

SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

**PUBLIC HEALTH IMPORTANCE OF T2DM
COMPLICATIONS/COMORBIDITIES, PREVENTION POSSIBILITIES**

BY

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The Examination takes place at the Library of the Department of Internal Medicine, Faculty of Medicine, University of Debrecen, on the 28th April 2015 at 11 am.

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The PhD Defense takes place at the Lecture Hall of Building “A” of the Department of Internal Medicine, Faculty of Medicine, University of Debrecen on 28th April 2015 at 1 pm.

Introduction

Public Health importance of type 2 diabetes

Type 2 diabetes mellitus (T2DM) is one of the major non-communicable diseases with great public health importance, which imposes a significant burden on both society and patients. According to latest International Diabetes Federation (IDF) estimations (2013) more than 382 million people suffered from diabetes worldwide. The number of T2DM patients will reach 592 million in 2035. The number of patients increasing continuously as population grows and societies grow old.

The estimations for the T2DM prevalence in Hungary show considerable heterogeneity. The routine data collection systems, which register different prevalences, are the following:

- Hungarian Central Statistical Office (HCSO)
- General Practitioners' Morbidity Sentinel Stations Program (GPMSSP)
- European Health Interview Survey (EHIS)

Comparing the data, collected in 2009 in these diabetes-related data collection systems, reliable system (e.g.: GPMSSP) seemed to under represent the disease above 50 compared to registries without having proper case definitions (e.g.: HCSO, EHIS). The estimations for younger age groups do not differ from each other.

According to the most reliable GPMSSP's report for 2010, the diabetes mellitus prevalence was 6.56% among males above 20 and 6.51% among females above 20 in Hungary. The corresponding incidences were 0.59% for males and 0.55% for females, respectively.

It was in harmony with a survey based diabetes mellitus prevalence, which estimated the prevalence of diabetes mellitus among 20-69 year-old population as 7.47% (95% CI 6.26-8.69; men: 9.49%, 95%CI 7.52-11.46; women: 5.58%, 95%CI 4.12-7.04).

Cost of patients with complications, exceed the health care costs of insulin users without complications. Care of T2DM and it's complications has a huge financial burden on health

systems. A T2DM patient's care cost 5 times higher compared to a non-T2DM patients' care. Costs of drug treatment and hospitalizations have a large impact on economic burden.

Overwhelming majority of DM-related socio-economical burden, human suffering and disability are elicited by diabetic complications. Most of this burden is related to the non-fatal major adverse outcomes (blindness, neuropathy, renal failure and loss of a toe or foot), and nearly half of DM patients die of cardiovascular diseases.

Diabetes mellitus related death is a significant part of premature mortality. In Hungary it was 1.5 times higher compared to EU average in 2012, based on the European Health for All Database.

Consequently, the main objective of T2DM care is to prevent or postpone the onset of complications/comorbidities. Clear and convincing evidences exist that early diagnosis and the appropriate glucose control play a key role in this respect.

Prevalence of T2DM-associated medical conditions

Not only the prevalence of T2DM, but also the prevalence of its complications/comorbidities increases. Although, the 3rd edition of IDF Diabetes Atlas has a huge database, in which comorbidities and complications/comorbidities are presented, but data are not up to date and the database is incomplete. There is no available database which does contain reliable information on Hungarian complications/comorbidities of T2DM.

Monitoring care

The well-elaborated theoretical framework for measuring and assessing quality of care is based on multifaceted indicator set on structures, processes and outcomes. Organization for Economic Co-operation and Development (OECD) defines nine indicators related to diabetes. This set involves four process indicators (annual HbA1c testing, annual LDL cholesterol testing, annual screening for nephropathy and annual eye examination), two proximal outcome indicators (HbA1c control, LDL cholesterol control) and three distal outcome

indicators (lower extremity amputation rates, kidney disease in persons with diabetes mellitus, cardiovascular mortality in patients with diabetes mellitus).

The Hungarian National Health Insurance Fund (HNHIF), which covers the whole country, is responsible for cost-effectiveness of T2DM care both at the level of primary and secondary care. Because cost reduction can be achieved by early detection of T2DM and by intensive glycemic control, one of the major tasks of HNHIF is to improve the effectiveness of services for preventing T2DM complications/comorbidities. Establishment of a monitoring system is essential for this goal.

HNHIF defines two process indicators (HbA1c check, ophthalmologic examination) related to diabetes mellitus. These indicators are the referral rates of adult diabetes mellitus patients in annual HbA1c check (HC) and annual ophthalmologic examination (OE). GPs are evaluated and partly financed based on these indicators. These indicators relied on the Hungarian Diabetes Association (HDA) recommendation.

Despite of the international usage of outcome indicators in monitoring, and the fact that the physicians evaluate the patients' status routinely by HbA1c level, only process indicators are used in Hungary for evaluation and financing. HbA1c level as an outcome indicator, to measure the effectiveness of glycemic control is not applied by the HNHIF monitoring.

Interventional possibilities, tertiary prevention

The disease burden of T2DM can be decreased by different preventive approaches. The primary level of prevention is the elimination of risk factors to prevent the disease development. This primary prevention uses, inter alia, health promotion tools (e.g.: patient education, nutritional and lifestyle consultancy). The secondary level of prevention is screening. It could result early diagnosis in preclinical phase, in order to start the treatment as soon as possible. Tertiary prevention means proper care for diagnosed patients to prevent or at least postpone the development of complications for a better quality of life.

There is no doubt that coordinated teamwork is a main part of proper care. In addition to the general practitioners, dieticians, physiotherapists, health psychologists or mental health psychologists, nurses and public health professionals play key role in proper care. The complex care is guided by the consensus statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes.

Objectives

Our objective was to investigate the efficiency of Hungarian T2DM care. We focused mainly on the effectiveness of long term care, through investigating complications/comorbidities and their prevention among adults above 50 years old. The analyses were:

- 1) to describe the achievement of the hemoglobin A1c target of <6.5% among Hungarian T2DM patients and to identify the influencing factors.
- 2) to explore the prevalence of T2DM-associated complications/comorbidities, and to create a database, by which:
 - a) absolute numbers of comorbidities and complications could be estimated for Hungary;
 - b) the change of lethal complications' (acute myocardial infarct, stroke) frequency can be monitored among T2DM patients.
- 3) to evaluate the adherence to long-term care guidelines and the usefulness of its monitoring applied in Hungary at present through:
 - a) evaluating the relationship between process-indicators related to primary care of T2DM and the outcome of care indicated by HbA1c level.
 - b) determining patient and GP related determinants of referral rates of ophthalmologic examination among T2DM patients in Hungary;
- 4) to describe the utilization of the interventional possibilities to prevent/postpone complications' manifestation through description of the
 - a) effect of diagnosis-time and initial treatment on the onset of T2DM complications/comorbidities in Hungary;
 - b) health behavior of T2DM patients in Hungary in the respect of complications' prevention.

5) to elaborate a set of diabetes monitoring indicators by participating in an international research and development project, where

- a) the usefulness of survey based data collection was checked;
- b) representative Hungarian data were converted and transferred into the European reference database.

Methods

Research Design and methods

The primary data collection of our investigations was based on the General Practitioners' Morbidity Sentinel Station Program (GPMSSP), which involves 11 Hungarian counties (Baranya, Bacs-Kiskun, Borsod-Abaúj-Zemplén, Győr-Moson-Sopron, Hajdu-Bihar, Heves, Jász-Ménfőcsanak, Komárom-Esztergom, Nógrád, Szabolcs-Szatmár-Bereg and Zala counties).

Our study was conducted with the help of 72 participating GPs of the 11 GPMSSP counties in 2008. A cross-sectional study was performed with T2DM patients above 50.

Case Report Form (CRF) contained information on complications and comorbidities. On case report forms, the practice code of the GP was recorded. Patients of the GP were coded by unique code, without names, to assure anonymity. Only GPs can identify their patients. GPs did physical examination, took blood sample for laboratory tests and measured the blood pressures of patients. The results were recorded on CRFs with additional demographic information. Self-administered questionnaires on life-style were filled out by the patients.

Sampling

Source population consisted of 169530 people above 50 registered by the GPMSSP. Sampling was performed from 15944 persons, who suffered from T2DM among them according to GPMSSP data at 31 December in 2006. Planned sample size was 1500. Sample was randomly selected from the source population which was stratified by age and gender.

During analyses the numbers of patients differ from each other as we excluded the incomplete records in order to get proper results. Completeness of records had been checked before every analysis and useful records had been selected. Exclusion of non-complete records resulted different response rates in different analyses.

Data collection

Case report forms (CRF) were filled out by GPs, on which demographic data of the patients (age and gender), results of physical examination (blood pressure was measured by GPs under standard conditions), information on complications and comorbidities (hypertension, lipid metabolism disorders, obesity, other ischemic heart disease, peripheral artery disease, retinopathy, neuropathy, nephropathy, stroke, AMI), applied treatment (non-pharmacological, OADs, insulin, pharmacological and non-pharmacological changes, cause of change), information on control examinations and on the compliance of the patients were recorded.

Results

ACHIEVING THE HEMOGLOBIN A1C TARGET OF <6.5% AMONG HUNGARIAN PATIENTS WITH TYPE 2 DIABETES

Less than half (48.99%) of the sample was male (n=509). Mean age ($\pm$ SD) was 66.48 ± 9.18 years. Mean HbA1c ($\pm$ SD) was 7.47% ($\pm$ 1.54%). The lowest HbA1c value was 4.7% and the highest value was 15.8%, respectively. There was a borderline significant difference between males' (7.38%) and females' (7.56%) HbA1c values ($p=0.057$).

Attending annual HbA1c check was in significant association with gender ($OR_{\text{female/male}}=1.41$; 95% CI 1.05-1.88), education level ($OR_{\text{secondary/primary}}=1.50$; 95% CI 1.12-2.02; $OR_{\text{tertiary/primary}}=2.84$; 95% CI 1.69-4.79), presence of retinopathy ($OR=1.55$; 95% CI 1.04-2.31) and presence of lipid disorders ($OR=1.76$; 95% CI 1.34-2.29).

Attending annual ophthalmologic examination was in significant association with presence of retinopathy ($OR=4.50$; 95% CI 3.02-6.70) and presence of lipid disorders ($OR=1.35$; 95% CI 1.01-1.80).

According to univariate analyses there was a significant association between gender and reaching HbA1c target level (6.5%) in both age groups (50-64 $p=0.005$; 65-X $p=0.002$).

Based on the results of multivariate analyses, having HbA1c value above target (6.5%) level was in significant association with gender ($OR_{\text{female/male}}=1.56$; 95% CI 1.14-2.13), education level ($OR_{\text{tertiary/primary}}=0.53$; 95% CI 0.32-0.88) and presence of retinopathy ($OR=1.71$; 95% CI 1.07-2.73).

PREVALENCES OF COMPLICATIONS/COMORBIDITIES OF TYPE 2 DIABETES

The population, covered by GPMSSP, consisted of 218 406 persons (20-X years). Of these, 13 815 persons suffers from diabetes (prevalence (P) = 6.32%) (P (above 50) = 12 297/103 482 = 11.88%). The sample size of our targeted diabetes study was 1324, of whom 1168 participated in the study (response rate 88%). After excluding cases with missing data (129 people), the response rate was 78%, respectively. The observed prevalences are stratified by age (50-64; 65-X) and gender.

Hypertension associated most to T2DM in both studied gender and age groups. Lipid metabolism disorder was the second most common among men and obesity was the second most common among women is in the younger age group. Acute myocardial infarction was the least common in both sexes in the 50-54 year-old age group.

We can conclude that the least frequent complication among 50-64 year-old age group female is AMI, while most common is hypertension among both genders. Lipid metabolism disorder takes the second place, the third is obesity.

There is no significant difference between the prevalence of stroke 13.3% 11.3%-15.5%, peripheral artery disease 12.8% 10.9%-15.0%, retinopathy 12.4% 10.5%-14.6%, neuropathy 10.9% 9.1%-13.0% and the 95% CI of AMI 6.1% 4.8%-7.7% and nephropathy 6.1% 4.8%-7.7% also overlaps.

Some complications/comorbidities were more frequent among older patients. Significant age effect could be detected among males by the prevalence of stroke (18.3% vs 9.5%), by ischaemic heart disease (42.8% vs 27%), and by obesity, however this comorbidity was more frequent among younger (42.8% vs 56.8%). Among females ischaemic heart disease was significantly more frequent among olders (49.3% vs 28.9%) and obesity was more frequent among younger also (52% vs 68.5%). A gender effect could be observed by peripheral artery disease, it was significantly more frequent among old males compared to old females (20.2% vs 11.4%). The prevelences of the following diseases decreased by age: lipid metabolism disorders among males (69.1% vs 58%), obesity and neuropathy among males

(13.9% vs 12.5%), however this decrease was significant only by obesity (among males: 56.8% vs 42.8%; among females: 68.5% vs 52%).

The most common comorbidities are hypertension (327 735), lipid disorder metabolism (286 915), obesity (239 648) and other ischemic heart disease (172 778). Stroke (59 302), peripheral artery disease (56 506) and retinopathy (55 501) follow them. The least frequent ones are neuropathy (47 892), nephropathy (26 674) and AMI (26 648). Based on our estimate, we can conclude that more than 24 thousand men and more than 31 thousand women above 50 have retinopathy associated with T2DM.

The most important comorbidities with potential fatal outcome were stroke 4.72% 3.58%-6.19% and AMI 1.15% 0.66%-2.02%.

The incidence of T2DM was constant between the two examined period (2004-2007: 0.0057 vs. 2008-2011: 0.0056) During the second period (2008-2011) there was a significant improve in 2-year cumulative incidence of AMI and stroke. Checking the two periods, a significant improve could be observed from the view of outcomes: $SIR_{AMI}=0.685$ 0.604-0.766; $SIR_{STROKE}=0.796$ 0.736-0.855.

RELIABILITY OF PROCESS-INDICATORS RELATED TO QUALITY OF PRIMARY CARE OF TYPE 2 DIABETES MELLITUS

The sample was representative of above 50 Hungarian T2DM patients (χ^2 -test, $p>0.05$): 56.46% of them were above 65 years. As for the education 48.14% were secondary educated. Having HbA1c level below target were 34.27% of men 95% confidence interval: 30.23-38.55, 22.94% of women 19.54-26.75. Annual ophthalmologic examination was done by 35.03% 32.16-38.01 and 57.05% 53.98-60.05 took part in annual HbA1c check.

According to the univariate analysis those patients had less than threshold HbA1c values who attended less frequently in both control examinations. Proportion of those patients who had their T2DM under good control ($HbA1c<6.5\%$) was significantly associated with both annual HC (among attended 25.04% vs. among did not attend 33.03%) and annual OE (among attended 23.74% vs. among did not attend 31.02%). The outcome indicator was in significant relationship with patients' socio-demographic (gender, age, level of education, family status) and clinical (having hypertension, retinopathy, lipid disorders, obesity) status.

By multivariate logistic regression analysis the participation in HbA1c check showed significant association with HbA1c level below 6.5% (adjusted for gender, age, educational

level, family status, duration of diabetes, and presence of hypertension diabetic retinopathy, hyperlipidemia, obesity). Those patients who attended HbA1c check annually had 0.73 times lower odds to have HbA1c level below target value (OR=0.73; 95% CI 0.54-0.98). Attendance in ophthalmologic examination showed similar tendency, however this association did not reach significance at the level of 5% (OR=0.81; 95% CI 0.59-1.12).

DETERMINANTS OF LOW REFERRAL RATES FOR OPHTHALMOLOGIC EXAMINATION IN PEOPLE WITH TYPE 2 DIABETES IN HUNGARY

The mean age ($\pm$ SD) of the patients was 66.61 ($\pm$ 9.21) and 48.55% of them were male in the sample. The prevalence of retinopathy was 12.42%. The overall RR for DR within 12 months was 34.65%. The RR showed significant difference ($p<0.001$) between patients without (RR=30.22%) and with retinopathy (RR =65.89%). Female GPs convinced more complication-free patients for retinopathy check (male GP's patients: RR =27.22%; female GP's patients: RR =34.59%; $p=0.017$). Contrary, male GPs were more effective among patients with retinopathy (female GP's patients RR=53.33%; male GP's patients RR =72.62%; $p=0.028$). Other factors proved to be independent of RRs.

This GP-gender effect has been confirmed by odds ratios (OR) adjusted for patients' gender, age, education level, marital status and GPs' age from multivariate logistic regression analysis: Female GPs were more successful among retinopathy free patients (OR=1.44; $p=0.014$). Male GPs achieved higher level of cooperation among patients with retinopathy (OR=0.42; $p=0.035$). The strongest influencing factor was the presence of retinopathy (OR=4.72; $p<0.001$). Other factors showed no significant association with RR.

EFFECT OF DIAGNOSIS-TIME AND INITIAL TREATMENT ON THE ONSET OF TYPE 2 DIABETES MELLITUS COMPLICATIONS: A POPULATION-BASED REPRESENTATIVE CROSS-SECTIONAL STUDY IN HUNGARY

The mean age ($\pm$ SD) of the study participants was 66.68 ($\pm$ 9.22), and 51.5% of them were women. The mean duration of diabetes was 8.72 ($\pm$ 6.16) years. Significantly elevated odds ratio for retinopathy (OR = 1.62, 95% CI 1.06-2.49) was observed in the late diagnosis group. There was no observed significant influence of early diagnosis on the manifestation of hypertension (OR = 1.17, 95% CI 0.67-20.77) microalbuminuria (OR = 1.16, 95% CI 0.75-1.79), stroke (OR = 1.38, 95% CI 0.86-2.21), IHD (OR = 1.15, 95% CI 0.8-1.64), lipid

disorders (OR = 0.83, 95% CI 0.62-1.12). nephropathy (OR = 1.19, 95% CI 0.68-2.1), neuropathy (OR = 0.91, 95% CI 0.59-1.39), and for PVD (OR = 1.1, 95% CI 0.68-1.78).

CHARACTERISTICS AND HEALTH BEHAVIOR OF TYPE 2 DIABETES MELLITUS PATIENTS IN HUNGARY

The analysed sample was consisted of 5051 subjects. ($N_{\text{diabetes mellitus}}=426$; $N_{\text{without diabetes mellitus}}=4625$). Less than half (45.5%) of the sample was male, and 54.5% was female. Less than 5% of the participants (3.01%) was under the age of 18, 76.28% were between the ages of 18 and 64, and 20.71% were above 65.

The prevalence of overweight and obesity was higher among T2DM patients compared to people without T2DM (81.8% vs 54.5%). Proportions of those who have regular physical activity were 65.4% vs. 82.0%. Proportions for daily vegetable consumption were 81.8% vs. 75.9%.

It was more likely to be obese for T2DM patients compared to people without T2DM, (OR=2.77, 95% CI 2.17 - 3.55) and they tend to be more inactive by physical activity (OR: 1.44, 95% CI 1.03 -2). However they significantly more likely stopped smoking (OR: 1.62, 95% CI 1.1 - 2.38). According to our results, there were no significant differences by nutritional and drinking habits.

INTERNATIONAL EVALUATION OF REGIONAL DIABETES INDICATORS

Using the database built up in our data collection, 71.4 % (35/49) of the EUBIROD indicators were computable.

Most of extractable data was stored in appropriate format, a smaller part needed conversion for BIROX in order to be transferable. We used different methods to gain the necessary information, such as MS-Excel functions.

The final international report processed data of the partners through descriptive statistics. According to the findings of EUBIROD report, in which the two cut-off values for HbA1c were 6.5% and 7.5%, Hungary is behind the average. The proportion of patients having HbA1c value below 6.5% is less than the average, and the proportions of patients having HbA1c above 7.5% is above the European average.

Conclusions

Achieving the Hemoglobin A1c Target of <6.5% among Hungarian patients with Type 2 Diabetes and identifying the possible influencing factors

Although, DEPAC group performed a survey in 2005, in which 2140 T2DM patients attended routine visit spontaneously, not representing properly Hungarian patients, were involved and NHIF collects continuously data for all T2DM patients cared by GPs only on two process indicators (proportion of T2DM patients with HbA1c check and ophthalmologic examination in 12 months), the overall effectiveness of T2DM care has not been reliable described in Hungary yet. Our survey aimed at contributing to eliminating this lack among T2DM patients above 50 years old.

We were able to estimate the effectiveness of T2DM care in the respect of three key indicators on a representative sample. Beside the two process indicators, monitored by the NHIF, an outcome indicator, the proportion of achieving therapeutic target HbA1c was measured on a sample of 1039 T2DM patients. In Hungary in the studied age group, the observed proportions were 57.07% for HC, and 34.65% for OE in the past 12 months. The overall proportion for having HbA1c below target value was 28.47%.

Around 83% of T2DM patients attended annual HC in the UK, 74% in Canada, 65% in Australia, 64% in New Zealand and 61% in the US. On the other hand, 61% attended annual OE in the UK, 48% in Canada, 67% in the US. The coverage of biannual OE in Australia and in New Zealand was 70% and 71%, respectively. Comparing referral rates on annual control examinations with these reference data, referral rates in Hungary are unambiguously low.

According to our survey, the proportion of those, who have their HbA1c value below target, is similar in Hungary as in other Eastern-Central European countries. Around 22% achieved the recommended target of 6.5% HbA1c value in the UK. The proportions were 57%, 73%, and 46% in Australia, in New Zealand, and in the US, where the recommended target HbA1c values were under 7%, 8%, and 7%. Although, these published data are obviously incomparable due to country specificity of data collection methods and differences of national guidelines, achieving target in Hungary seems to be less effective than in most of the reference countries.

The effectiveness of glycemic control seems to be worse in Hungary compared to other countries. We could identify the subgroups with rather poor quality of care, which should be targeted by interventions to reduce the gap between Hungary and the reference countries. The

identified high-risk group in the respect of HbA1c values is composed of female 50-64 year-old patients with diabetes for 5-9 years, with primary education and retinopathy. The target group to improve HC attendance is male patients with primary education, having retinopathy or lipid disorders and it is the group of T2DM patients with retinopathy or lipid disorders for OE attendance. In accordance with our findings related to the outcome indicator, GPs should focus not only on female patients with lower education level, but patients who have diabetes history of 5-9 years, have processed emotionally the new diagnosis, but are not motivated by experiences of complications/comorbidities' early symptoms.

The Hungarian T2DM guideline is in accordance with IDF recommendations. Because the therapeutic target achievements are less than the reference values, the effectiveness of its implementation has to be weak. Considering that the T2DM primary care does not require huge infrastructure, the effectiveness of utilization of available resources could also be low. It is probable that the poorly organized monitoring system is not encouraging for the most efficient use of resources especially in certain high-risk groups.

Prevalences of complications/comorbidities of Type 2 Diabetes

Based on our study, the prevalences of comorbidities and complications could be estimated in Hungary, so we can get a picture of the effectiveness of care through that. The estimation of the absolute number of complications/comorbidities can help assessing the care network capacity.

Contrary to our expectations there were complications with higher occurrence among younger patients. The observed decrease by age in prevalences of lipid metabolic disorder, obesity and neuropathy could be explained by the higher premature mortality of these patients. (Probably they die of these complications earlier that is why the prevalence of these morbidities were lower among older ones.) The findings suggest that the 50-64 years old T2DM patients are at high risk of death if they are obese, with lipid disorders and neuropathy.

The evaluation of the incidence of myocardial infraction and stroke among T2DM patients demonstrated that the quality of care improved significantly during the period of 2004-2011. The improvement was practically the same among males and females in the respect of AMI, which showed one third reductions. The same was observed for stroke among males. The stroke incidence among females has not changed in the studied period.

Reliability of process-indicators related to quality of primary care of type 2 diabetes mellitus

We utilized the opportunity to test process indicator based monitoring system usefulness in Hungary, where the official HNHIF monitoring applies exclusively process indicator for primary health care level diabetes care by conducting a special survey which collected data to calculate both the process (HbA1c check, ophthalmologic examination) and outcome (HbA1c value) indicators. We undertook this study because we wanted to contribute to the diabetes care quality improvement by advising development of monitoring technology. The importance of this approach is underlined by the fact that the organization of T2DM care in Hungary is far below the acceptable level, where referral rates of control examinations are quite low.

According to our univariate analyses those patients take part in higher frequency in HC and OE who have poorer glycaemic control, since inverse association was found between process indicators and HbA1c level. It has been confirmed by multivariate analyses as well.

Consequently the HNHIF indicator system shows those GPs more efficient and finances better, whose patients are in worse conditions (have higher HbA1c values). It is an obvious dysfunction because it is well-known that HbA1c level is the strongest prognostic factor.

The low HC and OE referral rates and the inverse association between these rates and care effectiveness (having HbA1c value below target level) together suggest that the general practitioners do not use the control examinations properly in preventing diabetes complications/comorbidities. Seemingly there is a huge intervention potential, but the exploitation of this opportunity is not supported by the HNHIF monitoring.

Using only process indicators consumes resources, however they can not guarantee the achievements of guidelines alone. Our study demonstrated that the very minimum requirement for monitoring technology is to apply both process and outcome indicators. Monitoring system, in which GPs could trust, are needed, in order to maintain their commitment to the quality development in the field of T2DM care.

Determinants of low referral rates for ophthalmologic examination in people with type 2 diabetes in Hungary

The epidemiology of Hungarian DR resembles in many respects to the developed countries' situation. The Hungarian 12.42% DR prevalence is not deviated significantly from the usual European registrations, the beneficial effect of early diagnosis on DR development has been demonstrated among Hungarian patients, and the Hungarian Health Insurance Fund uses the RRs for OE to monitor T2DM care quality. On the other hand, the overall RRs for retinopathy check in Hungary is extremely low (34.77%) compared to European references. In general, the compliance is increased by the presence of DR, and the patients' and GPs' socio-demographic characteristics are not associated with it. Contrary to countries with appropriate RR, where higher education level and higher income result higher RRs, education level showed no association with having eye examination in our study.

In stratified analysis, the gender of GP proved to be influencing factor. Among retinopathy-free patients only GP's gender had significant effect. Female GP gender was protective. Among patients with retinopathy, male GP gender seemed to be protective factor.

In spite of lack of direct measurements of communication practice in this study, our investigation suggested that GPs' empathy which is more characteristic for females and which could lead to better compliance, is fundamental in initial phase of chronic T2DM care. On the other hand, paternal authority, more masculine attitude connected rather to male GPs could have effect on patients at later stages. The observed associations can be interpreted by the gender affected authority-empathy balance. Women's connection patterns are more complex, and more emotional. The traditional masculine attitude tends to result in emotional distancing, and does not conduct to empathy. This gender difference in attitude had been convincingly demonstrated among medical students and among medical doctors as well.

Our observations further emphasize the importance of the appropriate patient conducting skills in T2DM care, and suggest that the unacceptably low RR for OE in Hungary could be increased by developing GPs' patient conducting abilities. Its relevance for medical curricula is obvious, because the communication abilities can be learned. Along with the increasing female-male ratio of GPs, the weight of this GP-gender effect is increasing primarily in developed countries.

Effect of diagnosis-time and initial treatment on the onset of type 2 diabetes mellitus complications/comorbidities

Our study had been based on the well documented importance of early diagnosis in preventing DM complications/comorbidities, and on the fact that applied protocols in the studied population relied on the dietary restrictions and the physical activity improvement generally accepted as interventions with well known risk decreasing role. Consequently our expectation was that the early diagnosis, which is reflected in the initial dietary therapy, is associated with lower complication prevalence. This expectation had been proved only in the case of retinopathy, where a significant effect could be detected. The prevalence of all the other investigated complications/comorbidities in the early and the late diagnosis groups had not shown significant difference.

According to these results it seems that all the prevention opportunities which had been potentially established by the early diagnosis of diabetes apart from the retinopathy could not be realized in Hungary.

Moreover, our study design was sensitive to lead-time bias (the postponing of complications' manifestation can be elicited by the early diagnosis without any contribution of the more effective care for early stage disease). Due to this bias the early diagnosis could seem to be protective without any benefit on the prognosis in our study. Consequently, our study overestimates the prognostic benefit of early diagnosis of T2DM. In spite of this overestimation, there was only one complication which seems to be prevented by early diagnosis. Considering the lead-time bias, we can refine the basic conclusion of our analysis that there is no proved benefit on complications/comorbidities manifestations among T2DM patients, because the only prognostic benefit of early diagnosis observed for rethinopathy can be attributed lead-time.

Tercier prevention of diabetes in Hungary (based on European Health Interview Survey, 2009)

Overall, the T2DM patients are more likely to be obese and seem to be more inactive than the socio-demographically matched non T2DM adults. It is in concordance with etiology of T2DM and shows that the life-style modification based long-term care should be improved in Hungary.

However it is more likely for T2DM patients to stop smoking. It seems that the T2DM patients are open to life-style modification. This positive attitude, which was experienced here, could be more intensively utilized by support teams to change eating habits or reduce alcohol consumption of T2DM patients.

International evaluation of regional diabetes indicators

The created database, from our targeted study was able to ensure the proper T2DM indicators for the EUBIROD set. A continuous register could be established through the gathered experiences from this international consortium. Assuming an optimal number of indicators in a set, which contains not only process indicators, but also outcome indicators could result an effective system. Too many indicators make it difficult for the GPs to generate precise report, so an optimal balance is needed (collect less, but relevant and accurate data). A reliable register could provide data to international projects, and could reflect the quality of care as well. Moreover it could identify critical points, where interventions could be planned, and guidelines could highlighten. We are in the middle range Europe-wide, however the continuous improvement of quality of care is essential for favorable outcomes, to cut spendings on care.

Discussion

Establishment of an accurate monitoring system is essential for the proper care of chronic non-communicable diseases, such as T2DM. There are many followable international examples with complete indicator sets. Monitoring systems gather useful information on the disease and its' complications/comorbidities. Guidelines should follow the results of these systems, and should be in harmony with international practice.

According to our findings (gender, education level, comorbidities) patients could be educated in appropriate ways to achieve better outcomes. Proper care could improve quality of life, through managing comorbidities and complications/comorbidities. Process indicators are very important as well (HC and OE). Regular control examinations give us a picture on the condition of the patient. Latest recommendations take more parameters into consideration, that is why, they use personalized (gender, age, comorbidities) HbA1c target range, instead of a concrete value. Focusing only HbA1c level without respecting other characteristics, and trying to lower it as much as possible could cause more harm, than benefit, because of the elevated risk for cardiovascular mortality.

However a slow progress could be observed in the effectiveness of care, Hungary is in the mid-field of European Union. According to Euro Diabetes Report 2014, which involves 30 countries, Hungary is 17th rank. This ranklist is based on 6 main indicator groups (prevention, case finding, range and reach of services, access to treatment/care, procedures, outcomes).

New findings

Around 71.53% of the patients had their HbA1c above target level (6.5%), which was recommended by guidelines in 2008. Protective factors were male gender, tertiary education level, absence of retinopathy.

Significant influence was found by gender ($OR_{\text{female/male}} = 1.56$ 1.14-2.13), education level ($OR_{\text{tertiary/primary}} = 0.53$ 0.32-0.88) and presence of retinopathy ($OR = 1.71$ 1.07-2.73) in case of reaching target level.

We have estimated the prevalences of complications/comorbidities and comorbidities, which were related to T2DM for Hungary.

We can conclude that hypertension is most commonly associated with T2DM in both gender (among men: 86.84%; 95% CI 83.61% - 89.51%), among women: 91.70% 89.02% - 93.77%), lipid metabolism disorder was the second (among men: 63.46% 59.17% - 67.54%, among women: 65.47% 61.31% - 69.41%) and obesity was in the third position (among men: 49.71% 45.37% - 54.05% among women: 58.11% 53.86% - 62.25%).

The AMI and stroke incidence among T2DM patients observed in 2008-2011 was significantly better than those from the period of 2004-2007, demonstrating the improvement of the T2DM care effectiveness in preventing lethal outcomes. There was a significant improve in 2-year cumulative incidence of AMI and stroke. $SIR_{\text{AMI}}=0.685$ 0.604-0.766; $SIR_{\text{STROKE}}=0.796$ 0.736-0.855.

Using process indicators (HbA1c check, eye examination) alone, without outcome indicators (HbA1c value) could be contra-productive by evaluating GPs' performances.

According to our results, HbA1c level was not related to the frequency of ophthalmologic examination ($OR=0.7$; 95% CI 0.53-0.94), however showed significant inverse association with HbA1c check rate ($OR=0.76$; 95% CI 0.56-1.04).

The importance of communication techniques were demonstrated, through our result, that female GPs managed better their patients without complications/comorbidities, while male GPs conducted their patients with complications/comorbidities more successfully, from the aspect of eye examination.

Female GPs were more successful among retinopathy free patients (OR=1.44; p=0.014). Male GPs achieved higher level of cooperation among patients with retinopathy (OR=0.42; p=0.035).

Early diagnosis had a significant role in preventing / postponing the development of retinopathy, in Hungarian practice.

Higher occurrence of retinopathy has been found in the late diagnosis group where oral drugs or insulin was applied as first treatment (OR=1.62, 95% CI 1.06-2.49).

T2DM patients are more likely to abandon smoking, less likely to reduce alcohol consumption and to improve dietary habits, compared to people without T2DM.

T2DM patients significantly more likely to stop smoking (OR: 1.62, 95% CI 1.1 - 2.38), compared to socio-demographically matched adults without T2DM.

Our GPMSSP based study was able to produce the majority of EUBIROD indicator set.

European Best Information through Regional Outcomes in Diabetes (EUBIROD), which project tries to implement a sustainable European Diabetes Register with the help of existing regional frameworks. Faculty of Public Health, University of Debrecen is one of the partners of EUBIROD, which is supported by the EU Public Health Program. We were able to extract and deliver 35 indicators out of total 49 (71.4%).

Recommendations

Establishment of an accurate monitoring system is essential for the proper care of chronic non-communicable diseases, such as T2DM. There are many followable international examples with complete indicator sets. (EUBIROD) Monitoring systems gather useful information on the disease and its' complications/comorbidities. Guidelines should follow the results of these systems, and should be in harmony with international practice. Patients could be educated to achieve better outcomes. Process indicators are very important as well (HC and OE). Proper indicator set is essential for appropriate care through effective national monitoring system.

Greater emphasis should be placed on monitoring comorbidities/complications, for proper tertiary care, as patients die primarily due to complications/comorbidities, not to presence of T2DM. The burden of patients and the cost of health financing could be reduced by preventing the development of comorbidities, through appropriate secondary and tertiary prevention. Our results emphasize the importance of the support team.

Because of the inadequate correspondence between outcome and process indicators, process indicators can not initiate a better quality in care by itself. They seem to be inappropriate in measuring quality of care without outcome indicators such as HbA1c value. The Hungarian indicator system should be harmonized with international practice.

Our observations further emphasize the importance of the appropriate patient conducting skills in T2DM care, and suggest that the unacceptably low RR for OE in Hungary could be increased by developing GPs' patient conducting abilities. It's relevance for medical curricula is obvious, because the communication abilities can be learned. Along with the increasing female-male ratio of GPs, the weight of this GP-gender effect is increasing primarily in developed countries.

Consequently our expectation was that the early diagnosis, which is reflected in the initial dietary therapy, is associated with lower complication prevalence. This expectation had been proved only in the case of retinopathy, where a significant effect could be detected. The prevalence of all the other investigated complications/comorbidities in the early and the late diagnosis groups had not shown significant difference.

SUMMARY

Overwhelming majority of DM-related socio-economical burden, human suffering and disability are elicited by diabetic complications/comorbidities. Most of this burden is related to the non-fatal major adverse, and nearly half of DM patients die of cardiovascular diseases.

The main objective of DM control is to prevent or postpone the onset of complications/comorbidities.

Current guideline on diagnosing, screening and treating diabetes, is made by Hungarian Diabetes Association (HDA) and it is in harmony with international recommendations. However in 2008, the recommended target level for HbA1c was 6.5%, nowadays, latest recommendations suggest a target range (6,5%-8%) instead of a concrete value, taking patients characteristics into consideration, like age of the patient, presence of complications/comorbidities.

The T2DM prevalence was 6.56% among males above 20 and 6.51% among females above 20 in Hungary.

Our main objective was to investigate the efficiency of Hungarian T2DM care.

We focused on the effectiveness of long term care, through complications/comorbidities and their prevention (these complications/comorbidities are rare below 50). Our study was conducted with the help of 72 participating GPs of the 11 GPMSSP counties in 2008. A cross-sectional study was performed with T2DM patients above 50. The sample size was 1324 persons.

According to our findings (gender, education level, comorbidities) patients could be educated in appropriate ways to achieve better outcomes. Proper care could improve quality of life, through managing comorbidities and complications/comorbidities. Process indicators are very important as well (HC and OE). Regular control examinations give us a picture on the condition of the patient. Latest recommendations take more parameters into consideration, that is why, they use personalized (gender, age, comorbidities) HbA1c target range, instead of a concrete value. Focusing only HbA1c level without respecting other characteristics, and trying to lower it as much as possible could cause more harm, than benefit, because of the elevated risk for cardiovascular mortality.

However a slow progress could be observed in the effectiveness of care, Hungary is in the mid-field of European Union. According to Euro Diabetes Report 2014, which involves 30 countries, Hungary is 17th rank. This ranklist is based on 6 main indicator groups (prevention, case finding, range and reach of services, access to treatment/care, procedures, outcomes).



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List of publications related to the dissertation

1. **Nagy, A.**, Nagy, B., Ádány, R., Sándor, J.: Determinants of low referral rates for ophthalmologic examination in people with type 2 diabetes in Hungary.
Diabetes Res. Clin. Pract. 102 (2), e29-e31, 2013.
IF:2.536
2. Di Iorio, C.T., Carinci, F., Brillante, M., Azzopardi, J., Beck, P., Bratina, N., Cunningham, S.G., de Beaufort, C., Debacker, N., Jarosz-Chobot, P., Jecht, M., Lindblad, U., Moulton, T., Metelko, Ž., **Nagy, A.**, Olympios, G., Pruna, S., Røder, M., Skeie, S., Storms, F., Massi Benedetti, M.: Cross-border flow of health information: Is 'privacy by design' enough? Privacy performance assessment in EUBIROD.
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List of other publications

4. **Nagy A.**, Sándor J., Ádány R.: Megbetegedési viszonyok.
In: Budapesti népegészségügy. Budapest lakossága egészségi állapota és népegészségügyi programja. Szerk.: Ádány Róza, Szentes Tamás, Medicina, Budapest, 69-112, 2014.
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Croat. Med. J. 51 (2), 151-156, 2010.
DOI: <http://dx.doi.org/10.3325/cmj.2010.51.151>
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