The analysis of factors associated with improved glycemic control in patients with insulin-requiring type 2 diabetes mellitus after treatment

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ABSTRACT

Aim To observe the effect of standardized ten-day diabetes prevention and control program on glycemic control, and to analyze factors contributing significantly to improvement of glycemic control after the program/intervention.

Methods A cross-sectional nested case–control study on 91 adult patients with insulin-requiring type 2 diabetes mellitus who underwent a standardized ten-day diabetes program in the Specialized Hospital “Merkur” in Vrnjačka Banja, Serbia, from June the 1st to August 1st 2010 was performed. All necessary data were obtained from patients’ medical files archived in this institution. Cases (n=32) and controls (n=32) were matched for age and sex.

Results Diabetes program led to a significant decrease in mean daily blood glucose (p=0.039), achieved at the expense of the reduction of postprandial hyperglycemia (p=0.013). Male patients, patients with mean daily glycemia above the acceptable range before the intervention, and patients who were receiving combined therapy (insulin plus oral antidiabetics) before the intervention, were significantly more likely to achieve such positive outcome (OR adjusted = 344.48, 12.83, and 25.44 respectively, with 95%CIs that not included 1).

Conclusion Standardized ten-day diabetes educational and rehabilitation program in the Specialized Hospital “Merkur” could be efficient in improving glycemic control, especially for male patients whose glucoregulation was poor despite the combined therapy with insulin and oral antidiabetic agents. Further investigation on determinants of efficiency of this program are necessary to understand better how to facilitate and support improvements in diabetes control at the population level.

Key words: diabetes mellitus type 2, glucoregulation, prevention, education, program.
INTRODUCTION

Diabetes mellitus (DM) represents one of the most important public health problems in Serbia due to its relatively high prevalence of 8.2% in general population and continuously rising incidence, as well as considerable increase in morbidity and mortality caused by accompanying complications associated with high direct and indirect disease costs (1).

The growing awareness of this problem over the past decade in our country has led to a series of actions carried out by regulatory authorities, including the establishment of the National Centre for Prevention, Treatment and Education of Patients with diabetes at the Specialized Hospital “Merkur” in Vrnjačka Banja, in accordance with previously adopted national strategy for prevention and control of this serious and incurable chronic disease (2).

The Specialized Hospital “Merkur” is unique in the region for its diabetes management programs, which provide a complete service (i.e. diagnostic procedures, preventive and curative care, and rehabilitation) for patients in one place (2). It is of particular importance that patients included in these programs undergo comprehensive education on all aspects of DM care, where they learn how to experience and maintain the best possible quality of life with the illness (2). These standards of care are intended to provide clinicians, patients, researchers, payers, and other interested individuals with the components of diabetes care, general treatment goals, and tools to evaluate the quality of care (3). While individual preferences, comorbidities, and other patient factors may require modification of goals, targets that are desirable for most patients with diabetes are provided (3).

In this regard, the ten-day standardized program aimed at screening and prevention of DM complications is being conducted sponsored by the Republic Fund for Health Insurance; it was originally intended only to patients receiving insulin, however, recently it has also become available to those taking oral antidiabetic therapy (4). Although more than 30,000 diabetic patients have been treated at the National Centre in Merkur hospital since its founding in 2008, it is estimated that the number of treated patients for unknown reasons remains very small compared to the total number of potential users (4). Such underutilization is especially surprising when one considers that specialized DM program is a free of charge service for the insured patients (4).

Since, to our knowledge, no studies dealing with the effectiveness of diabetes programs in the Specialized Hospital “Merkur” have been conducted to date, the referring physicians may be concerned with the real benefits of these programs, which could possibly lead to an increase in underutilization of programs by patients. Therefore, the objectives of our study were to observe the effect of standardized ten-day DM program on glycemic control in a group of patients with insulin-requiring type 2 DM treated at the Specialized Hospital “Merkur”, and to analyze which factors that are independent of the intervention efforts contribute significantly to improved glycemic control after the intervention in order to identify patients who are particularly eligible for the inclusion in this program.

PATIENTS AND METHODS

We performed a cross-sectional nested case–control study on 91 adult patients with insulin-requiring type 2 DM who underwent a standardized ten-day diabetes program at the Specialized Hospital “Merkur” in Vrnjačka Banja, Serbia, from June 1st to August 1st 2010. The study included participants of both genders and different age referred by their physicians from all over Serbia to the National Centre for diabetes at the Merkur hospital, if they met the following inclusion criteria: history of type 2 DM of at least 18 months that is no longer controlled with oral antidiabetic drugs, the absence of concomitant diseases that could affect glucose homeostasis, and if they gave the written informed consent for participation in the study. Patients with type 1 DM, patients with incomplete medical documentation or those who left the program before its ending, and patients who were taking medications that are known to have a considerable effect on glucose metabolism (e.g. corticosteroids), were not enrolled in this investigation.

In terms of observed outcomes, in a cross-sectional descriptive model we examined the influence of DM program on improvement of glycemic control by comparing mean daily glycemia, mean fasting and mean postprandial blood glucose levels before and after the intervention. Mean daily glycemia for each patient was derived from six daily measurements of serum glucose concentra-
tion: fasting glucose level (i.e. before the breakfast) and 2 hours after the breakfast, before and 2 hours after lunch, and before and 2 hours after dinner. In accordance with this calculation mean preprandial and mean postprandial blood glucose levels were obtained from values measured before and 2 hours after 3 regular meals a day.

In order to evaluate the association of various factors that are independent of intervention efforts with improved glycemic control, a nested case-control study was performed as follows: cases (n = 32) were defined as patients with observed decrease in mean daily glycemic values at the end of the treatment, and controls (n = 32) were defined as patients without such an outcome at the same time. Cases and controls were matched for age and gender, where both groups were randomly selected from the entire study population who completed the study in accordance with these matching criteria. For the purpose of case-control study analysis the following variables were observed as potential predictors of a positive outcome (i.e. improved mean daily blood glucose level, as stated above) for each patient: a) demographic characteristics - age and gender, b) Body Mass Index (BMI, weight in kilograms divided by the height in meters squared) and waist-hip circumference ratio (WHCR, waist circumference divided by the hip circumference, in centimeters) at admission to the hospital, as the anthropometric parameters of obesity, c) mean daily glycemia and glycated hemoglobin testing (HbA1c) were performed at admission, as parameters of quality of glycemic control before the intervention (HbA1c - as the indicators of long-term glycemic control before the intervention), and d) type of antidiabetic therapy before the intervention/DM program, which was dichotomized into two categories: patients who were only receiving insulin (two or four daily doses) vs. patients who were on insulin plus oral antidiabetics (one dose of human or analogue insulin with metformin and/or other oral antidiabetics).

All necessary data were obtained from patients’ medical files archived in the Specialized Hospital “Merkur” in Vrnjačka Banja. Continuous variables were summarized as means and standard deviations (SDs), while categorical (dichotomous) variables were expressed by frequency and percentage. Significance of differences in continuous variables before and after the intervention was evaluated using Student’s T-test for paired samples, but for comparison of means of continuous variables between cases and controls T-test for independent samples was performed. Dichotomous variables were compared using Pearson Chi-square test or Fisher exact test (when the number of expected frequencies was small). The strength of association between examined predictors and improvement in mean daily glycemia (as the observed dichotomous outcome) is expressed by crude and adjusted (for potential confounders) odds ratios (OR) with 95% confidence intervals (95% CI) that were estimated from binary logistic regression models. Two-sided significance level of 0.05 was considered for all statistical evaluations. The influence of examined predictive variables on probability of improvement in glycemic control was assumed to be clinically important if the OR was greater than 3 with 95% CI that did not include a value of one. All analyses were performed with statistical software SPSS version 18.0.

RESULTS

A total number of 91 patients were included in the study, 55 females (60.44%) and 36 males (39.56%), aged between 42 and 85 years (62.46 ± 8.85, mean ± SD).

Considering the average BMI of 30.14 ± 6.54 (mean ± SD) kg/m2 and average WHCR of 0.92 ± 0.08 (mean ± SD) m majority of participants had central obesity according to World Health Organization (WHO) classification. Also, the average HbA1c of 8.80±1.28 at the admission to specialized hospital indicated that majority of them were in poor glycemic control before the intervention.

Treatment with the standardized ten-day DM program resulted in a significant decrease in mean daily blood glucose (p=0.039, Table 1). This improvement in glycemic control, noted in 53.8% of the participants (49/91), was actually achieved at the expense of decrease in postprandial hyperglycemia since the fasting blood glucose levels did not significantly change (Table 1).

<table>
<thead>
<tr>
<th>Variables Before the treatment</th>
<th>After the treatment</th>
<th>Paired samples T-test p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean daily glycemia (mmol/L) (mean ± SD)</td>
<td>8.81 ± 2.96 8.26 ± 1.87</td>
<td>T = 2.093 0.039*</td>
</tr>
<tr>
<td>Mean preprandial glycemia (mean ± SD)</td>
<td>8.34 ± 3.24 7.99 ± 2.25</td>
<td>T = 1.181 0.241</td>
</tr>
<tr>
<td>Mean 2h postprandial glycemia (mean ± SD)</td>
<td>9.27 ± 3.01 8.54 ± 2.07</td>
<td>T = 2.548 0.013*</td>
</tr>
</tbody>
</table>

* significant difference
Baseline characteristics of participants included in nested case-control study, i.e. differences between cases and controls in examined predictive variables (Table 2). Two compared groups were very similar in regard to sex, age, BMI, and WHCR, while significant differences were found in parameters of glycemic control (mean daily glycemia and HbA1c); at that, the difference in mean daily glycemia was highly statistically significant (p<0.001).

Table 2. Baseline characteristics of cases and controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases (n=32)</th>
<th>Controls (n=32)</th>
<th>Statistical test value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (No/%)</td>
<td>male 12 / 37.5%</td>
<td>female 12 / 37.5%</td>
<td>χ² &lt; 0.001</td>
<td>1.000</td>
</tr>
<tr>
<td>Age (years, mean±SD)</td>
<td>61.47 ± 8.45</td>
<td>62.59 ± 8.63</td>
<td>T = -0.527</td>
<td>0.600</td>
</tr>
<tr>
<td>BMI before DM program (kg/m², mean±SD)</td>
<td>31.00 ± 6.26</td>
<td>30.51 ± 7.44</td>
<td>T = -0.287</td>
<td>0.775</td>
</tr>
<tr>
<td>WHCR before DM program (m, mean±SD)</td>
<td>0.92 ± 0.07</td>
<td>0.92 ± 0.08</td>
<td>T = 0.555</td>
<td>0.988</td>
</tr>
<tr>
<td>Mean daily glycemia (mmol/L, mean±SD)</td>
<td>10.28 ±2.74</td>
<td>6.70 ± 1.59</td>
<td>T = 6.390</td>
<td>0.001†</td>
</tr>
<tr>
<td>HbA1c before DM program (%), mean±SD)</td>
<td>9.21 ± 1.07</td>
<td>8.60 ± 1.14</td>
<td>T = 2.17</td>
<td>0.033†</td>
</tr>
</tbody>
</table>

Type of antidiabetic therapy before DM program (No/%)*

<table>
<thead>
<tr>
<th>Type of antidiabetic therapy before DM program (No/%)</th>
<th>Cases</th>
<th>Controls</th>
<th>Statistical test value</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>only insulin vs. insulin + oral antidiabetics; † significant difference; ‡ clinically significant association</td>
<td></td>
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</tbody>
</table>

A binary logistic regression analysis (Cox & Snell R square 0.596, Nagelkerke R square 0.795, Hosmer-Lemeshow Chi square 4.603, df=8, p = 0.799) revealed that sex, mean daily glycemia and type of antidiabetic therapy before the intervention (DM program) were significant predictors of improvement in glycemic control after the intervention as expressed by decreased average daily blood glucose level (Table 3). Indeed, male patients, patients with higher than normal mean daily glycemia before the intervention, and patients who were receiving combined antidiabetic therapy (insulin plus oral antidiabetics) before the intervention were significantly more likely to achieve such positive outcome after the DM program (ORadj = 344.48, 12.83, and 25.44 respectively, with 95% CIs that not included 1 for any of examined variables (Table 3). Although the HbA1c value before the DM program showed some influence on observed positive outcome in un-adjusted model (crude OR 1.64, 95CI 1.03 – 2.63, p = 0.038, Table 3), after adjustment the association was neither statistically nor clinically significant (95% confidence interval of adjusted OR included value of one, p > 0.05, Table 3).

DISCUSSION

Type 2 diabetes mellitus (T2DM) is an incurable disease that became pandemic in the past couple of decades. Due to its chronic complications, T2DM is regarded as the leading cause of cardiovascular morbidity/mortality, terminal renal insufficiency, blindness, and lower extremity amputations (5,6). Diabetes prevalence grows with age, and it is estimated that almost a half of diabetic patients are over 65 years of age (7). As many large studies show, it is essential to achieve strict metabolic control of T2DM with the aim of preventing further deterioration of existing complications (8,9). For example, the United Kingdom Prospective Diabetes Study (UKPDS) on 5000 patients with DMT2 revealed that for every percentage point decrease in HbA1c, there was a significant reduction in both macroangiopathic and microangiopathic complications (8, 9). Also ADVANCE and Kumamoto studies documented direct association between poor glycemic control and the development of complications (8,9).

Whereas many epidemiologic studies and meta-analyses have clearly shown a direct relationship between HbA1c and cardiovascular diseases (CVD), the potential of intensive glycemic con-
trol to reduce CVD has been less clearly defined. In the DCCT (Diabetes Control and Complications Trial), there was a trend toward a lower risk of CVD events with intensive control (9). People with diabetes should receive medical care from a physician-coordinated team (3,10). Such teams may include, but are not limited to, physicians, nurse practitioners, physician’s assistants, nurses, dietitians, pharmacists, and mental health professionals with expertise and a special interest in diabetes (3,10).

When it comes to DMT2 management, besides achieving optimal glycemic control, treatment of concomitant conditions like obesity, hypertension and dyslipidemia is very important in order to reduce cardiovascular morbidity and mortality (3). In Serbia a standardized educational and rehabilitation program in the Specialized Hospital “Merkur” in Vranjačka Banja is used to achieve these goals (2). Apart from patients’ education the program consists of comprehensive physical examination, laboratory workout, controlled and completely individualized physical activity on prescription, and individual dietary modifications adjusted to each patient’s caloric needs; in majority of cases the weight loss diet is performed, due to fact that almost all of the patients are overweight or obese (2). Education of patients involves giving them detailed information about the importance of adequate diet and regular physical activity, insulin self-medication, self-monitoring blood glucose levels, and recognizing and treating early symptoms of hypoglycemia (11).

According to our study, standardized educational and rehabilitation program in the Specialized Hospital “Merkur” is efficient in improving glycemic control measured by decrease in mean daily blood glucose level. We believe that this outcome is a consequence of adoption of lifestyle changes and improved self-care of disease under the influence of DM program. Therefore, public health messages, health care professionals, and health care systems should all encourage behavior changes to achieve a healthy lifestyle. Further researches are necessary to understand better how to facilitate effective and efficient programs for T2DM management (12,13). The fact that male patients in our study were more likely to have improved glucose control after DM program/intervention coincides with previous studies which demonstrated better adherence to non-pharmacological measures in males than in females with T2DM (13,14).

A finding of improved glycemic control that is achieved at the expense of reduction in postprandial blood glucose excursions could be particularly important considering the well-known association between postprandial hyperglycemia with a risk of cardiovascular morbidity and mortality (15-18).

The main disadvantages and limitations of our study refer to questionable generalisability of the results since the study population may not be fully representative of the target population of patients with insulin-requiring T2DM eligible for the inclusion in standardized DM program whose effects were observed. We have used useful strategies to avoid potential selection and measurement biases in the nested case-control study analysis such as matching of cases and controls for age and sex, selection of cases and controls from the same population (same facility: Specialized Hospital “Merkur”) and use of data recorded before the outcomes occurred, but some potentially relevant predictors of observed outcomes and confounders were omitted: severity of DM in terms of presence and severity of disease complications, duration of DM, types and dosage of antidiabetic drugs used before the intervention, compliance with the DM treatment before the intervention, chronic comorbid conditions, comedications, and lifestyle habits of patients before the intervention. Therefore, this study should be best regarded as a hypothesis-generating research imposing further investigations on factors associated with the efficiency of DM management programs in the Specialized Hospital “Merkur” in Vrnjačka Banja.

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TRANSPARENCY DECLARATIONS

Competing interests: none to declare.
REFERENCES


Analiza faktora povezanih s poboljšanjem glikoregulacije kod pacijenata sa zavisnim od inzulina dijabetes melitusom tip 2 nakon lečenja

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SAŽETAK

Cilj Utvrditi efekte standardizovanog desetodnevnog programa prevencije i edukacije dijabetičara na kvalitet glikoregulacije, te analizirati koji faktori značajno doprinose poboljšanju kontrole glikemije nakon intervencije.

Metode Napravljena je studija preseka s usaćenom studijom slučaj-kontrola, u koju je uključen 91 pacijent s tipom 2 dijabetesne bolesti u fazi zavisnosti od inzulina, koji su prošli standardizovani desetodnevni program u Specijalizovanoj bolnici “Merkur” u Vrnjačkoj Banji (Srbija), u periodu od 1. juna do 1. avgusta 2010. godine. Svi potrebni podaci dobijeni su iz medicinske dokumentacije pacijenata koja je arhivirana u ovoj ustanovi. Slučajevi (32) i kontrole (32) usklađeni su prema polu i starosti.

Rezultati Dijabetes program doveo je do značajnog smanjenja u prosečnoj dnevnoj vrednosti glikemije (p=0.039), koje je prevashodno ostvareno na račun smanjenja postprandijalne hiperglikemije (p=0.013). Verovatna pozitivnog ishoda značajno je veća kod pacijenata muškog pola (korigovani OR=344,48 95%CI ne obuhvata 1), pacijenata s povišenim srednjim vrednostima glikemije u dnevnom profilu pre intervencije (korigovani OR=12,83 95%CI ne obuhvata 1) i pacijenata na kombinovanoj terapiji inzulinom i oralnim antidijabeticima (korigovani OR=25,44 95%CI ne obuhvata 1).

Zaključak Standardizovani desetodnevni program edukacije i rehabilitacije dijabetičara u Specijalizovanoj bolnici “Merkur” može doprineti poboljšanju kontrole glikemije, posebno kod pacijenata muškog pola čija je glikoregulacija loša uprkos primeni kombinovane terapije inzulinom i oralnim antidijabeticima. Dalja istraživanja faktora koji utiču na efikasnost ovog programa neophodna su u cilju olakšanja i podrške naporima za poboljšanje kontrole dijabetesne bolesti na nivou populacije.

Ključne reči: dijabetes melitus tip 2, glikoregulacija, prevencija, edukacija, program.