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Original Article

Novel determinants preventing achievement of major cardiovascular targets in type 2 diabetes

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ABSTRACT

Background: T2DM management requires tight control of 3 critical quality indicators to prevent vascular complications: LDL-C, SBP, and HbA_{1c}. This study evaluated the rate of T2DM patients attaining these critical quality indicators, and the pathophysiological or cardiometabolic traits predicting goal achievement.

Patients and methods: Cross-sectional analysis evaluating combined goal achievement (LDL-C < 100 mg/dL; SBP < 130 mmHg and HbA_{1c} < 7.0%) in 1005 T2DM outpatients (654 men) followed in a university hospital multidisciplinary department. Triple-goal achievers were compared to non-achievers regarding sociodemographics; anthropometrics; homeostatic model assessment (HOMA; β-cell function (B); insulin sensitivity (S); hyperbolic product (B × S)); CV and glucose-lowering drugs; micro-/macrovascular outcomes; and 10-year UKPDS risk.

Results: Eighty-eight patients (9%; ((3 targets) group) reached all goals, whereas 917 patients (91%; ((0–2 target(s)) group) missed 1, 2 or all 3 goals. Compared to (0–2 target(s)), (3 targets) had shorter diabetes duration; less familial diabetes history; lower waist/visceral fat; higher β-cell function and hyperbolic product (B × S); lower (B × S) loss rate and less metabolic syndrome (all $p < 0.05$). They had lower apoB and triglycerides; and a 28% prevalence of atherogenic dyslipidemia (*vs.* 40% in (0–2 target(s)); p 0.0398). Microangiopathy (36% *vs.* 53%) and 10-year CAD risk (13% *vs.* 18%) were also significantly lower in (3 targets).

Conclusions: The subset of T2DM patients achieving all critical quality indicators are characterized by a less severe cardiometabolic phenotype, while exhibiting a less pronounced alteration of their residual β-cell function. These differences are related to fewer microvascular outcomes and lower 10-year CV risk.

1. Introduction

Measuring exposure to key cardiovascular (CV) risk factors (RFs), as continuous or discrete variables, is the cornerstone of risk assessment for patients in primary CV prevention, with global vascular control reflected by aggregate achievement of pre-set targets for major modifiable continuous outcomes variables [1–10]. According to guidelines, type 2 diabetes (T2DM) management requires tight control of three critical quality indicators to prevent long-term complications. Besides lifelong smoking cessation, low-density lipoprotein cholesterol (LDL-C), systolic blood pressure (SBP), and HbA_{1c} (as surrogate for chronic hyperglycaemia) are reckoned as key priorities regarding assessment and goal achievement [2,4–6,10]. This paradigmatic approach is consistent with the natural history of T2DM and the epidemiology of diabetic micro- and macrovascular complications. It also takes into account the synergistic effects of each RF on adverse CV outcomes affecting large arteries (when SBP coexists with high LDL-C), and small arteries (when hyperglycaemia joins with hypertension) [3,8,9].

Landmark prospective trials in patients with T2DM have established the effectiveness of targeting separately each critical variable with CV or glucose-lowering drugs [11–24]. In real-life, all

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modifiable RFs should be targeted synchronously, brought below target, and maintained at goal over time. Such a multifactorial approach has demonstrated its effectiveness in T2DM, with micro- and macrovascular outcomes markedly reduced following simultaneous improvement in all critical quality indicators [25].

There is limited data regarding how many ordinary T2DM patients reach these three targets, yet establishing this rate provides key information on practice's operational and clinical performance within a comprehensive benchmarking process [7,8,26]. In OPTIMISE (*OPtimal Type 2 dIabetes Management Including benchmarking and Standard treatment*) study (NCT00681850), triple goal achievement (LDL-C < 100 mg/dL; SBP < 130 mmHg; and HbA_{1c} < 7.0% (53 mmol/mol)) was reported in less than 1 in 20 T2DM patients followed in general practice [8,9]. The analysis of the determinants underlying this poor performance was however not considered in this trial. Hence this study aimed to analyze the phenotypic components associated with targets achievement, by documenting: (*i*) the proportion of T2DM attaining the three critical quality indicators when followed by physicians and multidisciplinary teams dedicated to diabetes management; and (*ii*) which pathophysiological and cardiometabolic traits predict simultaneous goal achievement.

2. Patients and methods

The aim of the survey was to review determinants associated with the control of risk factors, from a survey of most recent data available concerning patients who attended the outpatient diabetes clinic of St-Luc Hospital, as part of their routine medical care (1–2 *x*/year). The period during which the records of consecutive patients were analyzed extended from March 2012 to February 2013. For patients who consulted more than once over the review period, only the biological, therapeutic and clinical data on the most recent visit were taken into account. At the end of the survey period, the records analyzed related to 1005 consecutive adults with T2DM, followed in secondary care (specialized multidisciplinary department within an academic hospital). There were 654 men and 351 women. Ancestry was as followed: North-Caucasian (81%); North-African (9%); sub-Saharan African (7%); Turkish (1.5%); East-Asians (1.0%); and Indo-Pakistani (0.5%). Patients were divided according to whether or not they met (or failed to meet) an aggregate target of reaching goal for all three key modifiable CV RFs (HbA_{1c} < 7.0%; SBP < 130 mmHg and LDL-C < 100 mg/dL), with a (3 targets) group being compared to a (0–2 target(s)) group.

The following socio-demographic and clinical variables were recorded: age; gender; highest educational attainment (dichotomized as follows: secondary school with leaving certificate (no graduation) or below, and school leaving certificate (with graduation) *vs.* further education (but no degree), and university degree (or similar)); diabetes duration; family history (early-onset coronary heart disease and/or DM); smoking history; habitual ethanol intake; leisure-time (LT) exercise duration; LT spent in front of computer screens or television; performing self-measurement of capillary blood glucose (SMBG); and current medications (glucose-lowering drugs; CV drugs (blood-pressure (BP)-lowering agents; aspirin (as antiplatelet agent); lipid-lowering drugs (LLD): statins; fibrates and/or ezetimibe)).

Weight, height, body mass index (BMI); relative/total body fat, skeletal muscle mass (BodyFat Analyzer, Omron BF 500; Omron Healthcare Europe B.V., Hoofddorp, The Netherlands); waist circumference, and conicity index were also measured, the latter as surrogate for central/upper body adiposity, and calculated as waist circumference (m)/0.109 $\sqrt{}$ (weight (kg)/height (m)) [27]. Non-alcoholic fatty liver was considered in the presence of ultrasonic hyperreflectivity in the absence of etiological factors associated with liver steatosis, including excess ethanol intake. Hypertension was defined as systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg and/or current treatment with BP-lowering drug(s). The presence of a metabolic syndrome (MetS) was defined by a score ≥ 3/5 for the following items: (i) impaired fasting glucose or diabetes; (ii) hypertension; (iii) enlarged waist; (iv) hypertriglyceridemia; and (v) decreased high-density lipoprotein cholesterol (HDL-C), according to the IDF-NHLBI-AHA-WHF-IAS-IASO harmonized definition [28].

HbA_{1c}; fasting lipids (total cholesterol, HDL-C, triglycerides; LDL-C (computed using Friedewald's formula), and non-HDL-C (by subtracting HDL-C from total C)); apolipoproteins A-I (apoA-I) and B_{100} (apoB); hsCRP; uric acid; and albuminuria were determined. Estimated glomerular filtration rate (eGFR) was calculated using the *Modification of Diet in Renal Disease* equation [29]. Albuminuria was present when the urine albumin (mg/dL)/creatinine (g/dL) ratio (UACR) was greater than 30 mg/g. Total cholesterol and TG were determined using SYNCHRON® system (Beckman Coulter Inc., Brea, CA). HDL-C was determined with ULTRA-N-geneous® reagent (Genzyme Corporation, Cambridge, MA). ApoA-I and apoB were determined with immunonephelometry on BNII Analyzer® (Siemens Healthcare Products GmbH, Marburg, Germany). Atherogenic dyslipidemia (AD) was defined as the combination of low HDL-C (<40 mg/dL (males); <50 mg/dL (females)) and high fasting TG (≥150 mg/dL for both genders), based on the MetS definition's cutoffs for non-LDL lipids [28]. AD prevalence as dichotomous state, was established as the combined occurrence of low HDL-C plus high TG, from last available fasting TG and HDL-C measurements prior to LLD implementation (LLD(s)-treated patients), or from current fasting TG and HDL-C (LLD-naïve patients), respectively [30,31].

Computer-based Homeostasis Model Assessment (HOMA) of insulin sensitivity and β-cell function was previously detailed (http://www.dtu.ox.ac.uk). Values of insulin secretion (HOMA B; normal value 100%) were plotted as a function of insulin sensitivity (HOMA S; normal value 100%), defining a hyperbolic product area (B × S) (unit: $\%^2$; normal value 100%, corresponding to $10^4\%^2$), which represents the true, underlying β-cell function. (B × S) loss rate (% $year^{-1}$) was obtained by dividing (100%-(B × S)) by each subjects' age at the time of HOMA modelling [32–35].

Diabetic polyneuropathy (DNP), diabetic retinopathy (DRP), and diabetic nephropathy were defined using ICD-9-CM diagnoses and procedure codes, with diabetic nephropathy identified using eGFR values < 60 mL min^{-1}/1.73 m^2 as surrogate for reduced kidney function; since the latter may not *de facto* be attributable to diabetes, any eGFR-identified overt nephropathy was considered to represent diabetic nephropathy in the absence of a confirmed diagnosis of non-specific, non-diabetic nephropathy. The presence of a peripheral neuropathy was based on clinical examination (knee and ankle reflexes; Semmes–Weinstein monofilament test) and/or electromyography.

Coronary artery disease (CAD) diagnosis was based on medical history (myocardial infarction, angioplasty, stenting, revascularization surgery and/or significant coronary stenosis confirmed by angiography), systematic review of all procedures, and/or screening (exercise testing; echocardiography; magnetic resonance imaging; or other subclinical disease imaging techniques). Stroke was defined according to UK Prospective Diabetes Study (UKPDS) criteria: any neurological deficit ≥ 1 month, without distinction between ischaemic, embolic and haemorrhagic events [36]. Peripheral arterial disease (PAD) was defined by a medical history of lower-limb(s) claudication and/or clinical or imaging evidence for ischaemic diabetic foot, angioplasty, stenting, revascularization surgery and/or significant lower-limb artery stenosis at Doppler ultrasonography and/or angiography. The *United Kingdom Prospective Diabetes Study (UKPDS) Risk Engine* provided absolute 10-year