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ORIGINAL RESEARCH

Adequate prescribing of medication does not necessarily translate into good control of diabetes mellitus

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Background: Patients with diabetes mellitus in Lithuania have access to almost all the latest blood glucose-lowering drugs available in the rest of the world. This study evaluated the effects of prescribing of treatment (oral medications, insulin, or both) in Lithuanian patients with type 1 or 2 diabetes and poor blood glucose control.

Methods: The relevant information was obtained from specialized questionnaires completed by 26 consulting endocrinologists in Lithuania between October 1, 2008 and December 31, 2008. The study cohort comprised 865 randomly selected patients with diabetes mellitus and a glycosylated (HbA_{1c}) level ≥7%. In total, there were 95 patients with type 1 diabetes and 770 with type 2 diabetes.

Results: Linear regression for patients with type 1 diabetes revealed a weak trend towards higher doses of insulin reflecting lower HbA_{1c} values. The mean dose of insulin in patients with type 1 diabetes before an endocrinology consultation was 57.1 ± 15.7 U/day (0.8 ± 0.2 U/kg), which increased significantly to 63.3 ± 16.5 U/day (0.9 ± 0.2 U/kg) after an endocrinology consultation ($P < 0.05$). Treatment prescribed for patients with type 2 diabetes depended on the duration of disease. Earlier treatment recommended for 68% of patients with type 2 diabetes was subsequently changed by the endocrinologist. Linear regression showed that the insulin dose prescribed before a specialist consultation as well as that recommended by an endocrinologist was significantly correlated with body mass index.

Conclusion: Appropriate prescribing of blood glucose-lowering drugs does not always translate into good metabolic control of diabetes mellitus. The mean HbA_{1c} was 8.5% ± 1.3% in patients with type 2 diabetes treated with oral drugs alone versus 9.0% ± 1.3% in those treated with insulin alone.

Keywords: diabetes mellitus, control, blood glucose-lowering treatment

Introduction

Diabetes mellitus refers to a group of metabolic diseases characterized by hyperglycemia induced by defective insulin secretion or action, or both.[1] Patients with type 1 diabetes lack insulin, so compensatory treatment with insulin is necessary, whereas patients with type 2 diabetes develop metabolic disturbances because of insufficient insulin action or disturbances in insulin secretion, so may require treatment with a number of oral medications (biguanides, sulfonylureas, incretins, alpha-glycosidase inhibitors, thiazolidinediones, and derivatives of benzoic acid and phenylalanine) to help reduce hyperglycemia.[2,3]

The major aim of treatment in patients with diabetes is to normalize their metabolic disturbances and to protect against complications of the disease in

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the long term.[4–6] Clinical research has demonstrated that maintenance of blood glucose levels as close to normal as possible slows the onset and progression of the eye, kidney, and nerve damage caused by diabetes. The Diabetes Control and Complications Trial showed that intensive treatment of patients with type 1 diabetes slowed the progression of retinopathy by 54% and reduced the occurrence of microalbuminuria and peripheral neuropathy by 39% and 60%, respectively.[7] The UK Prospective Diabetes Study confirmed a relationship between exposure to hyperglycemia over time and the risk of macrovascular and microvascular complications in patients with type 2 diabetes.[8] Further, each 1% reduction in mean glycosylated hemoglobin (HbA_{1c}) was associated with a 21% reduction in risk of diabetes-related death, a 14% reduction in risk of myocardial infarction, and a 37% reduction in microvascular complications.[8] The Collaborative Analysis of Diagnostic Criteria in Europe study, which analyzed data from approximately 30,000 subjects participating in 20 epidemiologic studies in Europe, demonstrated a close relationship between increased mortality risk and two-hour glucose concentrations after a meal.[9]

According to the recommendations of the Ministry of Health in Lithuania, the amount of glucose in capillary blood on self-testing should be 4.4–6.7 mmol/L before a meal, <8.9 mmol/L two hours after a meal, and 5.5–8.9 mmol/L before sleep in order to maintain an HbA_{1c} level ≤7%.[10]

Treatment of patients with diabetes is a complex process in which diet, regular physical activity, and appropriate selection of effective medication play a major role, along with smoking cessation and weight loss. Diabetic patients in Lithuania have access to almost all the new blood glucose-lowering drugs available in the rest of the European Union. However, the success of treatment ultimately depends on the patient's compliance with the physician's directions and their level of self-control. Patients with type 2 diabetes who do not respond adequately to one blood glucose-lowering oral medication can be switched to a different class of medication and/or insulin therapy.[11,12] This study investigated the treatment of patients with type 1 or 2 diabetes and inadequate blood glucose control in Lithuania.

Materials and methods

Study sample

The study population comprised patients with type 1 or 2 diabetes recruited by 26 endocrinologists from several specialist outpatient clinics between October 1, 2008 and December 31, 2008. Patients attending these clinics were selected for participation in the study by random number generator. The inclusion criteria were age ≥18 years, type 1 or 2 diabetes diagnosed by a physician, and HbA_{1c} ≥7%. Patients were excluded if they were unable to provide written informed consent. The study was approved by the Kaunas regional biomedical research ethics committee.

Study outcome and measures

The questionnaires, completed by the participating endocrinologists, recorded demographic and clinical patient data including: age and sex; complaints; clinical diagnosis; date of diagnosis; presence of cardiovascular complications, nephropathy, retinopathy, and neuropathy, foot ulceration, phlegmons, gangrene, and lower limb amputations; height, weight, and waist and hip circumferences; systolic and diastolic arterial blood pressure; pulse rate; blood glucose level before and two hours after a meal; HbA_{1c}, potassium, urea, creatinine, C-reactive protein, total cholesterol, high-density cholesterol, low-density cholesterol, triglyceride levels and albuminuria; and conclusions of other medical specialists. Information was also collected regarding treatment with oral blood glucose-lowering agents and insulin before consultation as well as changes in treatment recommended during the endocrinology consultation.

Patient characteristics

The study sample comprised 95 patients with type 1 diabetes and 770 patients with type 2 diabetes. The mean age of the patients at onset of diabetes, at the time of completion of the questionnaire, and the mean duration of the disease are shown in Table 1.

Table 1 Mean patient age on completing the questionnaire and at onset of disease, and mean duration of disease

Characteristic	Type 1 diabetes		*P*	Type 2 diabetes		*P*
	Men	Women		Men	Women	
Age, years	40.7 ± 13.1	42.9 ± 13.9	>0.05	62.1 ± 10.1	65.3 ± 9.9	<0.0001
Age at onset, years	25.9 ± 12.7	28.2 ± 14.5	<0.05	54.1 ± 10.0	54.5 ± 11.5	>0.05
Duration of diabetes, years	15.1 ± 11.1	14.8 ± 9.3	>0.05	8.0 ± 6.3	10.8 ± 8.3	<0.0001

Note: Values are shown as the mean ± standard deviation.

Statistical analysis

The study data were analyzed using Statistical Package for the Social Sciences version 13.0 software (SPSS Inc, Chicago, IL, USA). The results are shown as the mean and standard deviation. Differences between frequencies were checked using the chi-square (χ^2) criterion. Correlations were analyzed using linear regression. The chosen level of statistical significance was two-sided $P < 0.05$.

Results

Data were collected from 56 (58.9%) insulin-treated males and 39 (41.1%) insulin-treated females with type 1 diabetes ($P > 0.05$). Mean HbA_{1c} was 9.2% ± 1.4% in patients with type 1 diabetes and 8.7% ± 1.3% in those with type 2 diabetes ($P < 0.05$); corresponding HbA_{1c} levels for men with type 1 and 2 diabetes were 9.2% ± 1.4% and 8.8% ± 1.4%, respectively ($P > 0.05$) and 9.1% ± 1.3% and 8.6% ± 1.3% for women ($P < 0.05$). The distribution of patients with type 2 diabetes according to sex and treatment is shown in Table 2. HbA_{1c} levels are shown for patients with type 2 diabetes according to type of treatment in Table 3.

Linear regression showed a weak tendency for higher doses of insulin to be associated with lower mean HbA_{1c} levels in patients with type 1 or 2 diabetes (r = –0.089, $P = 0.394$, and r = –0.077, $P = 0.151$, respectively). However, the correlation between HbA_{1c} level and amount of insulin prescribed per kilogram of body weight was not statistically significant for type 1 or type 2 diabetes (r = 0.006, $P = 0.956$, and r = 0.074, $P = 0.169$, respectively).

Mean body mass index was significantly lower in patients with type 1 diabetes than in those with type 2 diabetes. Linear regression did not show any statistically significant correlation between HbA_{1c} and body mass index in patients with either type of diabetes. Treatment of patients with type 2 diabetes depended on duration of disease (Table 4).

Eighty (84.2%) patients with type 1 diabetes were found to have an HbA_{1c} >8%, for whom a higher insulin dose was recommended during their endocrinology consultation (Figure 1). Their mean insulin dose before specialist consultation was 57.1 ± 15.7 U/day (0.8 ± 0.2 U/kg body weight), which was subsequently increased significantly to 63.3 ± 16.5 U/day or 0.9 ± 0.2 U/kg ($P < 0.05$).

Patients with type 2 diabetes treated with insulin only received a mean dose of 59.9 ± 18.4 U/day, and those treated with plasma glucose-lowering tablets and insulin received a mean dose of 56.8 ± 21.2 U/day, ($P > 0.05$). However, patients with type 2 diabetes being treated with insulin alone received a mean dose of 0.7 ± 0.2 U/kg, and those treated with both blood glucose-lowering tablets and insulin received 0.6 ± 0.2 U/kg ($P < 0.001$); at the endocrinology clinic visit, their mean HbA_{1c} levels were 9.0% ± 1.3% (median 8.7%) and 8.7% ± 1.3% (median 8.4%), respectively ($P > 0.05$). In 245 patients with type 2 diabetes treated with insulin alone, mean HbA_{1c} was 8.9% ± 1.3%, so endocrinologists recommended an increase in the insulin dosage from a mean of 59.7 ± 17.9 U/day to 68.2 ± 17.8 U/day ($P < 0.0001$). In 10 patients with type 2 diabetes and a mean HbA_{1c} of 9.2% ± 1.4% whilst on a mean insulin dosage of 73.4 ± 17.1 U/day, blood glucose-lowering tablets were added rather than increasing the insulin dosage further. Further, for 18 patients with type 2 diabetes who were treated with both blood glucose-lowering tablets and insulin but had a mean HbA_{1c} of 9.4% ± 1.5%, endocrinologists recommended an increase in the insulin dosage from a mean of 43.6 ± 21.4 U/day to 57.0 ± 16.7 U/day ($P < 0.05$) without addition of blood glucose-lowering tablets. For the 85 patients with type 2 diabetes and a mean HbA_{1c} of 8.5% ± 1.2%, the amount of insulin injected was increased from a mean

Table 2 Distribution of patients with type 2 diabetes according to sex and blood glucose-lowering treatment received

Sex	Treatment								Total	
	Diet		Oral tablets		Insulin		Combination therapy			
	n	%	n	%	n	%	n	%	n	%
Male										
n	20	6.9*	153	53.1	87	30.2	28	9.7*	288	100
%	54.1		40.8*		34.1*		27.2*		37.4*	
Female										
n	17	3.5*	222	46.1	168	34.9	75	15.6*	482	100
%	45.9		59.2*		65.9*		72.8*		62.6*	
Total										
n	37	4.8	375	48.7	255	33.1	103	13.4	770	100
%	100		100		100		100		100	

Notes: *$P < 0.05$ comparing men versus women. Combination treatment consisted of insulin and oral blood glucose-lowering tablets.

Table 3 Mean HbA_{1c} levels in patients with type 2 diabetes according to sex and blood glucose-lowering treatment

Sex	Treatment			
	Diet	Oral tablets	Insulin	Combination therapy
Male	8.4% ± 1.4%	8.7% ± 1.4%*	8.9% ± 1.4%	8.8% ± 1.5%
Female	8.4% ± 1.5%	8.4% ± 1.2%*	9.0% ± 1.3%	8.6% ± 1.2%
Total	8.4% ± 1.4%	8.5% ± 1.3%	9.0% ± 1.3%	8.7% ± 1.3%

Notes: *$P < 0.05$ comparing men versus women. Values are shown as the mean ± standard deviation. Combination treatment consisted of insulin and blood glucose-lowering tablets.
Abbreviation: HbA_{1c}, glycosylated hemoglobin.

of 59.6 ± 19.8 U/day to 69.3 ± 19.7 U/day ($P < 0.001$), without addition of blood glucose-lowering tablets. For 4.7% of patients with type 2 diabetes, the endocrinologists recommended changing the type of blood glucose-lowering tablets being taken. The units of insulin per kilogram of body weight recommended for the patients with type 2 diabetes using different insulin regimens and those actually injected are summarized in Figure 2.

Linear regression was used to investigate the relationship between body mass index in patients with type 1 or 2 diabetes and amount of insulin injected. The amount of insulin injected before consultation with an endocrinologist and that recommended during the specialist consultation was correlated significantly with body mass index (Figures 3 and 4). However, linear regression also showed a tendency for the units of insulin per kilogram received before the endocrinology consultation and those recommended during the consultation to be correlated with body mass index for type 1 and type 2 diabetes (Figures 5 and 6). Analysis of the data for waist-to-hip circumference ratio, body weight, and height produced similar results for both types of diabetes.

Discussion

In 2011, the Lithuanian National Health Insurance Fund spent 24,878,359 Euros on the treatment of diabetes, representing about 13% of the annual state budget assigned for medications and associated health care.[13] According to the International Diabetes Federation, the worldwide expenditure on diabetes care was 11.8% of the total global health care budget, with expenditure ranging from 5% to 13% of national health care budgets in individual countries.[14]

Medications are used to prolong survival and improve quality of life in patients with diabetes. Access to high-quality blood glucose-lowering drugs is adequate in Lithuania; however, the success of treatment depends not only on the actual availability of medicines, but also on the ability of patients to comply with treatment and on appropriate selection of medication by physicians. Only with adequate control of diabetes and properly chosen medication can patients be protected from the complications of diabetes and progression of the disease.[15,16] Long-term maintenance of HbA_{1c} levels <7% reduces the risk of complications from diabetes and progression to cardiovascular disease.[17,18]

Treatment of diabetes, especially with insulin, is very individualized and should be determined by a physician with appropriate training and extensive clinical experience. A study of 2023 patients with type 2 diabetes in seven European countries demonstrated that, in spite of five years of good blood glucose control, only 20% of those treated with combinations of blood glucose-lowering agents and 29.6% of those treated with insulin had HbA_{1c} levels <7%.[19] Further, a study evaluating diabetes control in eight Central and Eastern European countries showed that control of diabetes in Lithuania was satisfactory in only 17.1% of patients with type 1 diabetes and in 34.5% of those with type 2 diabetes.[20] Further, there was no significant difference between numbers of patients with type 1 or 2 diabetes and mean HbA_{1c} <7% in Lithuania and those in other Central and Eastern European countries.[20] These data suggest that many Lithuanians with type 1 or 2 diabetes have inadequate blood glucose control. The importance of control in both types of diabetes is stressed in publications by a number of other authors.[21,22]

Permanent hyperglycemia, oxidative stress, and activation of the c-Jun NH2-terminal kinase pathway affects cells negatively, accelerating the aging process.[23] Glucose toxicity causes mitochondrial dysfunction and increases the resistance of cells to insulin.[24] When blood glucose is normalized, the negative effects of oxidative stress are reduced more rapidly in patients with type 1 diabetes than in those with type 2 diabetes.[25,26]

The success of treatment in patients with type 1 diabetes depends on the relationship between diet, physical activity, and the amount of insulin administered. In the event of overeating, insulin requirements are higher,

Table 4 Mean duration of disease in patients with type 2 diabetes according to sex and blood glucose-lowering treatment

Sex	Diet[a]	Oral tablets[b]	Insulin[c]	Combination therapy[d]	*P*
Men	3.7 ± 3.3	7.0 ± 5.9	9.9 ± 6.3*	8.7 ± 5.2*	<0.05;[a–d] <0.05[b,c]
Women	4.0 ± 3.7	8.2 ± 7.2	13.5 ± 8.4*	11.7 ± 6.7*	<0.05;[a–d] <0.05[b–d]
Total	3.8 ± 3.4	7.7 ± 6.7	12.3 ± 7.9	10.9 ± 6.5	<0.05;[a–d] <0.05[b–d]

Notes: *$P < 0.05$ comparing men versus women. Values are shown as the mean ± standard deviation.[a–d] *P* value comparing treatment groups.

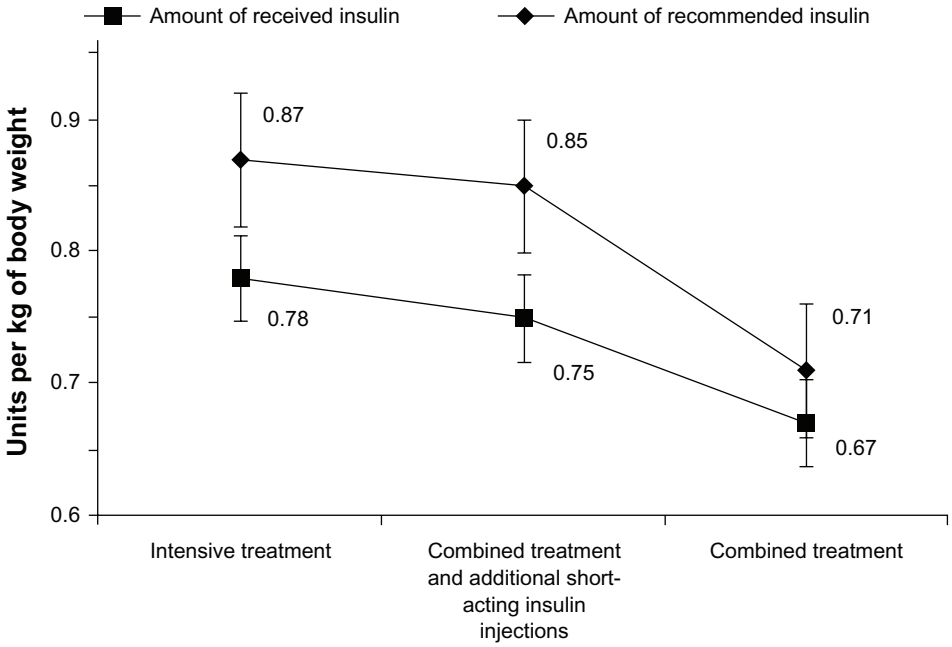

Figure 1 Amounts of insulin per kilogram of body weight prescribed for patients with type 1 diabetes before and after an endocrinology consultation. Intensive treatment comprised long-acting insulin injections and three short-acting or rapid insulin injections; combined treatment comprised mixed combinations of long-acting and short-acting insulin in one ampoule.

and greater amounts of insulin promote further binge-ing. Even a small, yet long-term and, therefore, already ordinary, excess amount of insulin in patients with type 1 diabetes can result in obesity, metabolic syndrome, and other metabolic disturbances typical as in patients with type 2 diabetes.[27] In these cases, dyslipidemia occurs as a result of decreased high-density lipoprotein cholesterol and increased low-density lipoprotein cholesterol, and can promote resistance to insulin in tissues and acceleration of atherosclerosis.[27]

In spite of all the modern medications available, treatment of diabetes remains a controversial and unresolved problem. Successful treatment of type 2 diabetes depends on timely diagnosis of the disease, appropriate choice of medication, a healthy lifestyle, and a health care strategy encompassing all these factors.[28,29] Insulin requirements can be lowered by

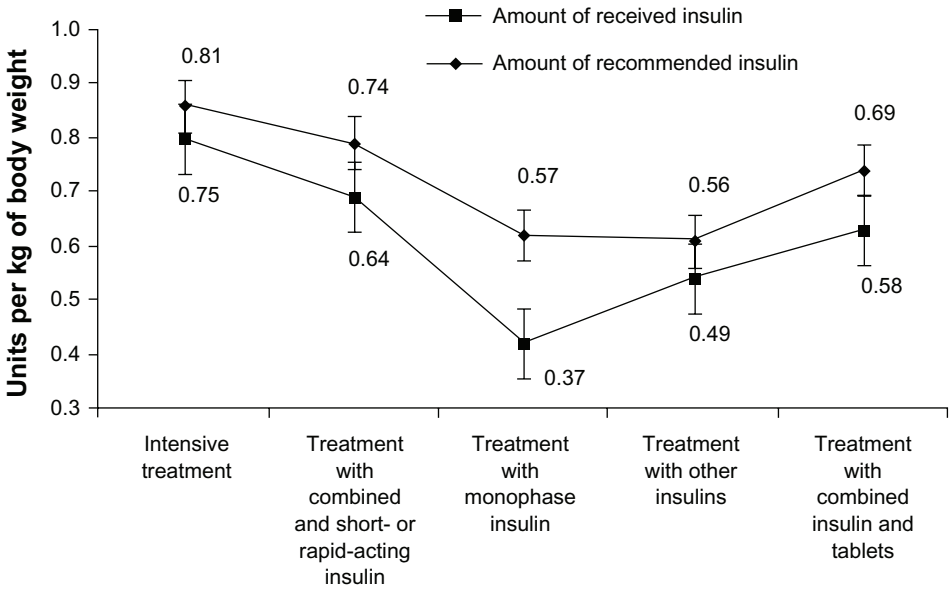

Figure 2 Amounts of insulin per kilogram of body weight prescribed for patients with type 2 diabetes before and after an endocrinology consultation.

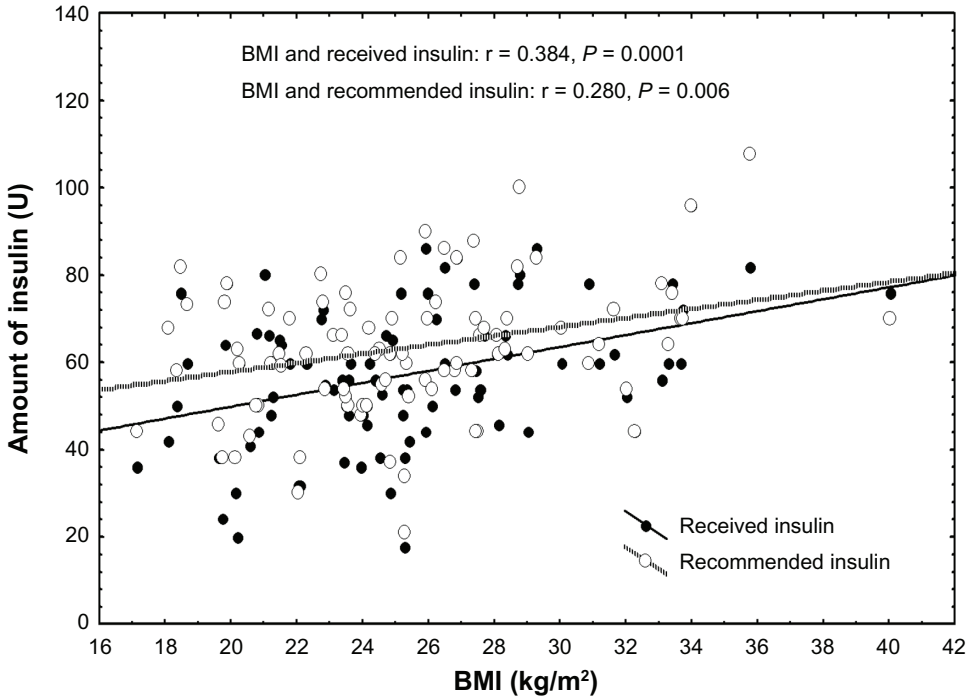

Figure 3 Correlation between received and recommended amounts of insulin and body mass index (BMI) in patients with type 1 diabetes.

reducing body weight and increasing physical activity, which improves glucose uptake at the cellular level.[30] In Lithuania, type 2 diabetes is often diagnosed when chronic complications of the disease are already present.[31] Treatment facilitating blood glucose control is reimbursed in Lithuania, but does not solve all the problems associated with management of type 2 diabetes. For example, thiazolidinedione drugs, which decrease resistance to insulin, are expensive and so are not a first-line treatment option for patients with type 2 diabetes; metformin, which has additional weight-regulating activity,

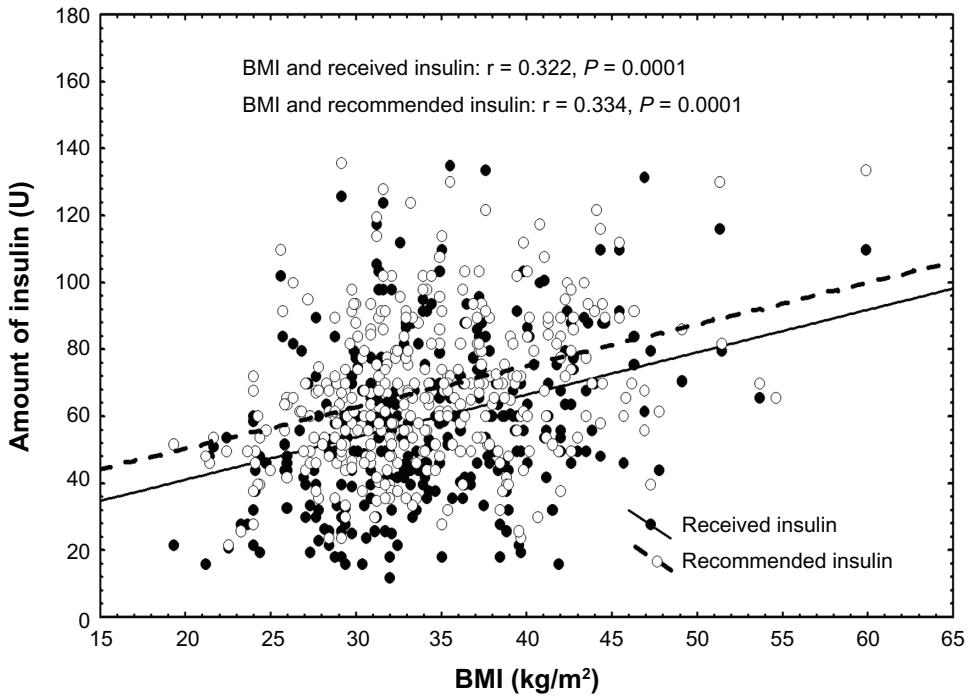

Figure 4 Correlation between received and recommended amounts of insulin and body mass index (BMI) in patients with type 2 diabetes.

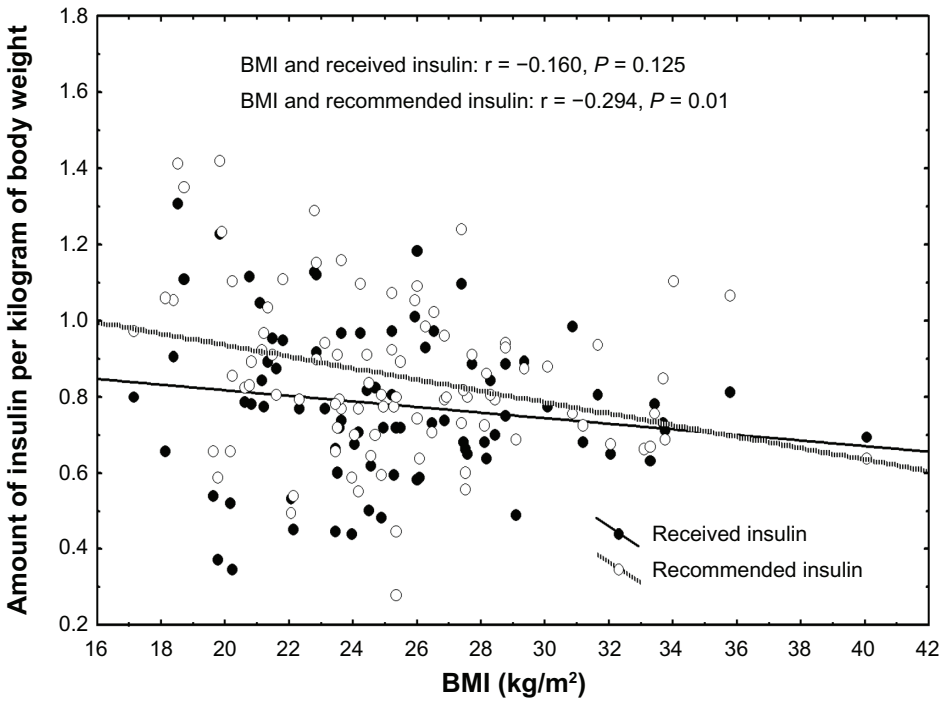

Figure 5 Correlation between the received and recommended amounts of insulin per kilogram of body weight and body mass index (BMI) in patients with type 1 diabetes.

could be prescribed earlier, ie, for all obese patients with type 2 diabetes. Unfortunately, the structure of the health insurance system in Lithuania is such that use of thiazolidinediones as first-line therapy is not reimbursed.

General practitioners seldom refer patients with $HbA_{1c} \geq 7\%$ to an endocrinologist. Our data show that, in many cases, endocrinologists recommended changes to treatment in these patients. However, medication was only changed when HbA_{1c} values reflected inadequate control of diabetes after three months of unaltered treatment, during which blood glucose values recorded by self-testing or at medical centers showed persistent hyperglycemia. Analysis of changes

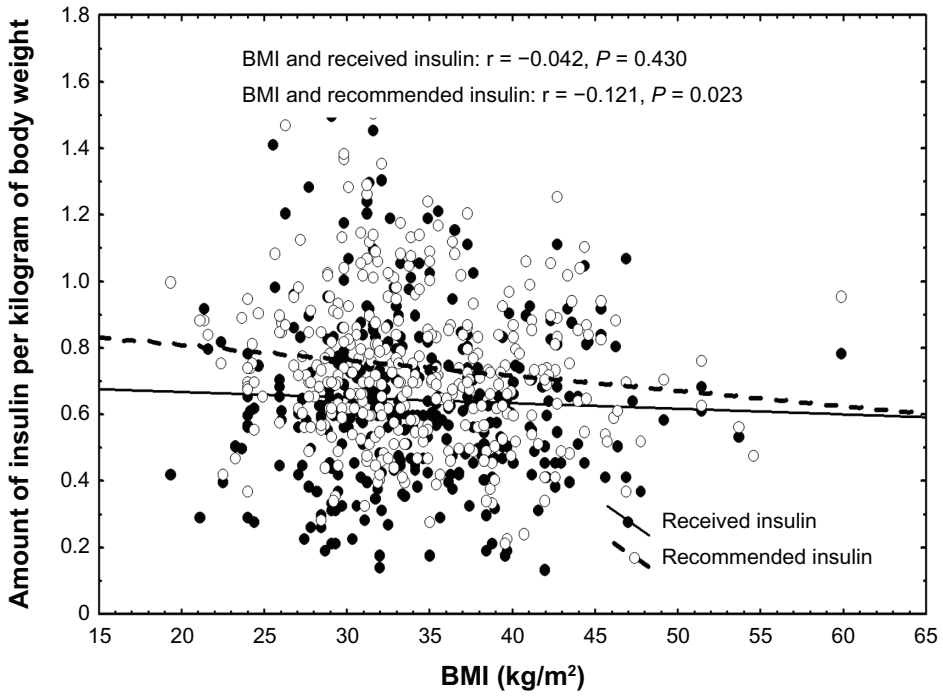

Figure 6 Correlation between the received and recommended amounts of insulin per kilogram of body weight and body mass index (BMI) of patients with type 2 diabetes.

made to the insulin dosage showed a general tendency for endocrinologists to increase the total amount of injected insulin. No significant association was found between the amount of insulin received or recommended and previously recorded HbA_{1c} levels. However, linear regression showed a tendency for the amounts of insulin, both received and recommended, to be positively and directly correlated with increasing body mass index or total body weight in both types of diabetes. There was also a tendency towards a decrease in the U/kg insulin dosage with increasing body mass index. However, with increasing body weight, there was a trend towards an increase in the U/kg insulin dosage, albeit not statistically significant, in patients with type 2 diabetes. These data raise the issue of whether the type of diabetes present is taken into consideration when prescribing insulin or whether insulin is considered only in terms of reducing hyperglycemia. Recognizing that less insulin is needed per kilogram of increasing weight in patients with type 1 diabetes, it is essential to satisfy the real insulin needs. Excess insulin increases body weight in patients with type 1 diabetes by increasing body fat.[7,27] Therefore, it is better to calculate insulin needs based on a normal rather than excessive body weight, although decreased physical activity, smoking, and use of antihypertensive medication, all of which influence insulin sensitivity, are associated with increased insulin requirements.[32] Recommendations have been published for the average insulin requirements in patients with type 1 diabetes according to body mass index and waist circumference, ie, 2.3 U of insulin per kg/m^2 and 0.8 U per cm of waist size.[32]

Multiple physiologic deficiencies, including resistance to insulin, insufficient insulin production due to progressive dysfunction of beta cells, excess hepatic production of glucose as a result of impaired insulin secretion, and increased secretion of glucagon by pancreatic alpha cells,[33] can contribute to failure of treatment using diet, metformin, sulfonylureas, and insulin.[34] In patients with type 2 diabetes, it is difficult to balance the amount of insulin needed for assimilation of glucose by muscles and peripheral tissues and that needed to inhibit glucagon secretion and glucose production in the liver. Insulin requirements in patients with type 2 diabetes can range from 0.7–0.8 U/kg up to ≥1.5 U/kg.[32] Consequently, preference has to be given either to reduction of insulin resistance in tissues and improved glucose assimilation in tissues or to maintenance of normal blood glucose levels and slowing down of glucose toxicity. These aims can be achieved by motivating patients to lose weight and increase their physical activity. This is especially important for patients with type 2 diabetes treated with diet, metformin, sulfonylureas, thiazolidinediones, and incretins. If type 2 diabetics are not motivated and opt to rely on medication to control their disease, they will make no effort to eliminate the risk factors causing their diabetes. When daily insulin injections become necessary, it is generally agreed that the etiologic phase of treatment has ended and there is only one aim left, ie, blood glucose control. It has been suggested that a gradual increase in the amount of insulin needed is inevitable to ensure good blood glucose control in the long term.[35]

It is important for patients with type 2 diabetes to understand the rationale behind and benefits of the treatment prescribed, because disappointment with treatment negatively affects the whole chain of events in diabetes control, with patients becoming disinterested, limiting their physical activity, abandoning their dietary measures, and losing self-control. Gradually, their disappointment in medications perceived to be "unhelpful" grows, with patients increasingly believing that "nothing bad happens" if they forget to inject their insulin, such that the disconnect widens between the treatment recommended and that actually used. Such patients tend not to inform their doctors about the insulin "saved" and become resistant to new recommendations, already knowing that they will not implement them. By this time, a set of circumstances conducive to progression of diabetes mellitus and its complications has appeared. It is difficult to remotivate such patients because, by this stage, not only type 2 diabetes but also depression has to be addressed.[36]

In our study, 4.8% of patients with type 2 diabetes were treated using diet alone. It is generally agreed that first-line treatment for type 2 diabetes should be diet, weight control, and physical activity for as long as possible.[37] In Lithuania, a considerable number of patients with type 2 diabetes are successfully treated with diet alone and without pharmacologic intervention. However, the patients with type 2 diabetes in our study treated by diet alone had mean HbA_{1c} values ≥7%, indicating inadequate blood glucose control, and all were prescribed medication upon consultation with an endocrinologist.

Limitations

One of the limitations of our study is the lack of data on patients with type 1 or type 2 diabetes who had an HbA_{1c} level ≤7%. These patients were not included, and their control was not compared with that in patients with HbA_{1c} ≥7%. Due to the great variety of oral medications in use, we did not analyze the effects of different types or doses of blood glucose-lowering medications. Another limitation is that

all the study data were collected by endocrinologists participating voluntarily in the study. Also, we were not able to evaluate the relationship between blood glucose control and the degree of patient education because of inadequate data available to assess the extent of previous patient training. Our study did not use data of patients with diabetes who did not see an endocrinologist.

Conclusion

In this study, mean HbA_{1c} was 8.5% ± 1.3% in patients with type 2 diabetes treated only with oral drugs and 9.0% ± 1.3% in those treated with insulin alone. Prescribing effective blood glucose-lowering drugs does not necessarily translate into good metabolic control in patients with diabetes.

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Disclosure

The authors report no conflicts of interest in this work.

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