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Research Article

A CLINICAL ENDOCRINOLOGICAL QUANTITATIVE STUDY OF SPECIFIC SYMPTOMATIC FEATURES AMONG GLOBAL TYPE II DIABETIC PATIENTS AND A PHARMACOGENOMIC ANALYSIS OF ANTI-DIABETIC PHARMACOTHERAPEUTIC AGENTS

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ABSTRACT

Introduction: The heterogeneity of type II diabetes mellitus manifestations depends on the subgroups of diabetes, the clinical variables, disease progression, genetic makeup and lifestyle factors; and this determines the response to treatment with novel glucose-lowering drugs, and lifestyle modifications
Objectives: The objective of this study is a clinical endocrinological quantitative analysis of specific symptomatic features among global type II diabetic patients, and a pharmacogenomic analysis of anti-diabetic pharmacotherapeutic agents.
Methods: The occurrence of specific symptoms among 25 new type II diabetes mellitus patients, and the detailed specific diabetic symptoms assessment, that is fatigue and polyuria, were recorded and graphically analysed with percentages, categorised according to their occurrences. A pharmacogenomic analysis of certain anti-diabetic pharmacotherapeutic agents was also conducted.
Results: among 25 patients, 9 patients had the symptom of fatigue, 3 patients had the symptom of polyuria, 3 patients had the symptom of both fatigue and polyuria, and 10 patients had neither fatigue, nor polyuria, as a symptom, that is, 36% of patients had fatigue, 12% of patients polyuria, 12% of patients had both fatigue and polyuria, and 40% of patients had neither fatigue, nor polyuria. The pharmacogenomic characteristics of the anti-diabetic pharmacotherapeutic agents were thoroughly analysed, which well-demonstrated their significance in their appropriateness in anti-diabetic type II treatment.
Conclusion: The diabetic symptom of fatigue was more predominant than polyuria. The anti-diabetic pharmacotherapeutic agents showed their pharmacogenomic efficacy.

INTRODUCTION

The heterogeneity of type II diabetes mellitus manifestations depends on the subgroups of diabetes, the clinical variables, disease progression, genetic makeup and lifestyle factors; and this determines the response to treatment with novel glucose-lowering drugs, and lifestyle modifications.[1] Glucagon-like peptide (GLP)-1 is an incretin hormone having different antidiabetic functions, like increased insulin synthesis,

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stimulation of glucose-dependent insulin secretion, increase in insulin gene expression and beta-cell survival, proliferation, differentiation and protection, inhibition of glucose production, increase in cardiac output and cardio-protection and slowing down of gastric emptying. The clinical benefits of GLP-1 peptide or analogues include improved insulin sensitivity, induction of glucose tolerance, reduction of hyperglycaemia, suppression of appetite, food intake linked to weight loss and reduction of abdominal and/or hepatic fat associated with obesity-induced T2DM with drastic alterations in adipokine profiles. These beneficial effects have been experimented in animal models using gene therapy, for the development of improvised techniques of anti-diabetic type II genetic therapeutic approaches.[2]

Objective: The objective of this study is a clinical endocrinological quantitative analysis of specific symptomatic features among global type II diabetic patients, and a pharmacogenomic analysis of anti-diabetic pharmacotherapeutic agents.

METHODS

Ethical Approval

At first, the Institutional Ethics Committee clearance and approval was taken. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practices contained within the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-E6 and ICH-E17), and in compliance with the global regulatory requirements. An informed consent was obtained from each patient.

Selection Criteria of the Study Participants

Inclusion criteria

The inclusion criteria were as follows: (i) patients of any gender, (ii) patients within 35 and 60 years, (iii) patients of around 60 kg average body weight, (iv) patients presenting with new type II diabetes mellitus, (v) type II diabetes mellitus American Diabetes Association diagnosis criteria,[3] (vi) cooperative and conscious patients, (vii) patients willing to undergo all pre- and post-treatment investigations and willing to complete the entire course of treatment, (viii) patients who have given consent and are willing to go for a follow-up, (ix) patients not taking any previous antidiabetic drug, and (x) patients not taking any concomitant medication.

Exclusion Criteria

The exclusion criteria were as follows: (i) uncooperative or unconscious patients, (ii) patients below 35 and above 60 years, (iii) patients with high-risk diseases or comorbidities, (iv) cardiac, renal, or any other associated complications or comorbidities, (v) any chronic disease intervening with the study data, (x) pregnant or lactating women, (xi) paediatric or geriatric patients.

Study design

This was a global, multicenter, prospective, quantitative clinical endocrinological study and a pharmacogenomic analysis.

Study population

The study population was 25 new type II diabetes mellitus patients.

Place of study

The place of research study and the compilation of the study literature were the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Endocrinology, Diabetology and Metabolic Medicine, Pharmacovigilance, Rational Pharmacotherapeutics, Pharmacogenomics, Evidence Based Medicine, Clinical Medicine, Clinical Pathology and Pathology, in Mamata Medical College, Rama Medical College, Rama University, Dr. Moumita Hazra's Polyclinic and Diagnostic Centre, Hazra Nursing Home, J.J.M. Medical College, Mahuya Diagnostic Centre and Doctors' Chambers and GIOSTAR Institute of Regenerative Medicine, Institutes, Hospitals and Laboratories.

Study period

The study period, including the research study and the compilation of the study literature, was 3 months: November, 2020; and November, 2021 to December, 2021.

Study procedure

The clinical pharmacological details of 25 new type II diabetes mellitus patients, regarding the patients' demographic characteristics, detailed specific diabetic symptoms assessment, that is fatigue and polyuria, the patients' disease details, and disease-related history were recorded with a proforma. Then, thorough general physical examinations and diabetological systemic examinations were done on the patients, with subsequent intensive clinical investigations and clinical pharmacoendocrinological treatment.

Biostatistical Analysis

The specific type II diabetic symptomatology, comprising of fatigue and polyuria, was recorded and graphically analysed with percentages.

Pharmacogenomic analysis of anti-diabetic pharmacotherapeutic agents

The thorough pharmacogenomic analysis of anti-diabetic pharmacotherapeutic agents was performed from wide ranged pharmacogenomic researches, reviews, case presentations and different types of anti-diabetic pharmacogenomic study literature to focus on their pharmacogenomic relevance, rationale and appropriateness as anti-diabetic pharmacotherapeutic agent.

RESULTS AND DISCUSSION

This diabetological study showed that among 25 diabetic patients, 9 patients had the symptom of fatigue, 3 patients had the symptom of polyuria, 3 patients had the symptom of both fatigue and polyuria, and 10 patients had neither fatigue, nor polyuria, as a symptom, that is, 36% of patients had fatigue, 12% of patients polyuria, 12% of patients had both fatigue and polyuria, and 40% of patients had neither fatigue, nor polyuria, as depicted in Figure 1.

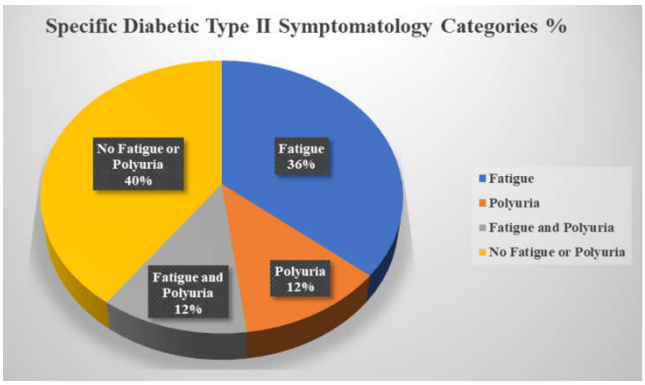

Figure 1 Specific Diabetic Type II Symptomatology Categories %

Several pharmacogenetic studies revealed that specific genes are associated with the corresponding anti-diabetic pharmacotherapeutic response. The genetic variants of *GLP1R, KCNQ1, KCNJ11, CTRB1/2, PRKD1, CDKAL1, IL6* promoter region, *TCF7L2, DPP4* and *PNPLA3* are associated with dipeptidyl peptidase-4 inhibitors (DPP-4i) response. *GLP1R, CNR1, TCF7L2* and *SORCS1* genetic variants are involved with the pharmacotherapeutic response to glucagon like peptide-1 receptor agonists (GLP-1 RA). *SLC5A2* is supposedly associated with the response to sodium glucose co-transporter 2inhibitors (SGLT2i).[1]

The *GLP1R* gene encodes the receptor for GLP-1, a peptide hormone expressed in pancreatic beta cells. The variants in the *GLP1R* gene (rs6923761; p.Gly168Ser) and *GLP1R* gene (rs3765467; p.Arg131Gln) were shown to involved with DPP-4is treatment, like sitagliptin, vildagliptin and linagliptin. People with type 2 diabetes with the A allele (GA/AA vs GG) responded better to therapy with DPP-4i, with >10% relative HbA1c reduction and a greater HbA1c decrease after 24 weeks of therapy.

The *KCNJ11* gene regulates one of the pancreatic beta cell ATP-sensitive potassium channels, that play a role in insulin secretion. A single nucleotide polymorphism (SNP) (rs7202877) that is located near *CTRB1/CTRB2* genes that encode chymotrypsinogen B1 and B2, is related to GLP-1-stimulated insulin secretion. The rs7202877 GG and GT genotypes were associated with a 0.5% smaller reduction in HbA1c compared with the TT genotype after 3 months of gliptin therapy. The serine/threonine protein kinase D1 enzyme, encoded by *PRKD1*, is involved in the regulation of cell proliferation, differentiation and apoptosis, immune reactions, cardiac contraction, angiogenesis and cancer development.

A genome-wide association study (GWAS) found that in people with type 2 diabetes treated with sitagliptin, saxagliptin, vildagliptin or linagliptin, a polymorphism in PRKD1 (rs57803087; intron variant) was associated with a greater response to the DPP-4i. A relationship between several SNPs in *CDKAL1*, encoding cyclin-dependent kinase 5 regulatory subunit associated protein 1-like 1 (*CDKAL1*), and type 2 diabetes risk was also revealed. The HbA1c decrease was greater in people who carried at least one variant allele in comparison with two copies of the common allele (for rs7754840, GG 0.4%, CG 0.5% and CC 0.8%; for rs7756992, AA 0.4%, AG 0.5% and GG 0.8%). The variation in the *TCF7L2* gene has been associated with an increased risk of type 2 diabetes. In a regression analysis, DPP4 genotype rs2909451 (intron variant) TT was associated with increased short-term DPP-4 enzyme activity during sitagliptin treatment. The variants in the *PNPLA3* gene, encoding patatin-like phospholipase 3 (PNPLA3), are also involved with diabetes. In GWAS, a genetic variant (rs738409) of PNPLA3 was associated with non-alcoholic fatty liver disease (NAFLD) and its histological severity. GLP1R SNPs around the exon region of the *GLP1R* gene were genotyped in a small sample of people with poorly controlled type 2 diabetes, who received exenatide treatment.

The CT/TT genotypes of rs761386 (intron variant) were related to higher glucose levels. The GLP1R rs6923761 (non-coding) A allele (GA/AA vs GG) was associated with weight reduction after liraglutide treatment in multivariable analysis. The cannabinoid type 1 receptor, encoded by the *CNR1* gene, involved in type 2 diabetes in obese patients, stratified by CNR1 genotypes (GA and AA genotypes vs GG genotypes), influences the appetite and body-weight regulation. The insulin resistance was found to decrease in individuals carrying the variant *CNR1* A allele. Liraglutide therapy resulted in comparable improvements of anthropometric measures and glycaemic markers in all CNR1 genotypes.

In a small pharmacogenetic study, type 2 diabetic patients and the *TCF7L2* rs7903146 CC genotype were matched with individuals with CT and TT genotypes and similar diabetes duration and body mass index. The rs7903146 (intron variant) T allele was associated with higher secretion of insulin, proinsulin and C-peptide. After exenatide treatment, T allele carriers showed lower postprandial plasma insulin and C-peptide levels compared with non-carriers. The data suggest that use of GLP-1 RA could play a role in beta cell function in individuals with the rs7903146 CT and TT genotypes.

In persons with newly diagnosed type 2 diabetes treated with exenatide, stratifying for *SORCS1* rs1416406 genotypes in VPS10 domain containing receptor, revealed differences in HbA1c, glucose values and beta cell function between the genotype groups (GG, GA, AA) following treatment. The reduced pro insulin / insulin ratio suggests that people with newly diagnosed type 2 diabetes and the rs1416406 GG genotype might benefit from exenatide treatment. The sodium–glucose cotransporter 2 (SGLT2) protein, which contributes to renal glucose reabsorption, is encoded by the *SLC5A2* gene. Baseline liver protein density fat fraction was lower in individuals with the *PNPLA3* rs738409 (p.Ile148Met) CC genotype (median 17%) than in those with the CG and GG genotype (20%). In response to the combination therapy, the relative PDFF reduction was greater in individuals with the CG and GG genotypes (relative change, −25%) than in those with the CC genotype (−16%). The relative change in PDFF observed following dapagliflozin monotherapy differed from that seen with the combination therapy (CG and GG, +7%; CC, −22%). *In vitro* studies showed that canagliflozin, metabolised by uridine diphosphate-glucuronosyltransferase (UGT) 1A9 and UGT2B4 into inactive glucuronides, suggested that *UGT1A9* gene variants result in an alteration of UGT enzymatic activity. Therefore, variants in the UGT genes could potentially influence the pharmacokinetics of canagliflozin or other SGLT2i. A pharmacokinetic model of canagliflozin demonstrated that carriers of the rare *UGT1A9*3* allele showed 26% higher median dose-normalised AUC values for canagliflozin, indicating a better drug availability. A smaller study based on phase 1 clinical trials confirmed the role of UGT genes in canagliflozin metabolism, with higher

plasma canagliflozin levels being observed in carriers of the *UGT2B4*2* genotype compared with non-carriers.[1]

Several successful clinical gene therapy applications are also revealed, against genetic diseases such as Leber's congenital amaurosis, X-linked SCID, ADA-SCID, adrenoleukodystrophy, chronic lymphocytic leukaemia, acute lymphocytic leukaemia, multiple myeloma, haemophilia, Parkinson's disease and thalassaemia. Gene therapy is a strategy curing or compensating the symptoms of diseases caused by defective or abnormal genes through introduction of exogenous normal genes. Therefore, the diseases can be potentially cured by a single treatment, and it is now transforming into a multi-speciality genetic treatment. In the recent times, genetic modifications comprises of gene addition, gene regulation, gene editing, and similar modifications.[4]

From the preceeding qualitative pharmacogenomic analysis of certain anti-diabetic pharmacotherapeutic agents, it was well-delineated that these were indispensably suitable, efficacious, safe and relevant anti-diabetic type II pharmacotherapeutic approaches for an improvised treatment.

CONCLUSION

This study sufficiently concluded that the diabetic symptom of fatigue was more predominant than polyuria, and most of the patients showed neither fatigue nor polyuria, as the specific symptomatic assessment, considered under this research study. These anti-diabetic pharmacotherapeutic agents established their comprehensive pharmacogenomic rationality, in their application as anti-diabetic type II treatment modalities.

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