Original research

Dyslipidemia: The untreated metabolic dysfunction in people with type 2 diabetes in Latin America. ARETAEUS study outcomes

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ABSTRACT

Objective: To assess oral antihyperglycemic agents (OAHA) and/or statin treatment initiation in patients with type 2 diabetes (T2D) and time from diagnosis to both types of treatment initiation and intensification.

Research design and methods: We reviewed 662 retrospective medical records of patients with T2D diagnosed by 31 general practitioner or specialist sites across Mexico, Argentina, and Brazil. Demographic and clinical information was abstracted from patients' medical records and summarized using descriptive statistics. Between-group differences were assessed with Student’s t-test for continuous variables and Fisher’s exact test for categorical variables. The starting time of each therapy (OAHA and statins, separately) was assessed using Kaplan-Meier estimates.

Results: At diagnosis, patients’ mean age was 53 years; 44% had hypertension, 42% were obese, and 23% had dyslipidemia. During the 2-year follow-up, 95% of patients received OAHA but only 29% of those eligible for statins received this prescription. Mean ± SD and median (Q1, Q3) time to first OAHA was 59 ± 141 days and 1 (1, 31) day, respectively, and 230 ± 232 days and 132 (30, 406) days, respectively, for a statin. During follow-up, 51–53% of patients with HbA1c/FPG values above target did not intensify hyperglycemia treatment.

Conclusion: Dyslipidemia treatment in patients with T2D was delayed despite its known deleterious effect on atherosclerosis development and β-cell mass/function. Anti-hyperglycemic treatment was not intensified when targets were not attained. This prescriptive inertia needs to be corrected because attainment of HbA1c treatment goals becomes more difficult, favoring the development of diabetes complications.

Introduction

Diabetes impacts a large number of people worldwide and its prevalence continues to grow, particularly in developing countries [1,2]. Type 2 diabetes (T2D) is frequently associated with other cardiovascular risk factors (CVRF) and chronic complications, resulting in a worldwide burden that negatively impacts patient health, productivity and the health care budget [3–5]. The latter impact has also been demonstrated in Latin American countries [6,7], namely the INTERHEART study showed that obesity, dyslipidemia and smoking together account for 78% of the population-attributable risk in this Region [8]. Data from the CARMELA study reinforce the concept, showing the high prevalence of these risk factors in Latin American cities [9].

Cardiovascular disease (CVD) is an important cause of mortality worldwide and is expected to increase in the future [10]. Several studies demonstrated that lipid metabolism disorders are significantly associated with the pathogenesis of atherosclerosis, a key process for the development of CVD; in particular, one third of coronary artery disease (CAD) cases are attributable to high serum low-density lipoprotein cholesterol (LDL-c) levels [11]. A systematic review and meta-analysis

Abbreviations: T2D, type 2 diabetes; CVRF, cardiovascular risk factors; CVD, cardiovascular disease; CAD, coronary artery disease; CHD, coronary heart disease; OAHA, oral antihyperglycemic agents

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showed that in 2011 mortality rate due to cardiac failure in people with diabetes was responsible for a 55.56% death rate in Argentina and 9.09 in Brazil in 2014 [12]. It has also been shown that in 2015 the number of deaths related to diabetes (40–64 years of age) in Latin America accounted for 313,205 cases [13]. Further, years of life lost have increased globally for causes such as diabetes or some neoplasms [14]. On account of these data, treatment and control of these levels is the primary goal of CVD prevention in most guidelines [15–17].

Despite these recommendations, several studies have shown that management of high cholesterol levels is often suboptimal [18–20]. In fact, data from the National Health and Nutrition Examination Survey (NHANES) in the US from 2005 to 2008 showed that 33.5% of adults over 20 years of age had high LDL-c, but only 48.1% were treated [21].

Despite the fact that T2D significantly increases the risk of CVD and that several clinical trials have clearly shown that drugs like statins exert beneficial effects upon coronary heart disease (CHD) and can be used for primary CVD prevention [22,23], many primary care physicians have not yet adopted evidence-based lipid management strategies. Moreover, a meta-analysis of 14 randomized trials of statin therapy (mean follow-up 4.3 years) with data from more than 18,000 patients with diabetes demonstrated a 9% reduction in all-cause mortality, and a 13% reduction in vascular mortality, for each mmol/L (38.67 mg/dL) reduction in LDL-c [24]. Thus, LDL-C appears to have the greatest role in the development of early atherosclerosis and CAD in people with diabetes and thus must be treated aggressively to reduce such risk [25].

Despite this evidence on morbidity and mortality, data regarding the initiation of OAH and statin therapy, as well as the degree of control of LDL-c and HbA1c levels in patients with T2D in Latin America are lacking [26–28]. Since this information is important to establish public health awareness and treatment policies, the current study was conducted to evaluate these issues in real-world clinical practice in Mexico, Argentina, and Brazil. In this context, our study examines: 1) the average time elapsed from T2D diagnosis to initiation of OAHA and/or statins, 2) the percentage of people eligible for, but not receiving treatment with OAHA and/or statins and 3) the average time elapsed before intensification of T2D monotherapy when patients have not attained their treatment goal.

**Patients and methods**

This multinational, retrospective chart review study included 662 eligible patients managed by 31 physicians (GPs and specialists) across Mexico, Argentina, and Brazil (Mexico: 15 sites/373 patients; Argentina: 8 sites/193 patients; Brazil: 8 sites/96 patients). Physicians and sites were randomly selected among those with experience in treating regularly patients with T2D and CVRF in those countries.

**Inclusion criteria**

Patients were eligible for the study if 1) they were at least 21 years of age at the time of T2D diagnosis, 2) their disease was diagnosed by a physician within 24–48 months prior to the date of signing the written informed consent form, 3) they had verifiable pre-diagnosis history of relevant medication use (for the treatment of diabetes or dyslipidemia) and diabetes-associated preexisting medical illnesses/risk factors (e.g., obesity, dyslipidemia, cardiovascular events, or hypertension) for 12 months prior to the initial T2D diagnosis, 4) they were under the care/treatment of the study physician for a minimum of two years following the initial diagnosis of T2D, and 5) they were willing to provide written informed consent.

**Exclusion criteria**

Patients were excluded if they were diagnosed with type 1 diabetes (diagnosis made after a ketoacidosis episode and treated with insulin immediately after), pregnancy, or had been pregnant since the diagnosis of T2D, treated with any pharmacological antihyperglycemic medication prior to the date of their initial T2D diagnosis or, treated with insulin as their first medication after that diagnosis or had participated in another interventional clinical trial during the data collection period.

**Patient selection**

Investigators screened their medical records to find participants diagnosed with T2D within the preceding 24–48 months who met the inclusion/exclusion criteria. Selected participants were invited to participate in this study and then asked to provide written informed consent according to local regulations. After consent was obtained, information on demographics and CVRF at the time of diagnosis was collected. Additionally, information was collected on T2D history, medication usage, and relevant comorbid conditions including potential disease complications at the time of diagnosis of T2D and in the 12 months prior to this diagnosis. The investigator also gathered information on all changes in relevant medications, CVRF and diabetic complications for the subsequent 2 years. Clinical and laboratory indicators were recorded at the time of diagnosis of T2D and during the follow-up period at a maximum frequency of once per quarter or less (as available in the medical record). When available, clinical and laboratory indicators were also collected for the 12 months prior to T2D diagnosis (Fig. 1).

**Statistical analysis**

All demographic and clinical data were summarized for the total study population using descriptive statistics. Numerical variables were summarized using the number of observations (N), mean and standard deviation. Categorical variables were summarized using the number and percent of participants in the analysis set belonging to each category. Between-group differences with respect to participant demographics and baseline characteristics were assessed for statistical significance with Student’s t-test for continuous variables and Fisher’s exact test for categorical variables. P-values less than 0.05 were considered significant.

The starting time of each therapy (OAHA and statins, separately) was assessed using Kaplan-Meier estimates. This method described the cumulative incidence of therapy (number of participants having started therapy, independent of current use).

**Results**

Table 1a summarizes the baseline characteristics of the study population. Mean age of the 662 eligible patients was 53 years, with slightly more female than male participants. Only 21.5% of patients were diagnosed by a diabetologist and less than half of the population sample was obese (BMI ≥ 30 kg/m²) and had hypertension. However, average BMI was 31 kg/m².

Mean HbA1c and fasting blood glucose levels were above diagnostic
values for diabetes according to international guidelines [29].

Although average total cholesterol values were only slightly above target values, LDL-c and triglyceride levels were above those recommended by international guidelines.

Micro- and macroangiopathic complications at diagnosis were present in around 1% of the population, thus suggesting some delay in the diagnosis of T2D and CVRF.

In the follow-up period, neither BMI values nor the lipid profile showed significant changes.

### Table 1
Baseline and follow-up characteristics of patients diagnosed with T2D in Mexico, Argentina, and Brazil.

| Overall (N = 662) | n | Mean ± SD or % |
|-------------------|---|----------------|
| a) Baseline | | |
| Age (years) | 662 | 53 ± 12 |
| Gender | | |
| Male | 310 | 46.8% |
| Female | 352 | 53.2% |
| Family History of T2D | 427 | 64.5% |
| Family History of CVD | 240 | 36.3% |
| Smoking Status | | |
| Never | 458 | 69.2% |
| Current/Former | 173 | 26.2% |
| Unknown | 31 | 4.7% |
| CV Risk Factors | | |
| Hypertension | 289 | 43.7% |
| Obesity | 280 | 42.3% |
| High Cholesterol | 150 | 22.7% |
| Diagnosis done by | | |
| PCP/GP/PM/IM | 463 | 69.9% |
| Diabetologist/Endocrinologist | 142 | 21.5% |
| Other specialist | 57 | 8.6% |
| Comorbid Conditions | | |
| Heart failure or diabetic cardiomyopathy | 7 | 1.1% |
| PVD or intermittent claudication | 7 | 1.1% |
| Diabetic retinopathy | 5 | 0.8% |
| Diabetic nephropathy | 4 | 0.6% |
| Diabetic neuropathy | 10 | 1.5% |
| Diabetic foot | 2 | 0.3% |
| Clinical data | | |
| BMI (kg/m²) | 294 | 31 ± 6 |
| Systolic blood pressure (mmHg) | 282 | 130 ± 14 |
| Diastolic blood pressure (mmHg) | 282 | 80 ± 8 |
| Laboratory data | | |
| HbA1c (%) | 142 | 7.9 ± 1.6 |
| Fasting plasma glucose (mg/dL) | 362 | 181 ± 77 |
| Total cholesterol (mg/dL) | 224 | 206 ± 43 |
| LDL-c (mg/dL) | 111 | 126 ± 31 |
| HDL-c (mg/dL) | 103 | 45 ± 11 |
| Triglyceride (mg/dL) | 213 | 199 ± 106 |
| b) Follow-up | | |
| Smoking Status | | |
| Yes | 70 | 10.6% |
| No | 592 | 89.4% |
| CV Risk Factors | | |
| Hypertension | 352 | 53.2% |
| Obesity | 302 | 45.6% |
| High Cholesterol | 268 | 40.5% |
| Clinical data | | |
| BMI (kg/m²) | 554 | 31 ± 6 |
| Systolic blood pressure (mmHg) | 542 | 128 ± 14 |
| Diastolic blood pressure (mmHg) | 542 | 79 ± 8 |
| Laboratory Measures | | |
| HbA1c (%) | 504 | 7.4 ± 1.4 |
| Fasting plasma glucose (mg/dL) | 547 | 145 ± 48 |
| Total cholesterol (mg/dL) | 472 | 192 ± 35 |
| LDL-c (mg/dL) | 313 | 114 ± 31 |
| HDL-c (mg/dL) | 296 | 44 ± 12 |
| Triglyceride (mg/dL) | 465 | 176 ± 96 |

### Table 2
Baseline clinical and laboratory data by OAHA and Statin Initiation Status.

| Initiated OAHA (n = 627; 95%) | Did Not Initiate OAHA (n = 35; 5%) |
|-------------------------------|-----------------------------------|
| n | Mean ± SD | n | Mean ± SD |
| a. By OAHA Initiation Status | | |
| Age at diagnosis | 627 | 53 ± 12 | 35 | 54 ± 9 |
| BMI | 352 | 31 ± 6 | 10 | 33 ± 7 |
| Systolic blood pressure | 324 | 130 ± 16 | 12 | 130 ± 15 |
| Diastolic blood pressure | 324 | 81 ± 9 | 12 | 85 ± 13 |
| HbA1c | 150 | 7.9 ± 1.6 | 6 | 7.2 ± 0.8 |
| Fasting plasma glucose | 373 | 187 ± 77 | 13 | 138 ± 39 |
| Total cholesterol | 235 | 206 ± 44 | 9 | 198 ± 22 |
| LDL-c | 110 | 125 ± 30 | 5 | 135 ± 38 |
| HDL-c | 102 | 44 ± 11 | 5 | 45 ± 15 |
| Triglyceride | 220 | 199 ± 106 | 9 | 150 ± 74 |
| b. By Statin Initiation Status (of those eligible to receive a statin) | | |
| Age at diagnosis | 152 | 57 ± 12 | 373 | 54 ± 11 |
| BMI | 96 | 30 ± 4 | 187 | 31 ± 6 |
| Systolic blood pressure | 87 | 131 ± 17 | 184 | 131 ± 15 |
| Diastolic blood pressure | 87 | 81 ± 9 | 184 | 81 ± 9 |
| HbA1c | 39 | 7.4 ± 1.4 | 89 | 7.7 ± 1.4 |
| Fasting plasma glucose | 94 | 192 ± 87 | 223 | 180 ± 71 |
| Total cholesterol | 56 | 208 ± 43 | 207 | 211 ± 44 |
| LDL-c | 39 | 133 ± 37 | 70 | 124 ± 25 |
| HDL-c | 32 | 45 ± 10 | 68 | 45 ± 11 |
| Triglyceride | 54 | 203 ± 86 | 141 | 187 ± 100 |

*P-value < 0.05, †P-value < 0.001.

Ninety-five percent of patients started treatment with OAHA after T2D diagnosis (Table 2a). Compared to those patients without treatment prescription, their fasting blood glucose as well as HbA1c levels were significantly higher. Anyhow, untreated patients still had abnormally high values of both fasting blood glucose and HbA1c levels. Most patients treated with OAHA (82%) initiated treatment as monotherapy, while the rest used different combinations of these drugs; the average time elapsed before starting treatment was close to 2 months. No significant differences were found between patients diagnosed by general practitioners, diabetologists/endocrinologists or other specialists.

Although 51% of patients who initiated OAHA monotherapy had HbA1c values ≥ 7% and 53% had FPG values ≥ 126 mg/dl during the follow-up period, only 20% intensified their treatment during such period (data not shown). The time elapsed until prescription of treatment intensification (i.e., add-on therapy) was 308 ± 213 days.

Data from the follow-up period (Table 2) showed an increase in the percentage of patients with hypertension, obesity, and dyslipidemia. In spite of a slight decrease in the average levels of HbA1c, fasting blood glucose, LDL-c and triglyceride levels remained above treatment target values in 18% and 35%, respectively. This observation suggests that these people were not appropriately treated to prevent the development and progression of diabetes chronic complications.

Of the patients eligible to receive statins according to ADA guidelines [29], only 29% initiated this treatment (Table 2b) after an average period of 8 months. Unexpectedly, diabetologists and endocrinologists started the statin prescription less often than general practitioners.

Comparing the clinical and metabolic profiles of the treated and untreated groups, the only significant difference was that people in the
former group were older age and had lower BMI (Table 2b).

Discussion

In our study, following T2D diagnosis OAHAs were prescribed only after a period in which fasting blood glucose and HbA1c levels were markedly above treatment target levels. Delayed diagnosis/treatment of T2D has been reported previously in Argentina and Mexico [30,31], even though the ADA has developed recommendations to test for T2D in high-risk populations [29]. This attitude was associated with a delayed intensification treatment prescription that played against prevention of diabetic chronic complications, increased cost of care and decreased quality of life of people with the disease. Similarly, Brown and Nichols reported that practitioners delayed treatment intensification for long periods even in the presence of sustained high HbA1c levels [32], a prescriptive inertia that also favors the development and progression of chronic complications [33].

Statin treatment initiation was also delayed in spite of the presence of high LDL-c levels, either before or after diagnosis of T2D, even though large-scale clinical trials have demonstrated that statins substantially reduce cardiovascular morbidity and mortality in both primary and secondary prevention [34-37]. Based on our results we could assume that physicians involved in the study are neither aware of the above mentioned benefits nor of the ADA guideline recommendations to use statins in patients over 40 years of age with diabetes presenting with one or more CVRF regardless of the value of serum lipids [29]. Patients in our study also had high triglyceride levels, which have shown indirect association with increased risk of death and major CV events [35]. Similar prescriptive attitudes have been reported in other latitudes: only 47% of people who suffered a stroke were treated with lipid-lowering drugs although 72.5% of the cases presented dyslipidemia, and only 24.8% of those treated attained LDL-c target values (≤100 mg/dL) [38]. Although dyslipidemia in patients with T2D has mostly been related to the prevention of macrovascular complications, the Verona Study demonstrated that it also affects microvascular complications, highlighting the importance of high fasting triglycerides/HDL-c ratio in relation to increased risk of developing diabetic retinopathy or nephropathy [39]. A post-hoc analysis from the ADVANCE study also highlighted low levels of HDL-c as a prognostic factor for the development of diabetic-related renal events, in particular new-onset albuminuria [36]. Similarly, the REALIST study showed that elevated levels of triglyceride and low levels of HDL-c were both significant and independently associated with diabetic microvascular complications [40].

Statin prescription however, does not always attain its aim: in patients with a combination of coronary heart disease plus diabetes, target LDL-c values (2.6 mmol/L) were reached by only 31.8% of patients treated with simvastatin 40 mg/day at entry and by 50.0% after 12 months of follow up [41]. Low patient compliance with drugs prescribed contributes to this low target value attainment [42].

Untreated dyslipidemia could also impair other metabolic functions not always considered: LDL-c can decrease maximal glucose-stimulated insulin secretion in isolated human and murine islets [43] and it also does under in vivo conditions [44]. Data in the literature suggest that the deleterious effect of increased LDL-c on β-cell function/mass could be potentiated by the simultaneous decrease in HDL-c concentration [43,44], making the attainment of HbA1c target values more difficult, as recently reported [45].

Our data also show that these dual negative effects of dyslipidemia are not seriously considered by our physicians since an important percentage of people with LDL-c and TG levels are not treated or not appropriately treated to bring them down to target values. Another factor that contributes to this problem is the low frequency of dyslipidemia assessment in general population and in particularly in people with T2D [46].

Although clear and statistically significant, our data have some limitations that should be considered: 1) the sample size was small, which limits its statistical power; 2) certain geographic areas may have been under-represented or not represented in the study population; 3) some patient charts were incomplete; and 4) we cannot discard some kind of population bias. Despite these limitations, the current study provides important real world information for decision makers and public health authorities regarding deficiencies in the quality of care provided to people with T2D. All together, they call attention to the urgent need to implement efficient strategies to decrease the present and future diabetes burden for patients as well as for the health care system. According to evidence provided by randomized long-term prospective studies, education implemented at every level could be an effective tool to achieve this goal [47,48].

Conclusion

Even though the majority of patients in our population were treated with an OAHAs, statin prescription and intensification of OAHs therapy were delayed and suboptimal. These data demonstrate the existing treatment gap between guideline recommendations for the prevention of chronic complications and current real-world practice, at least in clinics from the three Latin American countries studied.

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Author contribution

J.JG, RA, FGE, KL, KB, CDG, SY, OH, PK, and KT were involved in the conception and design of the study. J.JG, RA and FGE were responsible for patient recruitment and data collection in their own countries, as well as preparation of the draft manuscript. All co-authors interpreted the study data, critically revised the draft for intellectual content and approved the final manuscript.

Conflict of interest

J.JG, RA, FGE, OH and PK have disclosed that they received research support from Merck & Co. Inc., Kenilworth, NJ USA for the conduct of this study. KL, KB, CDG, SY, RRS and KT have disclosed that they are/were full-time employees of Merck & Co. Inc., Kenilworth, NJ, USA at the time of the analysis and may potentially own stock and/or hold stock options in the company. RA and J JG have served as advisors to Merck Sharp and Dohme Corp., Sanofi, Eli Lilly, andNovo Nordisk, as well as speakers for all these companies and AstraZeneca; they have also received unrestricted research support from Sanofi, Eli Lilly, Novo Nordisk and AstraZeneca. FGE has served as a speaker and an advisor to Novo Nordisk, Sanofí, AstraZeneca, Merck Sharp and Dohme Corp., Takeda, Boehringer Ingelheim Pharmaceuticals, Inc., andEli Lilly. KB is currently employed byBoehringer Ingelheim Pharmaceuticals, Inc.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcte.2019.01.002.

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