Silvina Guaita María (Orcid ID: 0000-0001-5576-6239)

Pozzilli Paolo (Orcid ID: 0000-0001-5090-636X)

DMRR-19-RES-106

TREAT-TO-TARGET HbA1c AND LIPID PROFILE TO PROLONG β -CELL
MASS/FUNCTION AND OPTIMIZE TREATMENT-GOAL ATTAINMENT

Juan J.Gagliardino¹, Jorge Elgart¹, Luján Forti², Guaita María Silvina², Jean M.Chantelot³.

¹CENEXA. Centro de Endocrinología Experimental y Aplicada (UNLP-CONICET), School
of Medicine, National University of La Plata, La Plata, Argentina

²Sanofi, Buenos Aires, Argentina

³Sanofi, Paris, France

*Corresponding Author:

Dr. María Silvina Guaita

Phone: +54 911 57541174

Address: Cuyo 3532, B1640GJC Martínez, Buenos Aires, Argentina

E-mail: Mariasilvina.Guaita@sanofi.com

Word count: 2568

Tables: 2

Figures: 2

Short Running Title: Lipid profile in people with type 2 diabetes

Keywords: Lipid Profiles - Hemoglobin A1c- LDL Cholesterol- β -cell-A1c Target

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/dmrr.3166

Abstract

Aim: To evaluate the relation between different serum lipid fractions and other known barriers to attain the HbA1c $\leq 7.0\%$ (53 mmol/mol) target.

Methods: Data on 2719 patients with type 2 diabetes were collected from the five waves of the International Diabetes Mellitus Practice Study implemented in Argentina (2006 to 2012) including: demographic/socioeconomic profile, clinical, metabolic (HbA1c and serum lipids) data, and treatment type; also, percentage of treatment goal attainment. Descriptive statistical analyses included ANOVA, Chi2 test, and Fisher's exact test; univariate and multivariate logistic regression analyses, that identified predictive factors for HbA1c $\leq 7\%$ (53 mmol/mol).

Results: The average age was 63 years, primary/secondary education, health insurance, 10-year type 2 diabetes duration, most associated with cardiovascular risk factors and some microvascular/macrovacular complications; 94.5% received antihyperglycemic drugs.

Percentage of people on target: HbA1c 51.2%, blood pressure 23.5%, total cholesterol 62.6%, LDL-cholesterol 38.9% and triglycerides 61.1%. HbA1c on target depended markedly on treatment type: more of those treated with lifestyle changes and significantly fewer of those receiving insulin. Only 4.1% had all parameters simultaneously on target. Multivariate logistic regression analyses showed that achieving HbA1c $\leq 7.0\%$ (53 mmol/mol) was associated with higher educational level, shorter diabetes duration, and having reached goals for LDL-cholesterol and triglycerides, whereas opposite results were obtained with insulin treatment and longer diabetes duration.

Conclusions: High LDL-cholesterol and triglycerides levels simultaneously potentiate development/progression of chronic complications, exerting this effect in the long term by decreasing β -cell mass/function, thereby making it more difficult to reach HbA1c values able to prevent complications.

1. Introduction

Type 2 diabetes is a chronic disease frequently associated with other cardiovascular risk factors (CVRF) that facilitate development/progression of chronic complications and increase treatment costs (1), thereby becoming a heavy burden on patients and the health budget (2,3).

This disease is characterized by sustained hyperglycemia caused by progressive failure of β -cell secretion failing to cope with increased demand for hormone by peripheral tissues (insulin deficiency + insulin resistance) (4-7). This deficient response results from progressive impairment of β -cell mass and function (8-10); consequently, at some stage of the disease, insulin administration may be necessary to attain recommended HbA1c target values, which requires overcoming physicians' and patients' barriers (7,11,12). Time-course changes in treatment type leads to a different percentage of people with HbA1c on target: in a previous International Diabetes Mellitus Practice Study report (IDMPS), we showed that for people with type 2 diabetes, short disease duration and use of few oral glucose-lowering drugs (OGLDs) were predictive factors of attaining target HbA1c values in all regions studied (13).

Available evidence also shows that diabetes is an independent risk factor for developing cardiovascular risk; with such events being the most common cause of death in type 2 diabetes (14,15). However, multifactorial care of people with type 2 diabetes (simultaneous treatment of hyperglycemia, hypertension, and dyslipidemia) effectively reduced rates of death and cardiovascular disorders (16). Also, this multifactorial approach could have additional advantages: since dyslipidemia exerts a direct deleterious effect on β -cell mass/function (17), its control might not only prevent occlusive atherosclerosis, but could also prolong β -cell half-life and consequently, improve chances of reaching HbA1c goal values.

We now provide additional evidence to support the latter assumption by evaluating the relation between attainment of $\text{HbA1c} \leq 7.0\%$ (53mmol/mol) values and of different serum lipid

fractions, as well as other known barriers to attain this goal by analyzing data from the five waves of the IDMPS implemented in Argentina between 2006 and 2012.

2. Methods

2.1. Study design

IDMPS is an international, multicenter, prospective, observational study on patients with type 1 and type 2 diabetes. This survey is designed following STROBE guidelines as described elsewhere (13,18). Briefly, IDMPS is composed of 5 cross-sectional registries (operationally called “waves”) over a 5-year period to assess changing practices in the management of people with diabetes. Each wave consists of two phases: a 2-week cross-sectional registry and a 9-month longitudinal survey. A 3-month interval separates the end of the longitudinal survey and the start of the next wave. Only cross-sectional registry data from Argentina are analyzed in the present report.

2.2. Data collection and outcome measures

Data were collected on case report forms recording demographic and socioeconomic profile, medical history, medications, glycemic control, blood pressure and lipid status, self-care, access to patient education, follow-up mode, work absenteeism, and hospitalization. Outcome measurement included attainment of treatment goals defined as HbA1c $\leq 7\%$ (53 mmol/mol), blood pressure $\leq 130/80$ mmHg, and LDL cholesterol ≤ 100 mg/dl (19).

2.3. Sample size estimation and selection of physicians

The number of subjects to be recruited in each participating country was determined on a country basis. Based on the assumption that insulin is the least prescribed therapy, the sample was determined in order to establish the frequency of insulin-treated patients (13,18). Therefore, physicians with experience on the initiation and titration of insulin therapy were

invited to participate. A total of 210 Argentinian physicians participated in the 5 waves (2719 patients with type 2 diabetes).

2.4. Study implementation

A steering committee advised the project team on the study design and registry structure, monitored study progress, reviewed and validated all study-related documents, and proposed and approved decisions on protocol amendments, analyses, and publications. The study was coordinated by Sanofi-Aventis Intercontinental. In each country, the study was advocated by a leading diabetologist who compiled and endorsed the list of investigators. The latter were assisted by local Sanofi-Aventis staff in collecting relevant information including clinical and laboratory parameters. Ethics approval was obtained from institutional boards from each country. All participants provided their written informed consent.

2.5. Statistical analysis

Statistical analyses were conducted with the Statistical Package for Social Sciences version 15 (SPSS Inc., Chicago, IL, USA). Descriptive Analysis, ANOVA, Chi2 Test, and Fisher's Exact Test were used as appropriate. Univariate and multivariate logistic regression analyses were run to identify predictive factors for $HbA1c \leq 7\%$ (53 mmol/mol). Potential predictive factors included gender, age, diabetes duration, education level, health insurance, Body Mass Index (BMI), blood pressure, lipid profile (Total Cholesterol, LDL Cholesterol, and TG), and diabetes treatment. A backward selection procedure identified predictive factors significant at 5%.

3. Results

Most of our study population was urban (93.9%), had a primary/secondary education, declared combined social security/prepaid health insurance, had some degree of

microvascular/macrovascular complications and were treated with different antihyperglycemic drugs (94.4%). Regarding treatments, most patients were treated with OGLDs (60.8%), while insulin treatment (alone [12.5%] or combined with OGLD [21.1%]) represented 33.6% (Table 1).

Their clinical-metabolic characteristics showed an average of 63 years of age, of 10-year duration of type 2 diabetes; most having associated CVRFs, specifically, overweight/obesity (87.5%), hypertension (73%) and dyslipidemia (70.3%) (Table 1). Average values for the parameters recorded showed blood pressure within target values recommended by ADA/EASD guidelines (23), moderate increase in fasting blood sugar, HbA1c levels close to those recommended by guidelines, and uneven control of their serum lipid profile (Table 1). In fact, whereas total cholesterol, HDL-c and TG levels were within control levels, those of LDL-c were above treatment goals (Table 1).

Despite this acceptable average value profile, a different picture emerged when it was considered the percentage of people on target for each parameter, i.e. values able to prevent development/progression of chronic complications (Table 1): for HbA1c it was 51.2%, for blood pressure 23.5%, for total cholesterol 62.6%, for LDL-cholesterol 38.9%, and for TG 61.1%. It has to be stressed that the percentage of people with HbA1c on target varied markedly depending on treatment type: higher in the group of people treated with lifestyle changes and significantly lower in those receiving insulin (Figure 1). However, when we measured the percentage of people having their HbA1c, blood pressure and complete lipid profile simultaneously on target, we found that only 4.1% attained that goal.

Regarding our main objective –to verify the negative influence of dyslipidemia on attainment of the HbA1c goal- when we tracked the population according to their HbA1c levels $\leq 7.0\%$ (53 mmol/mol), we found that those who attained HbA1c target values exhibited significantly lower levels of lipid fractions (Table 2).

The results of multivariate logistic regression analyses presented in Figure 2, show that for people with type 2 diabetes, achieving $HbA1c \leq 7.0\%$ (53 mmol/mol) was a positively association with a higher educational level (OR: 1.399, 95% CI: 1.107 - 1.767), and with having reached the goal for LDL-cholesterol (OR: 1.344, 95% CI: 1.091 - 1.656) and TG (OR: 1.854, 95% CI: 1.501 - 2.290), whereas it was negatively associated with insulin treatment (OR: 0.296, 95% CI: 0.186 - 0.470) and diabetes duration (either OR: 0.762, 95% CI 0.588 - 0.987 or OR: 0.541, 95% CI 0.420 - 0.696).

4. Discussion

Chronic type 2 diabetes complications result in high morbidity, mortality, and socio-economic costs, which can be significantly reduced by control of hyperglycemia and associated CVRF - unfortunately achieved infrequently (2, 20-22). In our study, approximately 50% of the population was on the target values recommended by ADA standards for HbA1c and other CVRFs (23).

On the other hand, the intensive multifactorial approach to treat these people has been shown to be an efficient and cost-effective way to prevent development and progression of these complications (16, 24, 25). However, in our country, only about 4% of the population attain this multifactorial goal.

For HbA1c the target is $\leq 7.0\%$; the attainment of this value depends on many factors: in our study, treatment type was significantly associated with different percentages of people on target: a higher percentage was attributable to healthy lifestyle and a lower percentage to insulin treatment. Similar polarizations were also found by other authors (26). In a previous IDMPs report performed worldwide, we found that people with short duration type 2 diabetes and use of few OGLDs were predictive factors of attaining HbA1c at target values in all regions studied (13). Similarly, the United Kingdom Prospective Diabetes Study (14),

which examined the time-course of islet dysfunction in patients with type 2 diabetes, showed that β -cell function - estimated by HOMA index - underwent progressive deterioration during the first 6 years of observation in patients without insulin therapy (27). Comparable data were reported by De Pablo et al: using a logistic model, they found that disease duration was predictive of glycemic control (longer was associated with higher frequency of poor glycemic control (OR = 1.033) and stable insulin treatment (OR = 4.054)) (28). These data suggest that early diagnosis may increase the likelihood of attaining glycemic targets, probably because people with type 2 diabetes show progressive deterioration of both β -cell mass and function (7,8,10). Accordingly, we may reasonably assume that remnant functional β -cell mass efficiently controls glucose homeostasis at an earlier stage of the disease, whereas later on this control depends on the physician-patient couple's abilities/commitment. However, other factors may also participate in triggering the impaired mechanism: the multiple variable analysis performed in our study demonstrated that educational level, disease duration, blood pressure, total cholesterol, LDL-cholesterol and TG levels as well as treatment type (except OGLDs), also significantly affect attainment of $\text{HbA1c} \leq 7.0\%$ (53 mmol/mol) (Figure 2). Reciprocally, HbA1c is not only a reliable biomarker of glycemic control but also may be a good predictor of serum lipid profile in people with type 2 diabetes: those with $\text{HbA1c} \leq 6\%$ – 9% (42–75 mmol/mol) and $>9\%$ (75 mmol/mol) tend to have moderate and severe dyslipidemia, respectively (29), even though further studies need to be driven to assess this. The principal aim of our study is to gain deep insight into the analysis of dyslipidemia's role in attainment of target HbA1c values.

People with normal glucose tolerance (NGT) and dyslipidemia characterized by abnormal high TG and low HDL-c have also been shown to have impaired insulin sensitivity and β -cell function: levels of these lipid fractions correlated with insulin resistance (IR), while they were negatively correlated with pancreatic β -cell response to IR (30). The HOMA-IR score is

a useful but costly indicator of IR and therefore frequently inaccessible for general purposes; for this reason, the TG/HDL-cholesterol ratio has been proposed for use as a simple IR marker (31, 32); with some ethnic restrictions, it might be inversely related to β -cell function (33). The cut-off value for this TG/HDL-cholesterol ratio was validated in our country as >3.5 and >2.5 for men and women, respectively (34). Following this reasoning, in a longitudinal assessment of the temporal relations between serum lipids and IR using cross-lagged path analysis models, Han et al found that abnormally high levels of TG and low HDL-cholesterol probably precede those of peripheral IR (35). They also showed a significant causal mediating effect of 2-h insulin on the unidirectional relation running from blood lipids to IR. These findings provide more evidence for effective IR prevention by improving dyslipidemia.

Further, LDL-cholesterol can decrease maximal glucose-stimulated insulin secretion (GSIS) already in the normal range (3.1 mmol/L) in isolated human and murine islets (17). These results were confirmed and extended by *in vivo* conditions: mice with hypercholesterolemia induced by feeding a cholesterol-rich Western type diet showed increased cholesterol content in their β -cells associated with reduced GSIS and hyperglycemia; while LDL-cholesterol decreased the proliferation of primary β -cells in mouse or human islets (17). Identification of plasma lipoprotein receptor in pancreatic β cells involved in their binding/processing, as well as the report that LDL-cholesterol particles reduce insulin mRNA levels and β -cell proliferation and also induce a dose-dependent increase in their apoptotic rate, support this assumption. Conversely, HDL-cholesterol particles antagonize the proapoptotic effect of LDL-cholesterol. The antagonistic effect of LDL-, HDL- and cholesterol on regulation of β -cell function and survival as well as on target tissue insulin sensitivity and consequently on type 2 diabetes development were reviewed by von Eckardstein and Siblira (36). These and other reports suggest that the deleterious effect of increased LDL-cholesterol on β -cell

function/mass could be potentiated by the simultaneous decrease in HDL-cholesterol concentration (17,37,38).

Related to the relation between HbA1c and LDL-cholesterol levels and their impact on cardiovascular complications, a retrospective study among US veterans with type 2 diabetes concluded that simultaneous target achievement of these two metabolic indicators rather than each one separately was associated with lower risk of microvascular and macrovascular events, fewer hospitalization days and outpatient visits; thus resulting in better outcomes and lower resource consumption (39).

Based on this evidence, we could conclude that dyslipidemia, particularly high LDL-cholesterol and TG levels, not only may potentiate development/progression of chronic complications, but also could exert this effect in the long term by decreasing β -cell mass and function which making more difficult to reach HbA1c target values able to prevent this effect. 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 high LDL-cholesterol and TG levels were not treated or not treated specifically to bring them down to target values.

We assume that, although consistent, our data have some weaknesses and must therefore be considered with caution: a) it is a retrospective data analysis; b) it is not a strict population study, since providers were mainly specialists, consequently not representative of large population health care quality. However, the latter factor is particularly alarming, since if serious failures were detected at this level, patient care at the primary care level must presumably be worse.

Data obtained from our ongoing primary care level, showing the beneficial effects of education of physicians, nurses, and type 2 diabetes patients for attaining target values of HbA1c and serum lipids, as well as its cost-effective ratio (40), support the concept that

education is a reliable tool to modify the current impaired prescription/adherence and to optimize the quality of care and prevention of complications.

Acknowledgments: The authors would like to acknowledge the patients who participated in the study, the involvement of the IDMPS steering committee and the study investigators from Argentina, and editorial support from Susan Rogers from CENEXA. The IDMPS global study was funded by Sanofi. This subanalysis publication was not funded.

Conflict of interest: The authors Juan.J. Gagliardino and Jorge Elgart do not present a conflict of interest. Lujan Forti, María Silvina Guaita and Jean Marc Chantelot are members of Sanofi's medical department.

JJG is part of the IDMPS global study steering committee, representative in Argentina and intellectual author of the publication. JE, SG, LF and JMC contributed to the analysis of the data and drafting of the manuscript. All authors have read and approved the final manuscript.

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Figure 1. People with type 2 diabetes on Target ($\text{HbA1c} \leq 7\%$ / $<53 \text{ mmol/mol}$) by Treatment

D&F: Diet and Physical Activity, OGLDs: Oral glucose lowering drugs

Figure 2. Multivariate Logistic Regression

* Reference modality in underlined and italic text

Accepted

Table 1. Characteristics of the study population

Parameter	Mean $\pm$ SD	%	N
Male (%)	-	51.8	1,376
Age (years)	63.4 $\pm$ 11.1	-	2,716
Diabetes duration (years)	10.2 $\pm$ 8.6	-	2,620
Educational Level			
– Illiterate (%)		1.0	27
– Primary / Secondary (%)		73.7	1,924
– University or higher (%)		25.3	662
Type of Coverage			
– Public (%)		40.7	943
– Private / Mixed (%)		59.3	1,374
BMI (kg/m ²)	30.8 $\pm$ 5.6	-	2,709
– Normal weight (18.5 $\leq$ BMI < 25) (%)	-	12.6	340
– Overweight (25 $\leq$ BMI < 30) (%)	-	38.0	1,029
– Obesity (30 $\leq$ BMI < 35) (%)	-	29.3	793
– Morbid obesity (BMI $\geq$ 35) (%)	-	20.2	546
SBP (mmHg)	130.2 $\pm$ 15.0	-	2,701
DBP (mmHg)	78.6 $\pm$ 9.7	-	2,702
SBP < 130 and DBP < 80 (%)	-	23.5	636
FBG (mg/dl)	137.5 $\pm$ 49.0	-	2,621
HbA1c (%)	7.3 $\pm$ 1.6	-	2,552
HbA1c $\leq$ 7% (53 mmol/mol)	-	51.2	1,306
Total Cholesterol (mg/dl)	189.5 $\pm$ 38.7	-	2,516
Total Cholesterol < 200mg/dl (%)	-	62.6	1,576
HDL-c (mg/dl)	49.5 $\pm$ 16.6	-	2,401
LDL-c (mg/dl)	111.2 $\pm$ 33.6	-	2,323
LDL-c < 100 mg/dl (%)	-	38.9	911
Triglycerides (mg/dl)	151.2 $\pm$ 83.4	-	2,493
Triglycerides < 150 mg/dl (%)	-	61.1	1,523
Hypertension (%)	-	73.0	1,976
Dyslipemia (%)	-	70.3	1,892

Micro- or macrovascular Complications (%)		43.9	1,119
Treatment type			
– D&F (%)		5.6	144
– OGLDs Only (%)		60.8	1,551
– OGLDs and Insulin (%)		21.1	538
– Insulin alone (%)		12.5	319

SD: standard deviation. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBG: Fasting blood glucose; HDL-c: High density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; BMI: Body mass index. D&F: Diet and Physical Activity, OGLDs: Oral Glucose Lowering Drugs

Table 2. Dyslipidemia according to HbA1c level.

Parameter	HbA1c > 7% (53 mmol/mol)	HbA1c ≤ 7% (53 mol/mol)	P-value
Total Cholesterol (mg/dl)	193.3 ± 40.1 (1,167)	184.2 ± 36.3 (1,243)	0.000
Total Cholesterol < 200 mg/dl (%)	59.2 (691)	68.1 (846)	0.000
HDL-c (mg/dl)	49.2 ± 18.4 (1,110)	49.9 ± 14.6 (1,207)	0.341
LDL-c (mg/dl)	114.5 ± 34.7 (1,071)	107.2 ± 31.7 (1,171)	0.000
LDL-c < 100 mg/dl (%)	35.6 (384)	42.9 (507)	0.000
Triglycerides (mg/dl)	162.6 ± 94.8 (1,154)	138.9 ± 67.7 (1,239)	0.000
Triglycerides < 150 mg/dl (%)	55.5 (640)	67.2 (833)	0.005

Values are mean ± standard deviation (SD). Number of cases in parentheses.

HDL-c: High density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol.