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Diabetes & its Complications

Metabolic Control of GP-led Hypertensive Type 2 Diabetes Patients on Oral Antidiabetic Drugs

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ABSTRACT

Objectives: *To assess the metabolic status of hypertensive type 2 diabetes patients on oral antidiabetic drugs (OADs) while managed by general practitioners (GPs).*

Methods: *82 GPs agreed to provide patient data for retrospective analysis. The patients' inclusion criteria were: 1/ Age ≥ 40 years; 2/ Type 2 diabetes for >1 year; 3/ Treatment with OADs >3 months; 4/Arterial hypertension for >1 year; 5/ Stable doses of antihypertensive drugs for >3 months. Exclusion criteria were Type 1 diabetes, injectable antidiabetic treatments. Data were introduced in a specific electronic registry by the GPs themselves. An IBM SPSS 19.0 package was used for statistical analysis.*

Results: *5 926 patients' records met the entry criteria. 7.6% were aged 40 to 50 years; 22.6% - 51 to 60, 39.4% - 61 to 70. 53.75% were women. Normal BMI, overweight and obesity grade I - III were found in 16.2%, 42.1%, 27.6%, 9.7% and 4.2%. The waist circumference was <94 cm in 26.4% of men; and <80 cm in 10.7% of women. Fasting plasma glucose was ≤ 6.0 mmol/l in 19.2%; and ≤ 7.0 mmol/l - in 50.4%. Glycated hemoglobin was ≤ 7.0% in 62.9%; and ≤ 8.0% in 87.0%. The LDL-C was <1.8 mmol/l in 9.1%; and 1.8 to 2.6 mmol/l - in 19.6%. The blood pressure was <140/90 mm Hg in 77.4% of the patients.*

Conclusions: *The data about the glycated hemoglobin and the control of blood pressure are reassuring. An improvement is needed in controlling obesity and dyslipidemia.*

Keywords

Arterial hypertension, Epidemiology, GP Practice, Metabolic control, Type 2 diabetes.

Introduction

The projections of type 2 diabetes prevalence show an approximate increase of 40% in the following 25-30 years [1]. Two nation-wide

representative Bulgarian studies in 2006 and 2012 showed a rise in the prevalence of diagnosed diabetes from 5.0 to 7.1% and of undiagnosed one-from 3.3 to 2.5% [2,3]. The CODE-2 study in Europe showed a doubling of hospitalization and tripling of annual costs per type 2 diabetes patients in the presence of micro- or macrovascular complications [4]. Recent intervention trials such as STENO-2 and ADVANCE-ON showed that intensive multi-factorial treatment of diabetes could heavily reduce the incidence and progression of both micro- and macrovascular complications [5-7]. The constant improvement in the diabetes treatment paradigm has led to substantial decreases in the rates of myocardial infarction, stroke and amputation as shown in an analysis of diabetes-related complications in the United States, 1990-2010 [8]. The NHANES data analysis 1999-2012, however, registered an increasing trend of diabetes combined with hypertension or hypercholesterolemia, despite efforts to achieve better metabolic control [9].

General practitioners (GPs) play a substantial role in the management of Type 2 diabetes patients. The BULPRAKT-HEART Study conducted in 2004 gathered data on levels of glycated hemoglobin (HbA1c), while a registry-based analysis of diabetes patients treated by GPs for 2003 yielded information about the fasting plasma glucose [10,11]. A recent publication describing the diabetes care in Slovenia, Croatia, Serbia, Bulgaria and Romania found low rates of HbA1c measurements in the Balkans with over 60% of patients on oral antidiabetic drugs (OADs) not achieving good control [12].

The aim of the present study was to assess the metabolic status of type 2 diabetes (glycemic control, lipids, blood pressure, BMI and waist circumference) in a population-based representative sample of patients with Type 2 diabetes and coexisting hypertension managed by GPs.

Materials and Methods

Design

This retrospective registry-based cross-sectional observational nation-wide study was approved by the responsible authorities. One hundred and twenty general practitioners were invited to participate. They were selected by 2 criteria: 1/ The location of their practice in order to cover both urban and rural patient practices and to represent the national patient population as close as possible; 2/ Their usual patient population should include predominantly adult patients (> 40 years) with type 2 diabetes and/or arterial hypertension. Eighty-two general practitioners agreed to participate.

Methods

The included patients' data had to be selected in a consecutive order from the electronic databases of the individual GP practices. The patient's inclusion criteria were: 1/ Age ≥ 40 years; 2/ Type 2 diabetes mellitus (T2DM) diagnosed according to the local guideline for the management of diabetes by GPs, with at least 1 year duration (13); 3/ The diabetes treatment should include diet, physical activity and oral antidiabetic drugs (OADs) without changes for at least 3 months; 4/ Presence of arterial hypertension for at least 1 year according to the local guideline for the management of arterial hypertension by GPs (14); 5/ Treatment with stable doses of antihypertensive drugs for at least 3 months prior to data chart review. Exclusion criteria were: age below 40 years, presence of diabetes type 1 and use of any injectable antidiabetic treatments (GLP-1 analogs, insulin). To avoid possible bias the participating GPs were asked to provide all the patient data present in their database that met the inclusion/exclusion criteria.

The patient data were entered into an electronic database: patient's age, gender, type of residence (urban / rural), duration of type 2 diabetes and hypertension, concomitant diseases (asthma, chronic obstructive pulmonary disorders, dementia, depression, and others); presence of macrovascular or microvascular disease. Information on cardiovascular risk factors included positive family history for CVD (<65 years in female relatives; <55 years in male relatives), waist circumference, body mass index (calculated as body weight in kg divided by the height squared in meters), recently measured systolic / diastolic blood pressure (SBP/DBP), fasting plasma glucose (in mmol/l), glycated hemoglobin A1c (in% and in mmol/mol), total cholesterol (TC), HDL- and calculated LDL-cholesterol (Friedewald formula), triglycerides. All laboratory data were based on records from the local laboratories. OADs included metformin, sulphonylureas, pioglitazone, alpha-glucosidase inhibitors (acarbose), glinids (repaglinide), DPP-IV inhibitors, SGLT-2 inhibitors or combined. The antihypertensive treatment included ACE inhibitors/ARB blockers, calcium channel antagonists, beta-blockers, diuretics, combined drugs; the lipid-lowering drugs-statins, fibrates, ezetimibe.

Sample size considerations and analysis

In 2012 approximately 577 124 people (9.6% of the population aged 20 years and older) - 337 980 men and 239 144 women in our country were expected to have diabetes mellitus (15). More than half of them were known to have concomitant arterial hypertension (approximately 300,000). Half of those hypertensive type 2 diabetes patients were expected to be on oral antidiabetic medication (OADs) and not using injectable therapies or insulin (approximately 150,000). 4% of all hypertensive type 2 diabetes patients on OADs selected on a random basis was regarded a sufficiently-powered sample to study their metabolic control.

Data were first reviewed for completeness and validity and patients with missing data were excluded from the analyses. An IBM SPSS 19.0 for Windows platform was used for data processing (IBM SPSS Inc., Chicago, IL). After checking the numerical data distribution descriptive statistics was performed and frequency tables were built. The thresholds for some numerical parameters were defined according to the national guidelines for the management of diabetes by GPs and endocrinologists (13,15). BP ≤ 140 / 90 mm Hg and triglycerides ≤ 1.7 mmol/l were regarded as optimal. Optimal LDL-cholesterol levels (in mmol/l) were ≤ 1.8 mmol/l in the presence of both macrovascular disease and diabetes; and ≤ 2.6 mmol/l in the presence of uncomplicated diabetes. HbA1c (in%) strata were: ≤ 6.5, 6.6 - 7.0, 7.1 - 8.0, 8.1 - 9.0, and ≥ 9.1%. A two-tailed Student's t-test and ANOVA were applied. Statistical

significance was set as $p \leq 0.05$, the power of the study at 80%.

Results

The data files of 161 132 patients were reviewed. 142 287 were aged ≥ 18 years; 15 933 of them (11.19%) had Type 2 diabetes and 45 393 (31.9%)-arterial hypertension. 62.99% of all patients with Type 2 diabetes had also hypertension, while only 22.11% of the hypertensive patients had concomitant Type 2 diabetes. From those only 5 926 patients with Type 2 diabetes and hypertension had valid and complete data according to the inclusion / exclusion criteria. Their age distribution was as follows: aged 40 to 50 years-7.6%; 51 to 60-22.6%, 61 to 70-39.4% and ≥ 71 years-30.4%. 53.75% of the study sample represented women.

The studied population with diabetes and arterial hypertension had the following distribution according to the BMI: 16.2% had normal BMI (12.6% of men and 19.4% of women), 42.1% had overweight (46.5% men / 38.3% women respectively), 27.6% had obesity grade I (28.3% men / 27.2% women), 9.7% - obesity grade II (9.0% men / 10.0% women) and 4.2 had obesity grade III (3.6% men / 4.8% women).

The waist circumference (WC) was below 94 cm in 26.4% of the men; and below 80 cm in 10.7% of all women. The WC was ≤ 94 cm in 18.9% of men aged 40-50 years, in 22.4% of those aged 51-60, in 26.4% between 61 and 70 years; and in 33.4% of those ≥ 71 years. The WC was ≤ 80 cm in 13.5%, 10.7%, 8.3%, and 13.0% of the women in the same age groups.

The proportions of patients with morning FPG below different thresholds are shown according to age and gender in Table 1. Fasting plasma glucose values were below 6.0 mmol/l in less than one fifth of the participants; and were below 7.0 mmol/l - in around half of them.

Age group	FPG ≤ 6.0 mmol/l		FPG ≤ 7.0 mmol/l		FPG ≤ 8.0 mmol/l	
(years)	Men	Women	Men	Women	Men	Women
40 - 50	13.5%	23.7%	44.4%	50.3%	68.4%	75.2%
51 - 60	17.1%	17.6%	49.4%	50.6%	72.1%	73.4%
61 - 70	16.7%	22.1%	46.9%	53.0%	70.7%	75.5%
≥ 71	19.3%	21.7%	51.2%	53.0%	75.4%	75.7%
Total	17.1%	21.1%	48.3%	52.2%	72.0%	75.2%

Table 1: Proportions (in percentages) of patients with fasting plasma glucose values below 6.0, 7.0 and 8.0 mmol/l according to age and gender.

Valid data for HbA1c measurements were available in 5 154 patients (87.0%) and are shown in Table 2. 62.9% of all patients had a glycated hemoglobin ≤ 7.0%; and 87.0% - ≤ 8.0%.

The calculated LDL-C fraction was <1.8 mmol/l in 9.1% of the studied population; and between 1.8 and 2.6 mmol/l - in 19.6%. Therefore, 81.3% of the participants had LDL-C levels >2.6 mmol/l. The distribution of triglycerides and LDL-C values in the different age groups is displayed in Table 3.

Age group (years)	HbA1c ≤ 6.5%	HbA1c 6.6 - 7.0%	HbA1c 7.1 - 8.0%	HbA1c 8.1 - 9.0%	HbA1c ≥ 9.1%
40 - 50	41.5%	19.8%	23.0%	6.2%	9.6%
51 - 60	38.3%	23.3%	25.7%	6.5%	6.2%
61 - 70	39.8%	22.7%	24.4%	7.5%	5.6%
≥ 71	42.0%	23.0%	23.0%	6.4%	5.7%
Total	40.2%	22.7%	24.1%	6.8%	6.0%

Table 2: The distribution of HbA1c in the different age groups is shown (men + women).

Age group (years)	Triglycerides < 1.7 mmol/l (150 mg/dL)	LDL-C < 1.8 mmol/l	LDL-C < 2.6 mmol/l (100 mg/dL)
40 - 50	31.9%	5.8%	21.5%
51 - 60	36.5%	8.9%	26.9%
61 - 70	43.4%	9.3%	29.0%
≥ 71	51.5%	9.9%	31.5%
Total	43.4%	9.1%	28.8%

Table 3: Proportions (in percentages) of the studied population with LDL-C and triglycerides within the target levels.

The reported blood pressure was <140/90 mm Hg in 77.4% of the studied population, while it was <140/85 mm Hg in only 64.0%. The distribution of good BP control according to age is displayed in Table 4.

Age group	Systolic BP < 140 mm Hg		Diastolic BP < 90 mm Hg	
(years)	Men%	Women%	Men%	Women%
40 - 50	62.1%	71.8%	68.9%	73.5%
51 - 60	58.6%	63.9%	67.7%	71.7%
61 - 70	57.4%	59.4%	70.2%	71.6%
≥ 71	61.2%	59.4%	76.8%	76.2%
Total	59.1%	61.0%	71.1%	73.3%

Table 4: Blood pressure in the target zone (<140/90 mm Hg) according to age and gender.

All these data show that blood pressure and glycemia were well controlled in the majority of patients while LDL-C, triglycerides and body weight were above the target in most of them. Table 5 shows how many patients met combined criteria for glycemic + lipid control, or glycemic + BP control, or all three together. A very small minority of the patients meets all target values, leaving room for further therapy improvement.

Age group (years)	HbA1c < 7.0% and SBP/DBP < 140/90 mm Hg		HbA1c < 7.0%, LDL < 2.6 mmol/l, and TG < 1.7 mmol/l		HbA1c < 7.0%, LDL < 2.6, and TG < 1.7 mmol/l, and BP < 140/90 mm Hg	
	Men%	Women%	Men%	Women%	Men%	Women%
40 - 50	8.9%	8.3%	1.9%	1.5%	1.5%	0.0%
51 - 60	9.5%	11.9%	2.6%	1.6%	2.1%	1.0%
61 - 70	9.0%	10.2%	2.8%	1.9%	1.5%	1.1%
≥ 71	12.2%	9.9%	4.1%	2.5%	2.8%	1.5%
Total	9.9%	10.3%	3.0%	2.0%	3.0%	1.2%

Table 5: The percentages of patients meeting combined criteria for glycemic + lipid control, or glycemic and BP control, or all three together,

are shown.

Discussion

We performed a study based on GP-led diabetes outpatient-clinics in order to assess glycemic, lipid and blood pressure control in patients with type 2 diabetes on OADs and treated hypertension in a nation-wide representative sample. Our results are reassuring when glycated hemoglobin and blood pressure are examined separately - almost ⅔ of the patients had achieved good control. However, the situation with the lipid profiles looks quite differently with less than a half with normal triglycerides and only ¼ with normal LDL-cholesterol, despite treatment. If all three parameters are examined in a combined fashion, less than 15% will have optimal metabolic control (glycemia + blood pressure + lipids). If body weight (BMI) and waist circumference were added, less than 10% would meet the combined criterion. These results show a treatment gap leaving room for improvement in the field of obesity and lipid abnormalities.

The metabolic control of diabetes has a profound impact on the prevention and delay of micro- and macro-vascular complications. New analyses proved a clear and fast benefit of lipid- and blood pressure lowering strategies, while the role of glycemic control remains postponed in time and mainly on the micro-vascular outcomes [16-18]. The combined effect of all three interventions was proven in interventional trials such as the STENO-2 and the ADVANCE-ON studies [5,19].

Our data should be reviewed in the light of previous publications coming from international and national studies although bearing in mind that patients were not similar in terms of age, duration of diabetes, medications used etc. In a cross-sectional analysis on 5382 type 2 diabetic patients in the primary care setting in Spain between 2011 and 2012, 17.1 and 67% applied to ADA/EASD recommendation of HbA1c target of <7 and <8% [20]. A Chinese study examined the data of 9065 adult T2DM outpatients (5035 men) between 2010 and 2012 and found glycemic control rate in only 32.6%, with the triple control rate for glycemia, blood pressure, and lipidemia - in only 11.2% [21]. Specialist-led diabetes practices are also not always able to achieve optimal glycemic control in the majority of patients. This was shown in a Canadian registry-based study including 10 590 patients with T2DM [22]. In this study mean HbA1c was 7.6%, with 38% of patients meeting the Canadian Diabetes Association target of ≤ 7.0%. An Indian study found the following percentages of T2DM patients at target: for HbA1c - 45%, for BP <130/80 mm Hg - 27%, and for LDL <100 mg/dl - 37% [23]. A large sample of 4926 T2DM patients was reviewed in the National Health and Nutrition Examination Surveys (NHANES) from 1988-1994, 1999-2002, 2003-2006, and 2007-2010 [24]. In 2007-2010, 52.5% of people with diabetes achieved A1C < 7.0%, 51.1% achieved BP <130/80 mmHg, 56.2% achieved LDL <100 mg/dL, and 18.8% achieved all three ABCs. These levels of control were perceived by the authors as significant improvements. Looking at these data we might be reassured about our results, which are quite similar.

We also compared our data to previous publications based on large population samples in our country. The mean fasting plasma glucose of 130 829 T2DM patients in the year 2000 was 8.14 ± 2.79 mmol/l, and it was below 6.5 mmol/l in only 25.9% of the participants [10]. The situation today looks slightly better (Table 1).

The National Examination of glycated hemoglobin evaluated 32 356T2DM patients during the year 2003 [11]. Approximately 40% of the included patients had a HbA1c < 6.5%, approximately 50% - between 6.5 and 9.5%, and 9% - between 9.51 and 12.5%. Again, the situation nowadays looks much better. The data on BP and lipid control in T2DM in our country are very scarce. A nation-wide epidemiological study reported data on lipids, obesity and BP coming from the whole population in 2012 [25-28]. Arterial hypertension was found in 38.9% of the studied subjects (766 of a total of 1967), and was more prevalent in men - 45.1% than in women - 33.5% [25]. These figures are quite similar to the percentages of T2DM patients achieving optimal BP control in our study. In the nation-wide epidemiological study 46.9% the men had hypertriglyceridemia versus 22.2% in the women, while low HDL was found in 35.7% of the females and 29.7% of the males [26]. These data unfortunately did not allow separate analysis for diabetes patients. In these series of studies the prevalence of normal BMI was 28.1%, 37.0% - of overweight, and 33.2% - of obesity [27]. Waist circumference was >94 cm in 61.6% of the men and >80 cm in 63.2% of the women [28]. In conclusion, looking at the metabolic situation of the general population, we might feel reassured about the GP-led diabetes patients. Their metabolic status looked not much worse than that of the whole population.

Major limitations of our study are the cross-sectional design and the inclusion of a subgroup of type 2 DM patients - those on OADs with prevalent hypertension being managed by GPs. The cross-sectional design cannot detect temporal changes in cardiovascular risk factors. As an example, a population-based CVD prevention program in Sweden found that between 1991-1995 and 2006-2010, mean age-adjusted cholesterol and systolic blood pressure declined (the former by around 0.5 mmol/l and the latter - by 3 mm Hg) with corresponding decreases in the age-standardized prevalence of hypertension and hyperlipidemia [29]. Mean age-adjusted 2-hour plasma glucose and BMI increased (by 0.2 mmol/l and by 0.6-1.1 kg/m^2) with increases in the age-standardized prevalence of diabetes and obesity [29]. A similar trend was noted in the Tromso study assessing CV risk factors in relation to the diabetes status [30]. During the 14 years of follow-up the subjects with DM2 had decreasing levels of total and HDL-cholesterol and blood pressure (BP), and increasing levels of triglycerides, BMI, and anti-hypertensive treatment.

The second limitation of our study is that we assessed a targeted subgroup of hypertensive type 2 DM patients. Our main hypothesis was inspired by the increasing trend of diabetes combined with hypertension or hypercholesterolemia as reported in the NHANES data analysis 1999-2012 [9]. In this specific analysis the treatment goal was achieved in 20.1% in the subgroup with concurrent diabetes and hypertension - a finding very close to our results [9].

The major strength of our study is that it allows an up-to-date assessment of the metabolic control and CV risk factors in a subgroup of T2DM patients at particularly high risk due to the concurrent hypertension. It showed some improvements in metabolic control during the last 12-13 years with a reassuring trend in glycated hemoglobin and blood pressure. Unfortunately it showed also a treatment gap leaving room for improvement in the field of obesity and dyslipidemia.

Summary and Conclusions

The management of hypertensive type 2 diabetes patients by GPs in our country is quite adequate to contemporary guidelines for CV risk factor prevention. However targeted efforts are needed to invert the negative trends in the prevalence of obesity and atherogenic diabetic dyslipidemia.

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Conflicts of Interest

The authors declare no conflict of interest related to this study. However, M.A.B. has received speaking fees from Novo Nordisk, Elli Lilly, Aventis, Servier, Boehringer-Ingelheim, Berlin-Chemie, Astra-Zeneca, Amgen, MSD, and others; and participated in Advisory boards with Amgen, Servier, MSD.

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