95.99±17.97	95.25±19.24	96.53±17.01	0.608
Hip Circumference (Mean±SD)		108.11±14.40	109.17±14.73	107.31±14.14	0.354

SD=Standard Deviation, FBS=Fasting Blood Sugar, SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure, BMI=Body Mass Index

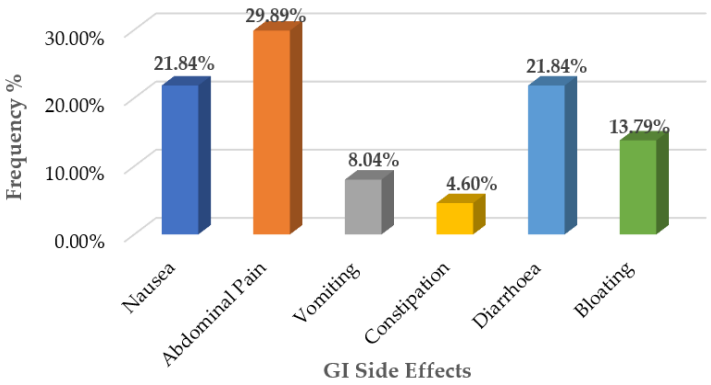

Figure 2: Frequency of Gastro-Intestinal Side Effects

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Table 2: Association between OCT1 gene Polymorphism M420del (rs72552763) and Gastro-Intestinal side effects

OCT1 Gene Polymorphism	Total Population N=210	Gastrointestinal Side effects N=90	Controls N=120	OR	95% CI	P-Value
Genotypes						
Aa	30(14.29%)	20(22.22%)	10(8.33%)	0.318	0.141-0.720	0.005*
aa	180(85.71%)	70(77.78%)	110(91.67%)	3.143	1.390-7.108	0.005*
Alleles						
A	30(7.14%)	20(11.11%)	10(4.17%)	0.318	0.141-0.720	0.005*
a	390(92.86%)	160(88.89%)	230(95.83%)	-	-	1

OCT1= Organic Cation Transporter 1, OR=Odds Ratio, CI=Confidence Interval

Discussion

Genetic variation in the genes that encode metformin transporters has been proven to cause pharmacokinetic variability and various glycemic response to metformin (16). These variability in metformin efficacy clearly suggest the implication of individual genetic imprints(18). Genetic variations in some drug transporters such as OCT1 can dramatically alter the pharmacokinetics and pharmacodynamics of many drugs consequently, the OCT1 genetic polymorphisms could affect metformin responses as variation in bioavailability and volume of distribution is a major source of variation in the pharmacokinetics of metformin. Furthermore, the gene encoding OCT1 is highly polymorphic, with a number of coding missense single nucleotide polymorphisms that affect its activity and function (18). It is therefore possible that the structural changes in OCT1 caused by any of these polymorphisms, or even a combination of both, may affect the function of the transporter protein (19). Therefore, the polymorphisms of OCT1 provide a genetic tool to study the in vivo role of OCT1 in pharmacokinetics and pharmacodynamics in humans (20). Four OCT1 variants, R61C (rs12208357), M420del (rs72552763), G401S (rs34130495), and G465R (rs34059508), showed reduced metformin transport in vitro (9). Consequently, the reduced transport of metformin by OCT1 could increase metformin concentration in the intestine, resulting in increased risk of gastro intestinal (GI) intolerance and drug discontinuation (11).

In this study we found the mutant allele a, and the aa genotype of M420del (rs72552763) SNP to be the most prevalent with frequencies of 92.86% and 85.71% respectively. The AA genotype was not found among our study participants. These findings are similar to that obtained among Japanese-Indonesian T2DM subjects and the 153 Han Chinese participants (16,21,22). Our findings are in contrast to studies involving 108 T2DM Iranian participants and 103 healthy Caucasian subjects respectively(23,24). These similarities could be attributed to ethnicity and lifestyle of these populations that can promote the development of mutations (17). In contrast to the majority of other functional SLC22A1 variants that are population specific, the M420 deletion can be found in some populations in different regions in the world. Also, studies have shown that the presence of M420del causes partial or complete loss of OCT1 function. In the case of metformin, the presence of M420del polymorphism causes a decrease in the activity of metformin transporter, leading to a reduced antihyperglycemic response as a result of a reduction in the metformin concentration transported to the hepatocytes as its action target (22). Moreover, many non-synonymous polymorphisms of SLC22A1, found primarily in white populations exhibit reduced activity in cellular assays. (25). In a study by Gong *et al* , it was shown that, in OCT1 deficient mice, glucose lowering effects of metformin were completely abolished and it was found that the hepatic metformin concentration in the liver was significantly lower than in the control mice(5). OCT1 is expressed on the basolateral membrane, intestinal clearance of metformin may be reduced in individuals with reduced function variants of OCT1 gene polymorphisms, particularly the R61C (rs12208357) and M420del (rs72552763) which are the most common OCT1 loss of function associated with metformin intolerance and thus, gastrointestinal side effects (26).

Further results from this study showed that individuals possessing the aa genotype were 3 times more susceptible to develop Gastro-Intestinal side effects (OR= 3.143, P=0.005), contrary to those possessing the Aa genotype (OR=0.318, P=0,005). These results are similar to that obtained in a study including an unspecified population of newly diagnosed T2DM patients on metformin which showed for the first time the association between OCT1 variants (R61C and M420del) and common metformin-induced gastrointestinal side effects (OR=2.31, P=0.034) (4). Our results are also similar with a previous study in Latvia demonstrating significant associations of the OCT1 variants M408V and the 8-bp insertion rs36056065 with the presence of common metformin gastrointestinal adverse effects, whereas the R61C and M420del or OCT1 haplotypes had no effect (19). Again, in a study of 92 participants of unspecified populations, these two variants were significantly associated with gastro

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intestinal side effects. In addition, in a GoDART study involving 2216 participants, it was found that individuals having such polymorphisms and receiving treatment with OCT1 inhibitors were over 4 times more likely to develop intolerance to metformin. However such association was not found between such polymorphisms and metformin responses in the Danish and Latvian populations (18). In a study were 23 Human organic cation transporter 1 SNPs were analyzed, it was found that, Met420del is the only SNP linked with an increased probability of imatinib treatment failure in patients with chronic myeloid leukemia as it significantly decreases imatinib uptake (27). It is thus noteworthy that racial/ethnic differences appear to influence the association between OCT1 variants and the development of GI side effect. The most common metformin GI side effects in our study was abdominal pain and diarrhea. This was similar to a study by Taha *et al* where diarrhea was the most frequent common GI side effects (28). Also, it was found that other identified risk factors for metformin intolerance in our study were older age and female sex.

The pathophysiology of metformin induced GI intolerance or the mechanism by which metformin causes GI side effects remains uncertain, however, there are a number of putative mechanisms explaining how the GI side effects due to metformin therapy occurs. The side effects may simply relate to the high concentration of metformin in intestinal enterocytes (29). An alternative mechanism may involve serotonin, either as a result of stimulation of serotonin release from enterochromaffin cells, or by reducing serotonin transport via the serotonin transporter (SERT), resulting in increased luminal serotonin (29). Nevertheless, it is hypothesized that GI intolerance is related to high concentration of metformin in the intestine after oral administration of the drug and also that, reduced transport of metformin by OCT1 could increase metformin concentration in the intestine, resulting in increased risk of GI intolerance and drug discontinuation (11).

Conclusion

In summary, this study showed that the OCT1 M420del (rs72552763) single nucleotide polymorphism was associated with susceptibility to the development of GI side effects in patients with Type 2 Diabetes and the aa genotype might be a risk factor for the development of GI side effects in patients with Type 2 Diabetes mellitus. However, the limitation of the relatively small sample size should be noted. Thus, further studies with larger sample sizes should be conducted to confirm this conclusion.

Authors Contributions

WFM, XJPM, AMN, CFT contributed to the design of the study. XJPM, AMN, JPKC coordinated the study. XJPM, ACNN, JY, MMMM, TTW, EMM, LNN supervised the sample collection. CFT, XJPM, MLBM performed the molecular analysis. CFT, WOTN, MD, XJPM performed data analysis and interpretation. CFT, XJPM wrote the manuscript. WFM critically revised the manuscript. All authors contributed in the revision of the manuscript and approved the final version of the manuscript prior to submission.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflict of interest.

Availability of Data and Materials

All data generated and/or analyzed during this study are included in this published article.

Acknowledgments

The authors wish to acknowledge the contributions of the staffs of the diabetic unit of the Etoug-Ebe Baptist Hospital including all the study participants and also the Laboratory for Public Health Research Biotechnology (LAPHER-BIOTECH) of the Biotechnology Center, University of Yaounde I, Cameroon.

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Anwar S, et al., Fortune J Health Sci 2024
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