Time Elapsed for Switching from Oral Antidiabetic Therapy to Insulin Therapy in Type 2 Diabetic Patients and Evaluation of the Factors Affecting This Period

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A B S T R A C T

Background We aimed to determine the time elapsed for switching from oral antidiabetic therapy to insulin therapy in patients with type 2 diabetes mellitus and the factors that affect this period.

Material and Methods Three hundred fifteen patients with type 2 diabetes mellitus who were followed up in the diabetes outpatient clinic were included in the study. The gender, education level, age of onset of diabetes, presence of hypertension, smoking and body mass index of the patients were examined, and the effects of these variables on time elapsed for switching to insulin therapy were analyzed in three phases.

Results Three hundred fifteen patients (117 males, 198 females) were enrolled in the study. The mean time elapsed for switching from oral antidiabetic therapy to insulin therapy was 9.93±6.67 years. The effects of education level, age at the onset of diabetes, presence of hypertension, and body mass index on time elapsed for switching to insulin therapy were found to be statistically significant ($p < 0.05$); whereas the effects of gender and smoking were not significant ($p > 0.05$). The time elapsed for switching to insulin therapy shortened as the education level, the age at the onset of diabetes, and body mass index level increased. It was found that hypertension in patients with type 2 diabetes mellitus prolongs the time elapsed for switching to insulin therapy.

Conclusion The body mass index level, presence of hypertension, education level and age at the onset of diabetes were the significant factors affecting the time elapsed for switching to insulin therapy.

Introduction

Type 2 diabetes mellitus (DM) has reached a pandemic worldwide, and the extent of the problem has been gradually increasing. The global diabetes prevalence in 2019 was 9.3% (463 million people). It is estimated to be rising to 10.2% (578 million) by 2030, and 10.9% (700 million) by 2045.[1] DM is characterized by chronic hyperglycemia developed due to the impairment in carbohydrate, lipid, and protein metabolism resulting from the impairment in insulin secretion or insulin effect or both.[2] Progressive loss of ß-cells is the typical characteristic of type 2 DM; at the time of clinical diagnosis, the patients have lost approximately half of the insulin secretion capacity of ß-cells.[3,4]

The initial treatment for type 2 DM generally does not include insulin therapy. Diet, exercise, weight loss, and oral antidiabetic agents are adequate initial treatments for achieving glycemic control. Insulin is indicated for patients who cannot gain glycemic control despite oral antidiabetic drugs, diet and exercise.[5] Insulin therapy is a well-known and most commonly used treatment in which physicians have high clinical experience. Insulin is also the most effective treatment option to reduce glycemia. Any level of elevated haemoglobin A1c (HbA1c, glycosylated haemoglobin) to, or close to, the therapeutic goal may be decreased by using insulin.[6] Some of the goals of insulin therapy in patients with type 2 DM are to eliminate symptoms of hyperglycemia, prevent diabetic ketoacidosis, and reduce the incidence of infections.[1] Maintaining glycemic control reduces the risk of microvascular and macrovascular complications.[7] Insulin therapy also positively affects triacylglycerol and high-density lipoprotein cholesterol levels.[8] Insulin therapy is an effective treatment method in patients with type 2 DM, but there is an inconsistency between the guidelines and clinical practice about the time to start insulin therapy.[9]

The present study aimed to determine the time elapsed for switching from oral antidiabetic therapy to insulin therapy in patients with type 2 DM and the factors that affect this period.

Material and Methods

This study was conducted on patients with type 2 DM in the diabetes outpatient clinic. Despite the optimal combination and dose of oral antidiabetic drugs being determined, insulin therapy was started in accordance with current diabetes guidelines for patients whose blood sugar could not be regulated. Written informed consent was obtained from the patients included in the study, and the ethics committee approved the study.

Three hundred and fifteen patients (117 men and 198 women) were included in the study. Patients with pregnancy, malignancy, severe endocrine, nephrological, haematological, psychiatric and neurological diseases were excluded from the study. Gender, age, education level, medical history, age of onset of diabetes, presence of hypertension, smoking status and body mass index (BMI) in the patients were recorded. The time to transition from oral antidiabetic therapy to insulin therapy (in addition to or in place of oral treatment) was calculated for each patient.

Statistical Analysis

Statistical analyzes were made with the obtained data. The effects of the recorded variables on the time elapsed for switching to insulin therapy were analyzed in three phases. Since one of the primary goals of the present study was to identify the factors affecting the time elapsed for switching to insulin therapy, correlation analysis was performed in the first phase of the analysis. In the second phase, associations were analyzed using a regression model including these factors. The third phase examined whether there was a statistically significant difference between the determined groups in terms of variables. IBM Corporation SPSS (Statistical Package for Social Sciences), version 23.0, New York, US was used for statistical analyses. Jarque-Bera normality test was performed for the data to identify which method would be used for the analyses; a p-value <0.05 indicated that the data were not normally distributed. Therefore, non-parametric tests (which do not require normal distribution) were used. Mann-Whitney U test, a non-parametric test, was also used to analyze the differences between the groups. Kendall's tau-b correlation coefficient, one of the non-parametric measures

of association, was used to determine the correlation of the dependent variable (the time elapsed for switching to insulin therapy) with the independent variables (gender, education level, age at the onset of diabetes, hypertension status, smoking status, and BMI), and to evaluate the effects of these independent variables on the dependent variable, which were the main goals of the study. A significant but weak correlation was found in terms of defined variables. Therefore, associations needed to be tested via a regression model. Independent variables were analyzed by the method of Least Squares.

Results

A total of 315 patients with type 2 DM were evaluated in the present study. 117 (37.1%) of the patients were male, and 198 (62.9%) were female. The mean age of the patients was 60.29±9.04 years. Regarding the education level, 110 patients (34.9%) were illiterate, 40 patients (12.7%) were literate, 151 patients (47.9%) were primary school graduates, and 14 patients (4.5%) were high school or university graduates. Two hundred forty-seven patients (78.4%) were non-smokers, and 68 patients (21.6%) were smokers. Two hundred thirty-six patients (74.9%) had hypertension with type 2 DM, and 79 patients (25.1%) did not have hypertension. The mean age at the onset of diabetes was 46.58±10.54 years. The mean BMI value was 29.14±4.60 kg/m^2. The mean time elapsed for switching from oral antidiabetic therapy to insulin therapy was 9.93±6.67 years (*Table 1*).

Education level, age of onset of diabetes, BMI and presence of hypertension significantly affected the time elapsed to switch to insulin therapy ($p<0.05$), while gender and smoking status did not (*Table 2*). We found that as the education level, age of onset of diabetes and BMI level increased, the time elapsed for switching to insulin therapy shortened. However, we found that the presence of hypertension in patients with type 2 DM prolonged the time elapsed for switching to insulin therapy. The standardized (beta) coefficients, which indicate the degree of effect size, for the individual variables, were as follows: 4.606 for BMI, 4.415 for the presence of hypertension, 1.647 for education level, and 0.230 for age at the onset of diabetes. The model we used was statistically significant and the results obtained were reliable ($p<0.05$) (*Table 3*). The independent variables affected the time elapsed for switching to insulin therapy by 89% (*Table 4*).

Discussion

Type 2 DM is a progressive disease in which pancreatic ß cell functions are constantly decreased. As a result, most patients need insulin therapy. There is evidence that early glycemic control reduces long-term vascular complications and may increase pancreatic ß-cell lifespan. The importance of glycemic control in reducing the risk of vascular complications of diabetes is well known.[10,11] Long-term hyperglycemia leads to glucotoxicity and oxidative stress, which may cause microvascular and macrovascular complications.[12,13] Therefore, the primary goal in treating type 2 DM is to achieve glycemic control. Evidence suggests that good glycemic control prevents the occurrence of macrovascular events

Table 1. General characteristics of the study group.

Characteristics	Study group (n: 315)
Gender	
Male	117 (37.1%)
Female	198 (62.9%)
Age ranges (years)	
35-49	77 (24.4%)
50-59	171 (54.3%)
≥60	67 (21.3%)
Mean age (years)	60.29±9.04
BMI ranges (kg/m^2)	
<25	43 (13.6%)
25.0-29.9	151 (47.9%)
≥30	121 (38.5%)
Mean body mass index (kg/m^2)	29.14±4.60
Smoking	
Smoker	68 (21.6%)
Non-smoker	247 (78.4%)
Hypertension	
Present	236 (74.9%)
No	79 (25.1%)
Education level	
Illiterate	110 (34.9%)
Literate	40 (12.7%)
Primary school	151 (47.9%)
High school-University	14 (4.5%)
Age at the onset of diabetes mellitus (years)	46.85±10.54
Time elapsed for switching to insulin therapy (years)	9.93±6.67

Data were given as mean±SD (standard deviation) or n (%).

Table 2. The regression analysis.

Model	Coefficients[1]		t	Significance
	Unstandardized coefficients			
	B	Standard error		
(Constant)	24.485	4.823	5.077	0.000
Gender	−1.079	1.378	−0.783	0.435
Education	−1.647	0.593	−2.775	0.006
Age at the onset of DM	−0.231	0.056	−4.098	0.000
Hypertension	4.415	1.256	3.517	0.001
Smoking	2.071	1.365	1.517	0.132
Body mass index	−4.606	1.255	−3.673	0.000

[1]Dependent variable, the time elapsed for switching to insulin therapy, DM: diabetes mellitus.

Table 3. The results obtained from analysis of variance.

Model	ANOVA[b]				
	Sum of squares	df	Mean square	F	Significance
Regression	1128.733	6	188.122	5.450	0.000[a]
Residual	4590.838	133	34.518	-	-
Total	5719.571	139	-	-	-

ANOVA, analysis of variance, [a]Predictors: (Constant), body mass index, hypertension, smoking, age at the onset of diabetes, education, gender; [b]Dependent variable: the time elapsed for switching to insulin therapy.

Table 4. Model summary.

Model	Model Summary[b]			
	R	R square	Adjusted R square	Durbin-Watson
1	0.844[a]	0.897	0.861	1.763

[a]Predictors: (Constant), body mass index; hypertension, smoking, age at the onset of diabetes, education, gender, [b]Dependent variable: the time elapsed for switching to insulin therapy.

in diabetic patients.[10,11] In the UK Prospective Diabetes Study (UKPDS), it has been reported that good glycemic control with sulphonylurea or insulin reduces the risk of microvascular disease in patients diagnosed with new type 2 DM compared to conventional therapy.[14]

The initiation of insulin therapy at the appropriate time helps improve glycemic control and protect pancreatic ß cells from functional impairment caused by hyperglycemia.[15] Some studies have found that early insulin therapy can change the progression of diabetes.[16,17] Using insulin in combination with oral diabetic drugs at the appropriate time can prevent the progression of diabetes.[17] Despite the positive effects of insulin therapy in patients with type 2 DM, guidelines and clinical practice are not compatible with the timing of insulin therapy initiation.[9] In general, the mean time elapsed for switching to insulin therapy has been reported to be 8 to 9 years in the literature; however, the number of studies reporting a definite number is limited. In one arm of the UKPDS study, it was found that 53% of patients receiving sulfonylureas required insulin therapy within six years.[18] In our research, the mean time elapsed for switching from oral antidiabetic therapy to insulin therapy was 9.93±6.67 years.

The initiation of insulin therapy leads to many therapeutic barriers for physicians and patients. Insulin is still considered a "last resort" or an "end-stage" therapy. Fear of injections, hypoglycemia and weight gain anxiety are reasons for delayed insulin therapy.[19,20] We considered that there might be different factors that could affect switching to insulin therapy other than these factors, which are of psychological origin in general, and thereby investigated the documentable characteristics of the patients, including gender, education level, age at the onset of diabetes, hypertension status, smoking, and BMI. In contrast to our general expectation, gender and smoking were not significantly effective in the time elapsed for switching to insulin therapy, which may be attributed to the country's characteristics and tendency towards complication. However, education level, age at the onset of diabetes, BMI and presence of hypertension were significantly effective in the time elapsed for switching to insulin therapy (p<0.05). Patients with higher levels of education more easily adapt the insulin therapy. The patients diagnosed with diabetes at an advanced age require insulin therapy earlier, likely because of early complications. BMI was determined as the most influential factor in the present study; insulin requirement appears earlier in obese patients. We found that the presence of hypertension in patients with type 2 DM prolonged the time elapsed for switching to insulin therapy. We cannot provide a complete explanation for this observation. However, patients with hypertension as comorbidity may have better compliance with diet and treatment and a higher awareness of the disease.

Various insulin analogues are now available that can reduce the risk of hypoglycemia and cause less weight gain, thus reducing the anxiety associated with insulin therapy. Early initiation of insulin therapy can be made attractive by clinical data demonstrating the benefits of insulin therapy and the use of insulin analogues with proven safety. Additionally, educating patients on insulin therapy, blood sugar monitoring, diet and lifestyle changes can reduce anxiety about insulin and provide more successful treatment.

Conclusions

The BMI level, presence of hypertension, education level and age at the onset of diabetes were the significant factors affecting the time elapsed for switching to insulin therapy. As the education level, diabetes onset age or BMI level increases, the time elapsed for switching to insulin therapy may shorten. Hypertension accompanying type 2 diabetes mellitus may increase the time elapsed for switching to insulin therapy.

Authors' Contribution

Study Conception, Literature Review, Critical Review, Data Collection and/or Processing, Statistical Analysis and/or Data Interpretation, Manuscript preparing held by all authors.

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