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PRESCRIBING PATTERNS AND RESPONSE TO ANTIHYPERGLYCEMIC AGENTS AMONG NOVEL CLUSTERS OF TYPE 2 DIABETES IN ASIAN INDIANS

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ABSTRACT

AIM: To assess the prescribing patterns and response to different classes of antihyperglycemic agents in novel clusters of type 2 diabetes (T2D) described in India.

MATERIALS AND METHODS: We attempted to replicate the earlier described clusters of T2D In 32,867 individuals with new-onset T2D (within 2 years of diagnosis) registered between October 2013 and December 2020 at 15 diabetes clinics located across India, by means of k-means clustering utilising six clinically relevant variables. Individuals who had followup HbA1c upto 2 years were included for the drug response analysis (n=13,247).

RESULTS: Among the 32,867 participants included in the study, 20779 (63.2%) were males. The average age at diagnosis was 45 years and mean HbA1c at baseline was 8.9 %. The same four clusters described in India earlier were replicated. Forty percent of the study participants belonged to the Mild Age-Related Diabetes [MARD] cluster, followed by Insulin Resistant Obese Diabetes [IROD] (27%), Severe Insulin Deficient Diabetes [SIDD] (21%) and Combined Insulin Resistant and Deficient Diabetes [CIRDD] (12%) clusters. The most frequently used antihyperglycemic agents were sulphonylureas, metformin and dipeptidyl peptidase-4 inhibitors apart from insulin. While there were significant differences in HbA1c reduction between drugs across clusters, these were largely driven by differences in the baseline (pre-treatment) HbA1c.

CONCLUSIONS: In this new cohort we were able to reliably replicate the four subtypes of T2D earlier described in Asian Indians. Prescribing patterns show limited usage of newer antihyperglycemic agents across all clusters. Randomized clinical trials are required to establish differential drug responses between clusters.

Introduction

Type 2 diabetes (T2D) is a widespread metabolic disorder characterized by considerable heterogeneity in its pathophysiology, clinical manifestations and natural history [1]. Efforts have been made in various populations to identify distinct “clusters” of phenotypic characteristics and laboratory markers in individuals diagnosed with T2D, and to assess whether these clusters correlate with differential risk of diabetes complications [2,3]. A pioneering study by Ahlquist et al [2] in a Scandinavian population, led to the identification of five major subtypes of T2D termed as Severe Autoimmune Diabetes (SAID), Severe Insulin Deficient Diabetes (SIDD), Severe Insulin Resistant Diabetes (SIRD), Mild Obesity-related Diabetes (MOD) and Mild Age-Related Diabetes (MARD).This was also reproduced in several other ethinic groups [4-6].

Asian Indians represent an ethnic group with high predilection for T2D, who have been shown to have certain differences with respect to clinical features compared to white Caucasians, such as onset of diabetes at younger ages and lower levels of obesity, as well more severe beta-cell insufficiency early in the disease course [7,8]. An earlier attempt at identifying clusters of T2D in the Asian Indian population replicated two of the clusters identified by Ahlquist et al viz. SIDD and MARD,while two novel clusters termed CIRDD(Combined Insulin Resistant and Deficient Diabetes) and IROD (Insulin Resistant Obese Diabetes) were also described [9].

More than seven distinct categories of drugs are available for the management of T2D at present.There is little information available on the overall prescribing patterns of antihyperglycemic medications in India. However, there is considerable interest in

assessing how individuals in each of the clusters of T2D, respond to various classes of antihyperglycemic medications. In the present paper, we attempt to analyse the prescribing patterns for T2D in India, and assess the response to different classes of antihyperglycemic agents among the recently described “clusters” of Asian Indian patients with T2D by doing a retrospective analysis of medical records collected from multiple diabetes care practices across India.

Materials and Methods

Study population and inclusion criteria

Retrospective data on individuals with new-onset T2D (within 2 years of diabetes diagnosis) who were registered between October 2013 and December 2020 was collected from 15 diabetes clinics located in 12 states and one Union Territory of India **(Figure 1).** Diabetes was diagnosed if the fasting plasma glucose level was ≥126 mg/dL (7.0 mmol/L) and/or 2-hour postload glucose level was ≥200 mg/dL (11.1 mmol/L) and/or if the patient had been prescribed pharmacotherapy for diabetes by a physician [10],while T2D was diagnosed by absence of ketosis, good beta-cell reserve as shown by fasting C-peptide assay >0.6 pmol/mL and absence of pancreatic calculi (on abdominal radiograph)[11]. In order to assign individuals into clinical clusters, data on age at diagnosis, body mass index (BMI), waist circumference, glycated hemoglobin (HbA1c), serum triglycerides and high density lipoprotein (HDL) cholesterol were collected from 32,867 individuals with new onset T2D. Height (in cms) was measured using a stadiometer, weight (in kg) was measured with an electronic weighing scale and waist circumference was measured using a nonstretchable measuring tape. BMI was calculated using the formula: weight (Kg)/(height in m)^2. HbA1c, triglycerides and HDL-cholesterol were determined by standard methodologies followed in the respective labs in the 15 study centres (Serum

triglyceride analyzed by enzymatic method, HDL-cholesterol by direct method and HbA1c by high performance liquid chromatography).

Other data collected included medication use (if any) at the time of first visit and at the follow-up visits up to two years from first visit. Baseline drug information was available for 30,152 individuals and follow-up HbA1c was available from 4.2 -7.4 months) was available in 14,240 individuals **(Figure 2).** Among these, 10,013 drug-naïve individuals who were prescribed medications at first visit were included in the analysis. Individuals who were not drug-naïve were included in the study if new medications were added at baseline (n=2941). Individuals in whom no changes were made to previous medications at baseline and who had a follow-up HbA1c available within 3 months were included (n=293), whereas those without a follow-up HbA1c (n=933) were excluded. Therefore, a total of 13,247 individuals were included in the drug response analysis. Written informed consent to use anonymized medical data was obtained from all study participants and approval was obtained from the Institutional Ethics Committee.

Statistical analysis

Baseline characteristics were described using means and standard deviations for normally distributed variables, and median and interquartile range for non-normally distributed variables. Clustering methodology has been previously described [9]. Briefly, k-means clustering was done with a k value of 4 using k-means function (with a maximum iteration of 10,000) in R V.3.6.0. Cluster forming tendency of the data was validated by the Hopkins statistic value. The optimal number of clusters was

149 determined based on silhouette width. Cluster-wise stability was computed by Jaccard
150 bootstrap method. Cluster analysis was performed onscaled and centered values.
151 Cluster labels were assigned based on the phenotype characteristics of individual
152 cluster mean values of the variables.
153 Sensitivity analysis was done using duration of diabetes <1 year, <3 years, and <5
154 years. Clustering tendency of the three different duration groups had Hopkins statistics
155 values of 0.14, 0.16 and 0.16 respectively indicating that there was no significant
156 difference between the duration groups.
157 HbA1c response was presented as absolute difference in HbA1c and percentage
158 difference [(pre-treatment HbA1c – post treatment HbA1c)/pre-treatment HbA1c]. In
159 our regression models, we presented the therapy as a predictor and HbA1c reduction
160 as the dependent outcome. Both univariate models and multivariable models were
161 presented. Multivariable models were adjusted for sex, time on treatment, BMI, waist
162 circumference, triglyceride levels and HbA1c at baseline. Models are presented with
163 the step-wise inclusion of variables. Model 1 is univariate (HbA1c reduction), Model 2
164 is adjusted for sex, BMI, waist circumference and time on treatment, Model 3 is
165 adjusted for sex, BMI, waist circumference, time on treatment, HDL-C and triglycerides
166 and Model 4 is adjusted for sex, BMI, waist circumference, time on treatment, HDL-C,
167 triglycerides and baseline HbA1c. We employed two sets of analyses using models
168 described above. In the first analyses set, we demonstrated the within-cluster effect of
169 medications when compared to metformin use. In the second set that was analyzed,
170 we demonstrated the across-clusters effect of a therapy while using those prescribed
171 the therapy in MARD as the reference. The second analyses was performed in order
172 to demonstrate the bias in comparing individuals prescribed different therapies, who
173 would intrinsically have differing disease severity.We also examined the HbA1c

reduction in response to therapies in the SIDD, IROD and CIRDD clusters in comparison to the MARD cluster taken as the reference. Models are presented in the same step-wise method as described above.

Results

Among the 32,867 participants included in the study, 20779 (63.2%) were males. The average age at diagnosis was 45 years and the baseline HbA1c was 8.9 %. Mean BMI in males and females was 26.7 kg/m^2 and 28.4 kg/m^2 respectively,while waist circumference was 94.8 cm in females and 96.6 cm in males. Mean HDL-C and triglycerides were 41 mg/dL and 159 mg/dL respectively.

Table 1 describes the characteristics of individuals in the various clusters. Forty percent of the population belonged to the MARD cluster, followed by 27% who belonged to the IROD cluster, 21% to the SIDD and 12% to the CIRDD clusters. The distribution of other characteristics followed the expected distributions of the clusters in Asian Indians as previously described. The youngest age (36.1 years) of diagnosis was observed in the SIDD cluster, who also had the lowest BMI (23.3 kg/m^2) and waist circumference (85.3 cm). The SIDD cluster also had the highest baseline HbA1c (11.2%). Individuals in the IROD cluster had the highest BMI (32.9 kg/m^2) and waist circumference (108.9 cm), and systolic (130.4 mmHg) and diastolic (81.4 mmHg) blood pressure. The CIRDD cluster represents a combination of characteristics of SIDD and IROD, with a relatively young age of diabetes diagnosis (41.9 years), and high BMI (26.8 kg/m^2) and HbA1c (9.4%) at baseline. They also had the lowest HDL-C and the highest triglycerides (365 mg/dL). The MARD cluster represented the mildest presentation of T2D and had the oldest average age at diagnosis (50.7 years),

lowest HbA1c at diagnosis (7.6%), highest HDL-C (43 mg/dL) and lowest triglycerides (139 mg/dL).

The proportion of prescriptions of antihyperglycemic agents is provided in **Table 2**. Overall, metformin and sulphonylureas (SU) (in combination followed by singly) were the most commonly prescribed oral antihyperglycemic agents as per our analyses. Among the newer agents, dipeptidyl peptidase-4 inhibitors [DPP4i] were the most frequently used drugs, mostly in combination with metformin. In the SIDD cluster, insulin was frequently used with or without oral antidiabetic drugs [OAD](48.4%). This was followed by a combination of metformin and SU (13.7%) and triple therapy of metformin, SU and DPP4i (10.2%). In the IROD cluster, the most frequently prescribed medication was a combination of metformin and SU (26.9%), followed by insulin and an oral agent (21.5%). In the CIRDD group, the most common prescription at presentation was a combination of insulin and an oral agent (34.3%), followed by dual therapy of metformin and SU(21.8%), and triple therapy of metformin, SU and DPP4i (19.4%). Finally, in the MARD cluster, the most common prescription was dual therapy of metformin and SU (32.6%), followed by metformin monotherapy (17%).

Table 3 shows the mean difference in HbA1c between baseline and follow-up (unadjusted HbA1c response) and the average interval between HbA1c measurements. The treatments used reflect the baseline HbA1c, with insulin being initiated in those with the highest HbA1c. Consistent with this, the greatest absolute reduction with insulin as monotherapy or in combination with oral agents, were found in SIDD and CIRDD as compared to IROD and MARD. In the SIDD group, dual therapies with SU/DPP-4i, Metformin/ Sodium-glucose co-transporter-2 inhibitors [SGLT2i], Metformin/thiazolidinediones [TZD] also produced significant reductions in

HbA1c, while in CIRDD, triple therapy with metformin/SU/TZD and metformin/SU/DPP-4i was associated with greater HbA1c reduction compared to dual therapy. In IROD and MARD, the absolute reductions in HbA1c were lower with all the commonly used therapeutic combinations compared to the other clusters, probably on account of the lower baseline HbA1c in these two clusters. The interval between the HbA1c measurements in the various clusters ranged from 4.2 to 7.4 months.

Table 4 shows the multivariable models of HbA1c response in comparison to metformin monotherapy within clusters. In the SIDD cluster, use of insulin was associated with greater reductions in HbA1c [13% (7%-18%)when used as monotherapy and 15% (10%-20%)in combination with oral agent)] compared to metformin monotherapy even after adjusting for anthropometric measures, duration of treatment and lipid parameters (Model 3). Similarly, monotherapy with SU was associated with a 7% (0.3%-14%) greater reduction, and triple drug therapy with an 8% (2%-13%) greater reduction in HbA1c compared to metformin monotherapy in the SIDD cluster.

Applying Model 3 to IROD, the insulin treated patients had the greatest reductions in HbA1c, when used as monotherapy 19% (8%-30%) or in combination with oral agent 18% (14%-22%) compared to metformin monotherapy. Combination of metformin and SGLT2i was associated with 7% (1%-15%) greater reduction, and triple drug therapy with 10% (6%-16%) greater reduction in HbA1c in this cluster compared to metformin monotherapy.

The most impressive reductions in HbA1c in the CIRDD cluster were associated with insulin monotherapy [24% (15%-32%) greater reduction in HbA1c compared to metformin monotherapy] and combination of insulin with oral agents [20% (14%-25%) greater reduction in HbA1c compared to metformin monotherapy]. Dual therapy with metformin and SU was associated with 11% (6%-17%), and metformin and DPP-4i with 9% (2%-16%) greater reduction in HbA1c in this cluster compared to metformin monotherapy, whereas triple drug combinations of metformin and SU with TZD and DPP-4i were associated with 14% (4%-24%) and 12% (6%-18%) greater reductions in HbA1c respectively compared to metformin monotherapy.

In MARD, relative reductions in HbA1c were 5% (1%-9%) or lower for all drug categories and combinations studied in comparison to metformin monotherapy.

However, on applying Model 4 and after adjusting for baseline HbA1c, the differences lost statistical significance across all cluster categories.

Table 5 shows multivariable models of HbA1c response in comparison with HbA1c response in the MARD cluster. Using MARD as reference, similar results were obtained with insulin showing best reductions of HbA1c in SIDD and CIRDD, secretagogues showing good reduction in SIDD, and CIRDD requiring early use of insulin and combination therapy.

Discussion

This study reports on the following findings: Firstly, in this independent cohort dawn from across India, we confirm the four subtypes of T2D namely SIDD, IROD, CIRDD and MARD as discussed in our original paper [9]. Earlier we had done the clustering

from a single diabetes clinic in India and the replication was done in a national epidemiological database. Being a cross-sectional study, the latter, despite being representative of India, lacked treatment details.In this study we have replicated our findings across 15 diabetes clinics in different parts of India. Secondly, based on observational data from these clinics, we describe, for the first time, patterns of drug prescriptions in new onset T2Din clinics across India. We also attempted to assess the relative efficacy of various drug categories across diabetes clusters, although the data were collected retrospectively.

The most commonly prescribed therapies in this newly diagnosed population with T2D in India were insulin, metformin, SU and DPP4i. Very few patients were prescribed newer antidiabetic agents such as SGLT2i and glucagon like peptide-1 receptor agonists (GLP-1RA). This pattern is similar to that reported in previous studies from India [12,13]. While many of the newer treatment options have been shown to have pleiotropic benefits in T2D, the limited use of these agents in India is most likely driven by affordability. It has also been shown even in the US that metformin, SU and insulin continue to be the most frequently used therapies for T2D [14]. However, in countries where patients do not have to pay for drug treatment out of pocket (such as the United Kingdom), newer agents such as DPP-4i and SGLT2i are fast replacing SU as the second most commonly prescribed oral antihyperglycemic medication [15]. The familiarity and comfort of the treating physician with tried and tested agents could also be a reason for the continued popularity of these older drugs in India.The fact that randomized controlled trials for efficacy of therapeutics are rarely conducted in non-white populations could further impact prescribing hesitancy.

Currently accepted therapeutic guidelines recommend initial monotherapy with metformin in individuals with T2D, unless the HbA1c is profoundly elevated [16-18]. The choice of second line therapy if metformin alone fails to control hyperglycemia, is based on factors such as risk of hypoglycemia, need to avoid weight gain, renal and cardiovascular status and patient affordability and preferences. Studies in European populations suggest that patient phenotype could have a bearing on response to antihyperglycemic medications. For instance, it has been shown that individuals with markers of insulin resistance respond poorly to DPP-4i [19]. It has also been suggested that men with lower BMI respond better to SU whereas obese women respond better to TZD[20]. However, there is, as yet,little information available as to whether the clinical phenotype of the patient would influence the choice of first or second-line pharmacotherapy for T2D in Asian Indians.

The “Asian Indian phenotype” of T2D is uniquely characterised by young age of onset, occurrence at relatively low BMI, and relatively early onset of beta cell dysfunction [7].A recent meta-analysis has suggested that Asian Indians respond differentially to various classes of antihyperglycemic agents compared to white Caucasians; however, these findings did not consider the heterogeneity in clinical phenotypes among Asian Indians with T2D and was not intended to assess the efficacy of non-metformin therapies as first line agents for T2D [21].

In their landmark study, Ahlquist et al [2] suggested that, based on the presumed pathophysiology, individuals in different subcategories of T2D could be expected to respond differentially to various classes of antihyperglycemic medications. They postulated that individuals in the ”insulin-deficient” clusters were more likely to respond

to insulin-providing therapies (including early initiation of exogenous insulin therapy) whereas those in the “insulin resistant" clusters would respond optimally to metformin. They also noted that a significant proportion of individuals were not being prescribed phenotype-appropriate medications, potentially leading to suboptimal glycemic control and potentially increased risk of complications. In our study, we found that some clinicians were indeed utilising phenotype-specific treatments in a fair proportion of their patients even in the absence of formal subclassification data to guide them. For instance, we find that insulin use was most frequent in the SIDD cluster, the subgroup with the most profound insulin deficiency, while use of metformin was highest in the insulin resistant, obese IROD cluster. This is likely because leaner patients tend to be preferentially put on insulin while overweight patients tend to be treated more with metformin. However, our results also suggest that there appears to be a large proportion of patients who are not on therapy appropriate to their phenotype and pathophysiology. We believe that knowledge of the subtypes of T2D would enable clinicians to fine-tune their management of diabetes so as to treat their patients more precisely and effectively.

As our study is a retrospective analysis of real-world data,our results reflect the diabetes management of physicians treating patients as per their clinical needs rather than randomising them to certain therapies as would be the case in a randomised controlled clinical trial. However, our results do provide some interesting clues as to the relative efficacy of different classes of antihyperglycemic agents in the various clusters of T2D. For instance, individuals with the insulin deficient SIDD and CIRDD phenotypes, who are younger and have difficult-to-control hyperglycemia, are likely to benefit from early initation of insulin and insulin secretagogues and more widespread

use of combination therapies as opposed to metformin monotherapy. However, recommendations on cluster-specific management of T2D would need to await the completion of well-designed randomised controlled trials which are being planned.

The main limitation of our study lies in its retrospective nature. Most of the differences in drug response across clusters are driven by baseline HbA1c, precluding firm conclusions on the relative efficacy of these agents. There could be a small chance of including Maturity Onset Diabetes of the Young (MODY) or other types of diabetes as T2D. However, as the overall prevalence of other subtypes is very low, it is unlikely to influence the overall results. Another limitation is that we were unable to account for the effects of lifestyle modification on glycemic response; however, the participants have been recruited from specialist diabetes clinics with standardised treatment protocols, where all participants have been provided with diet and physical activity advice in addition to pharmacotherapy. A third limitation is that we were unable to assess the efficacy of drug categories such as GLP1 receptor agonists, alpha-glucosidase inhibitors and (to an extent) SGLT2i, on account of the small number of patients prescribed these drugs, perhaps a reflection of the cost of these agents as most patients pay out of pocket for medications in India. The final limitation relates to the varying modes of data collection and standardisation of management across study centres; however, the majority of data (n=19002) comes from the electronic medical records of the coordinating centre, which is a single institution with branches all over India following standardized protocols. Data from the other study centres have been collected from manual as well as electronic medical records. However, all the sites follow common management guidelines from the Research Society for the Study of Diabetes in India (RSSDI). `

Conclusions

In conclusion, our results confirm the four distinct clusters of T2D in a patient population derived from multiple diabetes clinics across India. Our findings suggest that traditional antihyperglycemic agents continue to enjoy wide popularity among prescribers in India, while newer agents are yet to gain ground. Identification of distinct phenotypes of T2D (using easily measurable variables) could help clinicians decide upon the most effective forms of therapy for the individual patient, an important first step towards precision and personalised diabetes care. Randomised controlled clinical trials are necessary to compare the efficiacy of various classes of antihyperglycemic agents in different subtypes of T2D in India.

Authors' Contributions: RMA, VM, ERP and MKS conceived the study, and were involved in the interpretation of data and wrote the first and subsequent drafts of the manuscript. VM, RMA, VKP, JK, BS, SG, AS, KGS, ND, MC, PC, SD, MB, RC, AN, AG and RK provided data for analysis. SJ, MAK, NKR and MKS were involved in statistical analyses. RU, RP, CNAP, ASFD, SRJ, SA and SB were involved in the interpretation of data and provided comments on drafts of the manuscript. All authors contributed to revision of the manuscript and approved the final submitted version. RMA is the guarantor of this work, and as such had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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