Comparative Analysis of the Cost of Insulin Treated Patients in Bulgaria

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ABSTRACT
The goal of this study was to calculate and compare the direct medical cost of diabetes and its complications for insulin treated patients from the perspective of the health insurance fund. In a combined prospective and retrospective observational study with duration of 6 months, 433 patients were randomly selected and were divided into 3 subgroups: 153 patients on insulin analogues, 115 on human insulin, and 165 on a combination of insulin and oral antidiabetic drugs (OAD). The cost of therapy for each group of patients was calculated as a sum of the units of health care resources used and their individual price. The average cost attributable to each individual patient was calculated by dividing the total cost by the number of patients. A second step analysis was performed in a hospitalized subgroup of patients during the period. Insulin analogues, due to their higher prices, are with the highest cost per 6-month therapy (652.12 BGN), closely followed by the combination therapy cost (479.34 BGN) in case just insulin therapy is considered. In contrast, the cost of hospitalizations due to diabetes was found to be lowest in the group of patients on insulin analogues, followed by that for patients on a combination of insulin plus OAD therapy, and highest for the group on human insulin therapy. The main cost drivers are the medications for diabetes (46 % of the total cost on average), outpatient medications for diabetes complications (27%), and hospitalization due to diabetes (14 %). These cost components account for 87% of the total cost. When adding the cost of hospitalizations due to diabetes complications, 96 % of the total cost is reached.

A selection of the main treatment pattern linked to insulin/insulin analogue +/− OAD administration depends on individual patients characteristics (type of DM, Hb1Ac, age, complications etc.) as well as healthcare system organization (e.g. sequential therapy). It explains the cost structure differences between the heterogenic groups analysed. Intensification of the insulin therapy seems to be cost neutral from the total costs perspective.


Keywords: cost-of-illness analysis, diabetes therapy cost, insulin therapy cost
Materials and Methods

Methodology
The study was designed as a combined prospective and retrospective observational study with duration of 6 months. Thirty-five endocrinology specialists randomly selected from different geographical regions of the country, recruited insulin-treated diabetic patients, and collected information prospectively during a 3-month period, as well as reviewed patients’ records retrospectively for a 3-month period in 2010 and 2011.

Patient selection
Within a one-month period, five consecutive insulin-treated diabetic patients who agreed to participate were included in the observation. A sample size of 303 diabetic patients out of a total of 138 000 insulin users in Bulgaria was determined as representative. At the end of the first month, 433 patients who agreed to participate were selected and were divided into 3 subgroups: 153 patients on insulin analogues, 115 on human insulin, and 165 on a combination of insulin and oral antidiabetic drugs (OAD).

Health care resources observed
Information about the health care resources, namely, type of insulin and therapeutic regimen, medications for outpatient therapy of complications (hypertension, arrhythmia, polyneuropathy, retinopathy, nephropathy, myocardial infarction, and stroke), hospitalizations due to diabetes and complications, physician visits (GP and specialists endocrinologists, ophthalmologists, neurologists, nephrologists, and cardiologists), and medical devices (test-strips and glucometers) was collected about the selected patients.

Cost-of-illness analysis
The cost of therapy for each group of patients was calculated as a sum of the units of health care resources used and their individual price. The average cost attributable to each individual patient was calculated by dividing the total cost by the number of patients included in the group (regardless of the fact that they might not use a particular health care resource).

Then the second step of the analysis was performed for patients with hospitalization during the period. Information about these patients was extracted from the same three therapeutic subgroups: on analogues (n = 45), human insulin (n = 46) and OAD (n = 69) therapy, and their average cost of therapy was calculated.

The prices of drugs and medical devices for outpatient treatment were taken from the official web site of the pricing and reimbursement committee at the Ministry of Health (16). The cost of physicians’ visits and hospitalizations were taken from the National Health Insurance Fund tariffs (NHIF) (17).

All costs were calculated from the payers’ perspective, and no patients or indirect costs were considered. All the costs are presented for a six-month period in the national currency – Bulgarian Lev (BGN). The exchange rate in 2010 and 2011 is 1 Euro = 1.95 BGN.

Statistical methods
Descriptive statistical methods were applied for the analysis of patients’ characteristics and cost. Two and three independent sample Z-test analysis for proportions was applied to assess the statistical significance among the differences of the relative shares of the costs within the total cost of particular health care resources among the 3 subgroups of patients. T-test analysis was applied to assess the statically significant differences among the cost of therapy between the patient subgroups. Two-way ANOVA analysis was applied to test the cost differences by age groups and by dosage regimen.

Results and Discussion
According to the official information from NHIF, there are 300 000 diabetic patients in the country and near 10 % of them are type 1 diabetics. There are about 108 000 type 2 diabetic patients on insulin therapy. Thus, in total approximately 138 000 patients are treated with insulin.

The observed three groups of patients: on insulin analogues, human insulin, and combination therapy (insulin plus OAD) appear to be different. Patients on insulin analogues are on average 43.12 (SD 16.02) years old with 15.46 (SD 9.94) years of diabetes duration, and 42.59 % of them have complications. The patients on human insulin are 58.54 (SD 16.44) years old with 12.97 (SD 10.55) years of diabetes duration on average, and 48.6 % of them have complications. The patients on combination therapy are on average 58.94 (SD 9.90) years of age; with 12.52 (SD 6.57) years of diabetes duration, and 52.53 % of them have developed complications.

The cost of insulin analogues insulin analogues, due to their higher prices is with the highest for 6-month therapy (652.12 BGN), closely followed by the combination therapy cost (479.54 BGN) in case just insulin therapy is considered (Table 1). If the cost of OAD is added, the therapy of this subgroup reaches 532.01 BGN (SD 248.01). The SD of the group on insulin and oral antidiabetes therapy (OAD) therapy is with the highest value probably due to the great variations of the prices of the OAD on the market. The differences in the cost of insulin therapy between the three studied subgroups were found to be statistically significant ($P < 0.05$) (Table 1).

In contrast, the cost of hospitalizations due to diabetes is lowest in the group of patients on insulin analogues, followed by that of patients on human insulin therapy, and highest for the group on a combination of insulin plus OAD therapy.

The patients on combination therapy are usually with type 2 diabetes, which could not be adequately controlled with OAD and needed addition of insulin. These patients are frequently hospitalized, they have a lot of complications and, therefore, higher hospitalization cost due to complications. The differences in the cost of hospitalizations were found to be statistically significant among the three studied groups ($P < 0.05$).
Similar tendencies were observed when comparing the cost of medications for the treatment of diabetes complications. Again the cost was found to be lowest in the group of patients on insulin analogues, followed by that in the group on human insulin and the group on combination therapy. The cost of hospitalization due to complications is also the lowest in the group on insulin analogues (Table 1). Twice higher is the cost of hospitalizations due to complications in the group on human insulin in comparison with that in the group on insulin analogues.

The cost of consumables and physicians’ visits do not differ significantly among the groups. Patients on insulin therapy have limited access regulated by NHIF to a certain defined number of test-strips per year, as well as a number of visits to GPs and specialists at outpatient level, which could explain the similar costs in the groups (Table 2).

When summarizing all the costs, the group on combination therapy reaches the highest cost for the period of six months (1293.82 BGN), followed by that on insulin analogues (1170.38 BGN), and finally the group on human insulin therapy (927.26 BGN) (Fig. 1). This could be explained by the fact that, in Bulgaria, modern insulins are introduced as a second line after human insulin failure in the treatment cascade, although our subpopulation on analogues was younger than on human insulin, probably because these are the type 1 diabetic patients with an earlier onset of diabetes. In the group on insulin analogue therapy, the cost of insulin comprises about 56 % of the total cost. In the other two groups

**TABLE 1**

<table>
<thead>
<tr>
<th></th>
<th>Cost of medication therapy ± SD</th>
<th>Cost of hospitalizations due to diabetes ± SD</th>
<th>Cost of medications for complications ± SD (average for all patients included in the group)</th>
<th>Cost of hospitalizations for complications ± SD (average for all patients included in the group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin analogues n = 153</td>
<td>652.12 ± 201.22</td>
<td>117.11 ± 120.21</td>
<td>199.95 ± 190.36</td>
<td>68.45 ± 42.06</td>
</tr>
<tr>
<td>Human insulin n = 115</td>
<td>298.89 ± 94.37</td>
<td>128.4 ± 91.06</td>
<td>262.14 ± 283.26</td>
<td>117.24 ± 64.26</td>
</tr>
<tr>
<td>Combination therapy (only insulin cost) n = 165</td>
<td>479.54 ± 243.02</td>
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<tr>
<td>Combination therapy (insulin and OAD cost) n = 165</td>
<td>532.01 ± 248.15</td>
<td>206.91 ± 206.77</td>
<td>392.8 ± 306.48</td>
<td>99.2 ± 54.81</td>
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**TABLE 2**

<table>
<thead>
<tr>
<th></th>
<th>Cost of test-strips</th>
<th>Yearly cost of glucometers</th>
<th>Cost of GP visits</th>
<th>Cost of specialist visits</th>
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<tbody>
<tr>
<td>Insulin analogues n = 153</td>
<td>80.97 ± 50.39</td>
<td>3.71 ± 6.2</td>
<td>20.44 ± 8.93</td>
<td>27.63 ± 20.7</td>
</tr>
<tr>
<td>Human insulin n = 115</td>
<td>68.68 ± 44.44</td>
<td>3.96 ± 6.76</td>
<td>21.01 ± 6.46</td>
<td>26.94 ± 21.91</td>
</tr>
<tr>
<td>Combination therapy (insulin and OAD) n = 165</td>
<td>62.66 ± 33.28</td>
<td>3.51 ± 7.7</td>
<td>20.44 ± 6.87</td>
<td>28.76 ± 19.89</td>
</tr>
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**TABLE 3**

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<thead>
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<th></th>
<th>Insulin analogues</th>
<th>Human insulin</th>
<th>Combination therapy (Insulin and OAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional therapy</td>
<td>492.82</td>
<td>295.32</td>
<td>387.00</td>
</tr>
<tr>
<td>Intensive therapy</td>
<td>697.74</td>
<td>323.82</td>
<td>663.36</td>
</tr>
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</table>
the medications for diabetes account for 32% and 47% of the cost. The main cost drivers are the medications for diabetes (42% of the total cost on average), outpatient medications for diabetes complications (25%), and hospitalization due to diabetes (13%). These cost components account for 80% of the total cost. When adding the cost of hospitalizations due to diabetes complications, 89% of the total cost is reached.

Fig. 1. Structure of the average cost of therapy.

The cost of insulin either in monotherapy, or in combination therapy with OAD, accounts for the greatest percentage of total cost (Fig. 1). Applying z-test analysis for the proportion of independent groups, we found that the differences in the relative share of insulin therapy cost, medication cost for hospitalization, and cost of hospitalization due to complications are statistically significant among the three subgroups.

For the group of patients with hospitalizations during the observed six-month period the calculated cost of therapy and its structure changes as shown in Fig. 2.

Fig. 2. Structure of the average cost of therapy for patients with hospitalizations during the period.

In this second step analysis concentrated on the patients with hospitalizations, it was found that the cost of insulin therapy is only 21% on average, but the cost of hospitalizations due to diabetes reaches 21%, and cost of hospitalizations due to complications reaches 39%. Together with the medication cost for hospitalizations (16% on average), these components account for 93% of all costs (Fig. 2). From Fig. 2 it is also evident that the hospitalization cost due to diabetes and complications, as well as the medication cost for complications, is with lower relative share in the group on insulin analogues.

Within the main subgroups we further analysed the differences in the cost of insulin therapy for patients on intensive and conventional dosage regime (Table 3). The cost of therapy for patients on conventional regime appears to be slightly lower but the differences were found to be statistically significant. Thus, the insulin regime does influence the cost of insulin therapy.

We further explored the differences in the total cost of therapy by age groups (Fig. 3). For patients on insulin analogues, the less costly therapy is that in the group at the age of 45–59, while for human insulin and combination therapy the therapy among 20–44-year-olds appears to be less costly. ANOVA analysis of the cost of therapy for different age groups revealed that the differences are statistically significant among the three subgroups ($P = 0.019$), as well as among the compared ages ($P = 0.0017$).

Fig. 4. Differences in medication cost by age groups.

If only the medication cost is compared by age groups, it is evident that the cost is lowest in the group of patients on human insulin and also in the group of the 60–90-year-olds (Fig. 4). The differences in the cost of medications are not statistically significant among the compared ages in the three
subgroups ($P = 0.08$), but are significant among the subgroups ($P = 0.004$).

To the best of our knowledge, our study is the first one to focus in details on the cost of insulin treated patients in Bulgaria. This is also the first micro-costing study evaluating a patient sample for a period of six months. It confirms the results of similar studies that insulin analogues are most expensive but they ensure better glycaemic control and thus allow to lower the cost of hospitalizations due to diabetes (3, 15). It also confirms the results that the complications and hospitalization costs are important cost drivers, and for the group of patients who experience hospitalization, they account for 60% of the total cost.

With this study we also add new evidence on the differences in the cost structure in various treatment regime groups.

A lot of factors could influence the differences in the costs: general population age, prescribing habits, life style, type of diabetes, etc. Among these factors we explored the insulin regime: conventional and intensive therapy, and found that the insulin regime does influence the cost of insulin therapy. The age of patients affects the cost of therapy in a statistically significant manner (no other risk factors adjusted). Further analyses are needed to explain the reasons for these differences in detail.

Our study has some limitations, for example, the fact that we focus only on the payer cost, not applying the societal perspective covering direct but also indirect costs. Even from the payer’s perspective, we did not include the cost of clinical tests and regular visits because they are predefined for all diabetic patients. Heterogeneity of the subgroups, including the mean age, the average duration of diabetes, the degree of diabetes control correlating with probability of complications, may also be a limiting factor. It indicates that the groups should be analyzed separately and not directly compared without correcting for all these factors. Long-term cost-effectiveness analyses focused on concrete products are needed to draw conclusions regarding the best treatment options in the Bulgarian health care system.

**Conclusions**

A selection of the main treatment pattern linked to insulin/insulin analogue +/- OAD administration depends on individual patients’ characteristics (type of DM, Hb1Ac, age, complications, etc.) as well as the healthcare system organization (e.g. sequential therapy). It explains the cost structure differences between the heterogenic groups analyzed. Intensification of the insulin therapy seems to be cost neutral from the total costs perspective.

**REFERENCES**