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A Metformin Pharmacogenetic Study of Patients with Type 2 Diabetes Mellitus and SLC22A1 Gene Mutation

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Abstract

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AIM: The purpose of this study was to determine the profiles of patients with Type 2 diabetes mellitus (T2DM) and an SLC22A1 gene mutation to evaluate the effect of metformin pharmacogenetics.

METHODS: To assess the effect of pharmacogenetics, a mutation of the SLC22A1 gene in T2DM patients receiving metformin was investigated. Blood samples were taken from 50 diabetics of Minangkabau ethnicity who met the inclusion criteria and SNP genotyping and blood glucose levels were determined. DNA is extracted and purified from blood samples using **Qiagen** Genomic DNA Kits (ThermoFischer Scientific) reagents. The Chi-square test and independent sample T test were used to analyze the data. A statistically significant association was defined as $p < 0.05$. Finally, the GraphPad Prism 7.00 program was used to gather and analyze data.

RESULTS: The adjusted odds ratio for inadequate fasting blood glucose was 1.48 (95% confidence interval [CI] 1.18–1.95) in this study, while the adjusted odds ratio for diet discipline was 1.23 (95% CI 1.18–1.95). The adjusted odds ratio for low physical activity was 1.18 (95% CI 1.05–1.81). According to the sequencing data, the proportion of mutants is high at exon 2 rs683369 (G>C), while the percentage of wildtype and heterozygous mutants is the same at introns rs4646272 (T>G).

CONCLUSION: Obesity, diet discipline, and low physical activity were all found to increase the likelihood of insufficient fasting blood glucose in T2DM patients. Exon 2 rs683369 (G>C) has a high proportion of mutants, but introns rs4646272 (T>G) have the same percentage of wildtype and heterozygous mutants.

Introduction

Metformin, a medicine recommended for its relative absence of adverse effects and great patient tolerance, is the first line of the treatment for Type 2 diabetes mellitus (T2DM) [1], [2]. Metformin, on the other hand, does not operate similarly or ideally in all patients due to variances in individual genetic profiles, resulting in a decrease in the drug's effectiveness and safety [3], [4]. As a result, determining the genetic component behind metformin response variability is critical, particularly in areas with a high prevalence of T2DM [5], [6]. The previous research has found that the genetically unique Arab, Chechen, and Circassian groups have varied clinical features of diabetes, necessitating specialized diabetes management and treatment strategies for each [7], [8].

Metformin works by lowering hepatic glucose synthesis while boosting glucose absorption in the peripheral tissues [9]. Metformin is unusual in that it does not need to be broken down by the body to effect blood glucose management [10], [11]. Metformin, on the other hand, requires membrane transport proteins produced by solute carrier (SLC) genes to enter cells and reduce hepatic glucose synthesis [12], [13]. The OCT1 and

OCT3 proteins, which are predominantly important for hepatic and intestinal metformin absorption, are encoded by the SLC family 22 member 1 (SLC22A1) and 3 (SLC22A3) genes, respectively [14], [15]. Several single-nucleotide polymorphisms (SNPs) in the SLC22A1 gene have been shown to impact metformin pharmacodynamics and pharmacokinetics, and hence, patient responses to the medicine [16], [17].

Despite accounting for a significant amount of Jordan's disease burden, there have been little investigations on T2DM's hereditary component and the impact of the latter on metformin response. The aim of this study was to determine the profiles of patients with T2DM and an SLC22A1 gene mutation to evaluate the effect of metformin pharmacogenetics.

Materials and Methods

Study design

To assess the influence of pharmacogenetics, profiles of patients with T2DM and SLC22A1 gene mutation were compared between patients using metformin. The Ethics Committee of the Faculty

of Medicine, Universitas Andalas, Padang, West Sumatera, Indonesia gave the study ethical permission (No: 95/KEP/FK/2018). The Declaration of Helsinki was followed in all of the procedures used in this study. All recruited individuals provided written informed permission after being told of the study's aim and assured of patient confidentiality.

Patients recruitment

The participation of eligible subjects in this study were patients with T2DM in Padang, West Sumatera, Indonesia. The population sampled satisfies the following criteria: Age 25–50 years, fasting blood sugar levels <100 mg/dL, and blood sugar levels 2 h after providing glucose 75 g <140 mg/dL. If a sample's liver or kidney function is affected, it will be discarded. A total of 5 mL of blood is collected from the sample and kept at -80° C until needed.

Data collection

Direct interviews were used to obtain information in Padang City in 2018. Clinical data were gathered using a study-specific questionnaire that was filled out by health-care professionals interviewing the individuals. Demographic information was obtained as part of the clinical data. During the interview, a phlebotomist took blood samples to determine fasting blood glucose levels using ethylenediamine tetraacetic acid (EDTA) collection tubes.

Isolation and purification of genomic DNA

DNAs extracted and purified from blood samples using DNAzol® Genomic DNA Kits (ThermoFischer Scientific) reagents. The extraction of genomic DNA from whole blood is done according to the provider's instructions. Chloroform is used to extract DNA from homogenates, resulting in aqueous, interphase, and organic layers. With the addition of 100% ethanol and Trizol reagent, DNA was deposited from the interphase and organic layer. Furthermore, the DNA pellets were washed with 0.1 M sodium citrate in 10% ethanol and 75% ethanol in a sequential order. After resuspending the dry pellets in 8 mM NaOH, DNA can be kept at -20° C in HEPES buffer pH 7–8 with 1 mM EDTA.

PCR and SLC22A1 gene sequencing

Primer Blast (NCBI) software was used to create PCR primers and sequencing. HPLC was used to purify the produced primer. The PCR technique was used to reproduce the DNA fragments. The PCR procedure was carried out with the Gotaq™ PCR Core System kit (Promega) and a total volume of 50 L for each reaction. DNA samples were amplified

for 35 cycles, and the amplicon was kept at 4° C once the procedure was done. Electrophoresis of the application's results in a 2% agarose gel with Gelred and DNA ladder separated the results. Amplicon DNA was extracted and produced in quantities up to 500 ng for sequencing using Illumina's next generation sequencing technique.

Data analysis

Mean ± SD, median, and percentage were used to capture the quantitative data. The Chi-square test and the independent sample T test were used to analyze the data. Statistical significance was defined as a two-tailed $p < 0.05$. GraphPad Prism 7.00 was used to gather and analyze data.

Results

Profiles of patients with T2DM (Table 1).

Table 1: Profiles of patients with T2DM

| Variables | Adequate fasting blood glucose (n=25) (%) | Inadequate fasting blood glucose* (n=25) | p-value |
|---|---|--|--------------------|
| Sex | | | 0.996 ^b |
| Male | 7 (28.0) | 8 (32.0) | |
| Female | 18 (72.0) | 17 (68.0) | |
| Age (Years) | | | 0.086 ^b |
| 19–29 | 0 | 1 (4.0) | |
| 30–49 | 5 (20.0) | 4 (16.0) | |
| 50–64 | 19 (76.0) | 17 (68.0) | |
| ≥65 | 2 (8.0) | 3 (12.0) | |
| Ethnicity | | | 0.023 ^a |
| Minangnese | 23 (92.0) | 21 (84.0) | |
| Bataknese | 1 (4.0) | 2 (8.0) | |
| Others | 1 (4.0) | 2 (8.0) | |
| Occupational | | | 0.783 ^b |
| Working | 21 (84.0) | 20 (80.0) | |
| Not working | 4 (16.0) | 5 (20.0) | |
| Physical activity | | | 0.048 ^a |
| Low | 13 (52.0) | 5 (20.0) | |
| High | 12 (48.0) | 20 (80.0) | |
| Diet discipline | | | 0.041 ^a |
| Not good | 14 (56.0) | 11 (44.0) | |
| Good | 11 (44.0) | 14 (56.0) | |
| Regularly check blood sugar | | | 0.871 ^a |
| Regular | 21 (84.0) | 20 (80.0) | |
| Not regular | 4 (16.0) | 5 (20.0) | |
| Age at diagnosis T2DM (years) | 49.93±8.30 | 51.12±9.62 | 0.531 ^c |
| Basal Mass Index (BMI) (kg/m ²) | 23.71±6.42 | 25.42±5.20 | 0.047 ^a |

*p-value < 0.05 is considered significant^a, defined as fasting blood glucose level ≥ 126 mg/dL, according to the American diabetes association (ADA) guidelines^b. ^c Chi-square test^a, independent sample T test. T2DM: Type 2 Diabetes Mellitus.

Table 1 shows that ethnicity, physical activity, diet discipline, and body mass index are all associated with fasting blood glucose levels ($p < 0.05$). However, no significant relationship was seen between sex, age, occupation, and age at diagnosis of T2DM and fasting blood glucose ($p > 0.05$).

The unadjusted (univariate) and adjusted (multivariate) odds ratios and 95% CIs for inadequate fasting blood glucose (Table 2).

Table 2 shows that obesity was associated with a higher risk of low fasting blood glucose, with an

Table 2: The unadjusted (univariate) and adjusted (multivariate) odds ratios and 95% confidence intervals for inadequate fasting blood glucose

| Variables | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|-------------------------------|------------------------|----------------------|
| Sex | | |
| Male | 0.88 (0.34–2.25) | 0.85 (0.29–2.01) |
| Female | 0.92 (0.36–2.89) | 0.89 (0.31–2.11) |
| Age (Years) | | |
| 19–29 | Ref | Ref |
| 30–48 | Ref | Ref |
| 50–64 | 0.98 (0.31–3.22) | 0.95 (0.29–3.15) |
| ≥65 | 0.93 (0.28–2.99) | 0.89 (0.26–2.94) |
| Ethnicity | | |
| Minangnese | 0.83 (0.27–1.43) | 0.90 (0.21–1.32) |
| Bataknese | 0.88 (0.21–1.12) | 0.79 (0.19–0.98) |
| Others | 0.73 (0.19–1.09) | 0.69 (0.17–0.88) |
| Occupational | | |
| Working | Ref | Ref |
| Not working | 1.11 (0.37–3.32) | 0.98 (0.32–3.01) |
| Physical activity | | |
| High | Ref | Ref |
| Low | 1.20 (1.11–1.89)* | 1.18 (1.05–1.81)* |
| Diet discipline | | |
| Good | Ref | Ref |
| Not good | 1.25 (1.16–1.91)* | 1.23 (1.09–1.71)* |
| Regularly check blood sugar | | |
| Regular | Ref | Ref |
| Not regular | 0.71 (0.22–0.85) | 0.68 (0.21–0.81) |
| Age at diagnosis T2DM (years) | | |
| <50 | Ref | Ref |
| ≥50 | 0.98 (0.34–0.93) | 0.93 (0.32–0.88) |
| Body Mass Index (BMI) | | |
| Normal | Ref | Ref |
| Overweight | 0.97 (0.37–1.92) | 0.95 (0.31–1.88) |
| Obesity | 1.51 (1.21–2.01)* | 1.48 (1.18–1.95)* |

Ref: reference, *p<0.05 significance was considered, OR: Odds ratios, CI: Confidence intervals, T2DM: Type 2 diabetes mellitus

unadjusted odds ratio of 1.51 (95% CI 1.21–2.01) and an adjusted odds ratio of 1.48 (95% CI 1.18–1.95). Diet discipline was also significantly risk of inadequate fasting blood glucose; the unadjusted odds ratio was 1.25 (95% CI 1.16–1.91) and the adjusted odds ratio was 1.23 (95% CI 1.09–1.71). Low physical activity the unadjusted odds ratio was 1.20 (95% CI 1.11–1.89) and the adjusted odds ratio was 1.18 (95% CI 1.05–1.81).

Gene sequencing results in T2DM patients receiving metformin (Table 3).

Table 3: Gene sequencing results in T2DM patients receiving metformin

| Exon/Intron | SNPs | Genotypes | n | % |
|-------------|-------------------|-----------|----|------|
| Exon 1 | rs200710420 (G>A) | GG | 47 | 94.0 |
| | | GA | 3 | 6.0 |
| | | AA | 0 | 0 |
| Intron | rs1867351 (T>C) | TT | 28 | 56.0 |
| | | TC | 17 | 34.0 |
| | | CC | 5 | 10.0 |
| Intron | rs4646272 (T>G) | TT | 21 | 42.0 |
| | | TG | 21 | 42.0 |
| | | GG | 8 | 16.0 |
| Exon 2 | rs683369 (G>C) | TT | 47 | 94.0 |
| | | TC | 2 | 4.0 |
| | | CC | 1 | 2.0 |
| Intron | rs201942835 (G>T) | GG | 2 | 4.0 |
| | | GC | 13 | 26.0 |
| | | CC | 35 | 70.0 |
| Intron | rs4646273 (G>A) | GG | 49 | 98.0 |
| | | GT | 1 | 2.0 |
| | | TT | 0 | 0 |
| Intron | rs4646273 (G>A) | GG | 29 | 58.0 |
| | | GA | 18 | 36.0 |
| | | AA | 3 | 6.0 |

T2DM: Type 2 diabetes mellitus

Table 3 shows that rs200710420 (G>A), which is present in Exon 1, has a greater GG (wildtype) genotype (94.0%) than mutants and no homozygous mutants. Wildtype (TT) was likewise shown to be

greater (56.0%) than mutants in rs1867351 (T/C). Heterozygous (TC) mutants were detected in 34% of the cases, whereas homozygous mutants were found in 10.0% of the cases. There was rs4646272 (T>G) in the intron, with the same proportion of wildtype and heterozygous mutants (42.0%). Wildtype (TT) was reported to be greater (94.0%) than mutants in rs74795793 (T>C). Heterozygous mutants accounted for 4.0% of the total, whereas homozygous mutants accounted for 2.0%.

Exon 2 yielded a larger proportion of mutants than wildtype for rs683369 (G>C). Homozygous (CC) mutants accounted for 70.0% of the total, heterozygous (GC) mutants 26.0%, and wildtype (GG) mutants were detected in more than 49.0% of rs201942835 (G>T) mutants, heterozygous mutants were found in 2.0%, and homozygous mutants were not found. Wildtype (GG) was detected in a larger percentage (58.0%) than mutants in the intron rs4646273 (G>A). Heterozygous (GA) mutants were detected in 36.0% of the cases, whereas homozygous (AA) mutants were found in 6.0% of the cases.

According to the sequencing data, the proportion of mutants is high at Exon 2 rs683369 (G>C), while the percentage of wildtype and heterozygous mutants is the same at introns rs4646272 (T>G).

Discussion

Recent breakthroughs in identifying common T2DM variations highlighted their association with the disease's pathogenesis, which assists in the assessment of individual risk and treatment effectiveness [18], [19]. Despite its rising prevalence in Indonesia, T2DM has not been adequately investigated pharmacogenically in the Indonesian population. As a result, the present study is extremely important since it gives information on the relationship between metformin metabolism and Indonesian genetic profiles.

This study found that Exon 2 rs683369 (G>C) has a high proportion of mutants, but introns rs4646272 (T>G) have the same percentage of wildtype and heterozygous mutants. The extent to which T2DM-predisposing polymorphisms in the SLC22A1 genes are associated with good glycemic control was investigated in this study. The OCT proteins, which are organic cation transporters that play crucial roles in the regulation of essential metabolic processes, are encoded by the aforementioned genes, which are highly relevant to the field of drug transport [20].

This study revealed that obesity, diet discipline, and low physical activity were all found to increase the likelihood of insufficient fasting blood glucose in T2DM

patients. Obesity is a cause of diabetes and insulin resistance. Adipose tissue releases more non-esterified fatty acids, glycerol, hormones, and pro-inflammatory cytokines in obese people, which might contribute to the development of insulin resistance [21], [22].

The significant rise in the incidence of diabetes in emerging nations is due to dietary choices and a sedentary lifestyle. Recently, increased HbA1c levels in Type 2 diabetics have been identified as one of the primary risk factors for microvascular and macrovascular problems. Diet management can help patients with their increased HbA1c levels, preventing them from acquiring diabetic complications [23].

The majority of the advantages of physical exercise for diabetes control come from changes in insulin action, which may be achieved with both aerobic and resistance training. Physical training advantages are reviewed, as well as advice for various activities, physical activity-related blood glucose control, diabetes prevention, gestational diabetes mellitus, and safe and effective techniques for physical activity with diabetes-related problems [24].

The genetic connection of these SNPs with fasting blood glucose levels in the management of diabetes is also influenced by the age at which diabetes is diagnosed. When treating diabetic patients, several covariate variables should be taken into account. It is also crucial to understand the influence of these variables on T2DM patients' genetic connections with fasting blood glucose levels. One possible weakness of the present study is that the length of the illness was not taken into account, and people who had the condition for a longer period may have had lower endogenous insulin production, implying that endogenous insulin levels were varied among the subjects.

This research suggests that increased awareness of diabetes complications leads to improvements in dietary knowledge and physical activity. In addition, maintaining a healthy body mass index helps to keep the condition under control. Stakeholders (health-care practitioners, health-care institutions, diabetes-care organizations, and so on) should assist patients to recognize the relevance of nutrition in disease management, adequate self-care, and improved quality of life.

Conclusion

Obesity, diet discipline, and low physical activity were all found to increase the likelihood of insufficient fasting blood glucose in T2DM patients. Exon 2 rs683369 (G>C) has a high proportion of mutants, but introns rs4646272 (T>G) have the same percentage of wildtype and heterozygous mutants.

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