Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Predictors of switching to insulin from non-insulin therapy in patients with type 2 diabetes mellitus

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ARTICLE INFO

Article history:
Received 26 July 2010
Received in revised form
21 September 2010
Accepted 27 September 2010
Published on line 3 November 2010

Keywords:
Diabetes mellitus
Insulin-treated
Predictors
Risk factors
Switch to insulin

ABSTRACT

Aims: To estimate the switching rate and to identify factors that predict switch from non-insulin to insulin therapy in patients with type 2 diabetes using routinely collected data from a clinical information system at Isfahan Endocrine and Metabolism Research Centre, Iran.
Methods: During the mean (SD) follow-up period of 9.3 (3.4) years, 6896 non-insulin-treated patients with type 2 diabetes at baseline have been examined to determine predictors of switches to insulin therapy. Their treatment at the last clinic visit was compared with the initial visit treatment. The mean (SD) age of participants was 51.2 (10.3) years with a mean (SD) duration of diabetes of 5.8 (5.9) years at initial registration.
Results: The switch to insulin from non-insulin therapy was 2.5 (95% confidence interval 2.4, 2.6) (2.2 men and 2.7 women) per 100 patient-years based on 64,540 patient-years of follow-up. Using a Cox's proportional hazards model, younger age at diagnosis, female gender, higher BMI and HbA_{1c} were significant predictors of switch to insulin treatment.
Conclusions: These are the first estimate of switch to insulin from non-insulin therapy in Iran. Younger age at diagnosis, female gender, higher BMI and HbA_{1c} at registration were identified as predictors of switching to insulin.

1. Introduction

The goal of management of type 2 diabetes is to maintain blood glucose levels in the near-normal range. This is important to prevent sustained hyperglycemia with elevated glycated haemoglobin (HbA_{1c}), which is associated with long-term micro- and macrovascular complications and to avoid recurrent episodes of hypoglycemia. The management of type 2 diabetes starts with education, dietary modifications to increase dietary fiber and reduce total and saturated fat intake, physical activity and the attempt to reduce body weight in obese patients [1,2]. When these measures fail to control the elevated blood glucose, oral antidiabetic drugs (OADs) are usually used. In general, OADs are first prescribed as monotherapy; however, combination therapy with 2 OADs with different mechanisms may also be an option [2,3]. If oral medications are still insufficient, treatment with insulin is considered [3,4]. Insulin therapy is generally considered to be the last treatment option, when OADs fail to provide stable glycemic control [2,3]. Of the many possible start-up regimens, basal insulin – once or twice daily – in combination with OADs is often chosen as the first-line insulin therapy because of its simplicity [3,5,6]. The increasing number of patients with type 2 diabetes and recent insights regarding the importance of strict glycemic control are expected to result in a larger number of patients with type 2 diabetes receiving insulin treatment [7].

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0168-8227/$ – see front matter
doi:10.1016/j.diabres.2010.09.033

Information on the predictors of switch to insulin therapy from non-insulin is important for proper patient selection and positively impact the quality of life of the people with type 2 diabetes. Disease severity, a younger age at diagnosis [8,9] and poor adherence to treatment may also lead to poor metabolic control in patients with type 2 diabetes [10].

The objective of this study therefore was to estimate the rate of switch to insulin from non-insulin therapy and to conduct a preliminary investigation of the determinants of switch to insulin treatment in patients with type 2 diabetes using routinely collected data from a clinical information system at Isfahan Endocrine and Metabolism Research Centre, Iran.

2. Patients and methods

2.1. Participants and data collection

The recruitment methods and examination procedures of the Isfahan Endocrine and Metabolism Research Centre out patient clinics have been described before [11,12]. In summary, clinical data are collected for all consecutive patients at the first attendance and at review consultations (usually annually) using standard encounter forms. These include an examination of ocular fundus, lens, limbs, blood pressure, and construction of a problem list by the clinician, measurement of height, weight, fasting plasma glucose (FPG), HbA_{1c}, triglyceride, cholesterol, and serum creatinine, and reporting of smoking as part of a completed questionnaire on demography, family history, and smoking by the patient. A registry clerk enters data from these forms onto the computer after the clinic.

Generally, newly diagnosed patients were referred for lifestyle and weight management program by qualified nutritionists to evaluate the patient and if necessary recommend weight management program. All newly diagnosed patients attend classes and weight-related health education classes are available free.

2.2. Participants

Using routinely collected data from a clinical information system at Isfahan Endocrine and Metabolism Research Centre, Iran, we performed a retrospective longitudinal, observational study. The study population consisted of all prevalent cases of type 2 diabetes and all patients diagnosed during the study period. Between 1992 and 2008, a total of 13,411 patients with type 1 and type 2 diabetes were registered in the system. However, this study uses data only for 6896 (2656 (38.5%) men and 4240 (61.5%) women) patients with type 2 diabetes who had at least one subsequent review since registration and who were not insulin-treated at baseline and aged 30 years and over. The physician defined the type of diabetes according to the American Diabetes Association criteria [13]. Patients may have received no prior pharmaceutical therapy, or may have received OADs (one, two or more than two).

The study conformed to the Declaration of Helsinki. Institutional ethical committee approval was granted, and an informed consent was signed by each patient.

2.3. Procedures

Predictors of switching to insulin therapy were assessed using the following data from the patient's registration consultation: gender, age at diagnosis, age, educational level, duration of diabetes (the time between diagnosis and the baseline examination), body mass index (BMI) (weight/height^2 [kg/m^2]), smoking status (never, current), HbA_{1c} (measured by spectrophotometer; as an indicator of diabetic control), FPG, serum creatinine, triglyceride, cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) (calculated by the Friedewald equation [14]) at registration. Diabetes treatment (insulin, oral agent, and diet alone) at the last clinic visit was compared with the initial visit treatment.

Height and weight were measured with subjects in light clothes and without shoes using standard apparatus. Weight was measured to the nearest 0.1 kg on a calibrated beam scale. Height was measured to the nearest 0.5 cm. Height was assessed at baseline only. A physician measured the systolic and diastolic blood pressures of seated participants after subjects had been seated for 10 min by using a mercury sphygmomanometer and standard techniques.

2.4. Determination of rates of switch to insulin

The treating physician made decisions about insulin dose and injection frequency, and any concomitant medication, on an individual basis. Rates of switch to insulin were estimated as the number of cases of switch to insulin therapy per 100 patient-years of follow-up. As the relevant period was considered the date of completion of the baseline examination between 1992 and 2008 until the either (i) switch to insulin treatment, (ii) the date of the last completed follow-up, (iii) death, or (iv) end of follow-up on December 31, 2007, whichever came first. For ease of interpretability, we report the rates of switch to insulin in terms of percent per year.

2.5. Analysis

Statistical methods used included Student's *t*-test, chi-squared test, and Cox's proportional hazards model. We considered the following covariates in the multivariate-adjusted analyses: number of follow-up visits, duration of diabetes, age, gender, BMI, triglyceride, total cholesterol, FPG, HbA_{1c} and systolic blood pressure. Age-adjusted means were calculated and compared using general linear models. Analysis was performed using software SPSS version 18 for Windows© (SPSS Inc., Chicago, IL). All tests for statistical significance were two-tailed, and performed assuming a type I error probability of <0.05.

3. Results

3.1. Characteristics

Baseline characteristics of the 1686 (24.4%) participants treated with diet and 5210 (75.6%) with oral agent shown in Table 1. As expected, in both genders those treated with oral

Table 1 – Age, age-adjusted mean (SE) and proportion characteristics of patients with type 2 diabetes by treatment status at baseline and gender.

Baseline characteristic	Men			Women		
	Diet (n = 602)	Oral agent (n = 2054)	Difference (95% CI)	Diet (n = 1084)	Oral agent (n = 3156)	Difference (95% CI)
Age at registration (year)	51.9 (0.42)	53.7 (0.23)	−1.8 (−2.6, −0.8)**	47.9 (0.30)	50.7 (0.18)	−2.8 (−3.5, −2.1)***
Age at diagnosis (year)	47.1 (0.4)	46.9 (0.2)	0.2 (−0.8, 1.1)	44.0 (0.3)	44.6 (0.2)	−0.6 (−1.3, 0.08)
Height (cm)	167.5 (0.26)	167.4 (0.14)	0.1 (−0.4, 0.8)	154.1 (0.19)	154.0(0.11)	0.1 (0.0, 0.9)
Weight (kg)	74.6 (0.47)	74.1 (0.26)	0.5 (−0.3, 1.9)	69.5 (0.35)	67.6 (0.21)	1.9 (1.7, 3.3)*
Body mass index (kg/m^2)	26.6 (0.18)	26.4 (0.10)	0.2 (−0.5, 1.1)	29.2 (0.13)	28.5 (0.08)	0.7 (0.6, 1.2)*
Duration of diabetes (year)	4.8 (0.23)	6.3 (0.13)	−1.5 (−2.4, −1.2)*	4.4 (0.17)	6.2 (0.10)	−1.8 (−2.6, −1.8)*
Follow-up duration (year)	9.7 (0.14)	9.2 (0.08)	0.5 (0.2, 0.8)*	9.4 (0.11)	9.4 (0.06)	0.0 (−0.3, 0.1)
Number of follow-up visits	10.7 (0.56)	11.5 (0.30)	−0.8 (−1.9, 0.3)	14.5 (0.42)	15.6 (0.24)	−1.1 (−2.2, −0.2)*
Fasting glucose (mg/dl)	182.1 (2.95)	209.1 (1.60)	−27.0 (−33.8, −19.8)*	169.9 (2.20)	204.9 (1.28)	−35.0 (−39.4, −29.8)*
HbA_{1c} (%)	8.3 (0.15)	9.2 (0.07)	−0.9 (−1.2, −0.6)*	8.1 (0.10)	9.1 (0.06)	−1.0 (−1.2, −0.8)*
Cholesterol (mg/dl)	212.8 (2.13)	212.5 (1.15)	0.3 (−4.9, 4.1)	230.1 (1.58)	230.4 (0.92)	−0.3 (−5.1, 2.3)
HDL-cholesterol (mg/dl)	41.7 (1.08)	42.9 (0.59)	−1.2 (−3.6, 1.0)	46.7 (0.75)	46.3 (0.45)	0.4 (−1.4, 2.0)
LDL-cholesterol (mg/dl)	122.1 (3.14)	121.5 (1.71)	0.6 (−6.5, 6.3)	138.2 (2.19)	136.9 (1.29)	1.3 (−4.9, 5.5)
Triglyceride (mg/dl)	224.7 (6.63)	230.9 (3.59)	−6.2 (−20.1, 9.5)	221.3 (4.93)	240.7 (2.86)	−19.4 (−29.2, −7.0)*
Creatinine (μM/l)	1.0 (.04)	1.0 (0.02)	0.0 (−0.09, 0.09)	0.9 (0.03)	0.9 (0.02)	0.0 (−0.05, 0.05)
Systolic BP (mm Hg)	121.7 (0.73)	121.4 (0.40)	0.3 (−2.4, 1.0)	123.3 (0.55)	122.8 (0.32)	0.5 (−2.6, 0.02)
Diastolic BP (mm Hg)	75.9 (0.46)	74.6 (0.25)	1.3 (−0.02, 2.0)	76.2 (0.34)	75.4 (0.20)	0.8 (−0.7, 0.9)
Obesity (BMI≥30), no. (%)	100 (17.1)	313 (15.7)	1.4 (−2.0, 4.9)	469 (43.9)	1038 (34.0)	9.9 (6.5, 13.3)***
Smoking						
Never-smoker	385 (70.0)	1295 (71.9)	−1.9 (−6.3, 2.4)	938 (97.4)	2658 (96.8)	0.6 (−0.63, 1.8)
Current-smoker	165 (30)	505 (28.1)	1.9 (−2.4, 6.3)	25 (2.6)	87 (3.2)	−0.6 (−1.8, 0.63)
Education						
Primary or below	315 (54.3)	1247 (63.1)	−8.8 (−13.4, −4.2)***	857 (81.9)	2625 (88.5)	−6.6 (−9.2, −4.0)***
Secondary	138 (23.8)	382 (19.3)	4.5 (0.6, 8.3)***	138 (13.2)	266 (9.0)	4.2 (1.9, 6.5)***
Matriculation or above	127 (21.9)	347 (17.6)	4.3 (0.6, 8.3)***	52 (5.0)	76 (2.6)	2.4 (1.0, 3.8)***

Age-adjusted means were calculated using general linear models. Data are expressed as mean (SE) or number (%). The difference in the mean or percentage of the variables between diet and oral agent. CI = confidence interval.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

agent were older at baseline and had higher age-adjusted mean duration of diabetes, FPG and HbA_{1c} and had lower education than those treated with diet. There was a tendency towards slightly higher follow-up for those men treated with diet than for oral agent treated group. A higher proportions of women treated with diet were obese and had higher BMI but lower triglyceride. The mean (SD) age was 51.8 (10.0) years for those treated with oral agent, and 49.3 (10.7) years for those treated with diet.

Sulphonylurea derivatives were the most commonly used first-line treatment (51.5%), followed by metformin (36.5%) and combination treatment (12.0%) for those treated with oral agent.

3.2. *Switching to insulin therapy*

The rates of switch to insulin from diet and oral agent are presented in Table 2. During 64,540 (24,842 men and 39,698 women) patient-years of follow-up, 1599 (23.2%) (543 men and 1056 women) cases switched their therapy to insulin. The overall rate of switch to insulin was 2.5% (95% CI: 2.4, 2.6) per year. Rates of switch to insulin treatment were higher in women (2.7%, 95% CI: 2.5, 2.8 per year) than men (2.2%, 95% CI: 2.0, 2.4) ($P < 0.05$). Of the 1686 participant treated with diet at baseline 267 (15.8%) subsequently switched to insulin. Of the 5210 participants who treated with oral agent at initial registration, 1332 (25.6%) subsequently treated with insulin, giving a switch of 2.7% (95% CI: 2.5, 2.8) per year. This was higher than the rates of switch seen for diet-treated, 1.7% per year (95% CI: 1.5, 1.9) ($P < 0.001$).

On the other hand, of the 1686 participant treated with diet at baseline 946 (56.1%) switched to oral agent at a rate of 5.9% (95% CI: 5.6, 6.3) per year. Of the 5210 participants who treated with oral agent at initial registration, 391 (7.5%) improved to diet regimen, giving an improvement rate of 0.8% (95% CI: 0.7, 0.9) per year.

3.3. *Predictors of switching to insulin*

The age-adjusted mean differences between men and women who did and did not switch to insulin during mean 9.3 years follow-up period are shown in Table 3. Both men and women who switched to insulin treatment were younger at diagnosis of diabetes and had higher age-adjusted mean of duration of diabetes, follow-up period, number of follow-up visits and HbA_{1c}. Those men but not women, switched to insulin showed slightly lower BMI and obesity. Those women but not men, switched to insulin were younger and had higher FPG level at baseline.

The independent predictors associated with switch to insulin from diet or oral agent regimen was also analysed with multivariate model. A stepwise Cox's proportional hazard

Table 2 – Switch rates to insulin treatment from baseline to mean 9.3-year follow-up period.

Treatment status at baseline	Treatment status at follow-up					
	Men			Women		
	Outcome	Patient-year	Rate/100 patient year (95% CI)	Outcome	Patient-year	Rate/100 patient year (95% CI)
Insulin						
Diet	85	5863	1.4 (1.1, 1.8)	182	10,086	1.8 (1.5, 2.1)
Oral agent	458	18,979	2.4 (2.2, 2.6)	874	29,612	2.9 (2.8, 3.1)
Oral agent						
Diet	350	5863	6.0 (5.4, 6.6)	596	10,086	5.9 (5.5, 6.4)
Oral agent	1418	18,979	7.5 (7.1, 7.9)	2067	29,612	7.0 (6.7, 7.3)
Diet						
Diet	167	5863	2.8 (2.4, 3.3)	306	10,086	3.0 (2.7, 3.4)
Oral agent	178	18,979	0.9 (0.8, 1.1)	213	29,612	0.7 (0.6, 0.8)

CI = confidence interval.

model was performed to test 10 predictor variables: number of follow-up visits, duration of diabetes, age at diagnosis, BMI, triglyceride, total cholesterol, FPG, HbA_{1c} and systolic blood pressure, all included as continuous variables, and gender. Younger age at diagnosis (HR 0.97, 95% CI 0.96, 0.97) and higher BMI (HR 1.02, 95% CI 1.01, 1.03), lesser follow-up visits (HR 0.97, 95% CI 0.96, 0.97) and higher HbA_{1c} (HR 1.08, 95% CI 1.1, 1.3) significantly increased the risk of switching to insulin. Women also significantly had higher risk of switching to insulin (HR 1.2, 95% CI 1.1, 1.3) (Table 4).

Between baseline and the end of follow-up, the cholesterol and triglyceride increased more and the weight, BMI and systolic blood pressure decreased more among men and women switched to insulin treatment than those remained on

Table 3 – Age, age-adjusted means (SE) and proportions of selected baseline characteristics between 2545 patients with type 2 diabetes who did and 4351 who did not switch to insulin during mean 9.3 years follow-up period.

Characteristic	Men			Women		
	Not switched (n = 1764)	Switched (n = 892)	Difference (95% CI)	Not switched (n = 2587)	Switched (n = 1653)	Difference (95% CI)
Age at registration (year)	53.5 (0.2)	52.7 (0.3)	0.8 (−0.03, 1.6)	50.7 (0.2)	48.9 (0.2)	1.8 (1.2, 2.4)***
Age at diagnosis (year)	47.5 (0.2)	45.8 (0.3)	1.7 (0.9, 2.5)***	45.3 (0.2)	43.1(0.3)	2.2 (1.6, 2.8)***
Weight (kg)	74.7 (0.3)	73.4 (0.4)	1.3 (0.1, 2.1)***	68.5 (0.2)	67.4 (0.3)	1.1 (−0.03, 1.4)
Body mass index (kg/m^2)	26.6 (0.1)	26.2 (0.1)	0.4 (0.09, 0.7)**	28.8 (0.09)	28.5 (0.1)	0.3 (−0.09, 0.5)
Duration of diabetes (year)	5.6 (0.1)	6.6 (0.2)	−1.0 (−1.4, −0.4)***	5.4 (0.1)	6.2 (0.1)	−0.8 (−0.7, −0.07)***
Follow-up duration (year)	9.0 (0.08)	9.7 (0.01)	−0.7 (−1.0, −0.4)***	9.1 (0.07)	9.9 (0.09)	−0.8 (−0.9, −0.5)***
Number of follow-up visit	8.5 (0.3)	16.7 (0.4)	−8.2 (−9.1, −7.3)***	11.1 (0.3)	22.0 (0.3)	−10.9 (−11.6, −10.0)***
PG baseline (mg/dl)	200.9 (1.8)	206.2 (2.4)	−5.3 (−11.4, 1.04)	191.7 (1.4)	203.0 (1.8)	−11.3 (−11.3, −7.0)***
HbA_{1c} (%)	8.8 (0.09)	9.3 (0.1)	−0.5 (−0.9, −0.3)***	8.4 (0.07)	9.3 (0.07)	−0.9 (−1.0, −0.6)***
Cholesterol (mg/dl)	211.1 (1.2)	215.4 (1.7)	−4.3 (−7.9, 0.07)	229.2 (1.0)	232.0 (1.3)	−2.8 (−5.3, 1.2)
LDL-cholesterol (mg/dl)	120.0 (2.1)	123.6 (2.2)	−3.6 (−8.7, 2.1)	136.5 (1.6)	137.9 (1.5)	−1.4 (−5.2, 4.0)
HDL-cholesterol (mg/dl)	43.3 (0.7)	41.9 (0.8)	1.4 (−0.6, 3.4)	46.8 (0.6)	46.1 (0.5)	0.7 (−0.7, 2.3)
Triglyceride (mg/dl)	230.0 (3.9)	228.0 (5.4)	2.0 (−11.3, 14.7)	235.7 (3.2)	236.1 (4.0)	−0.4 (−11.1, 8.7)
Creatinine (μM/l)	1.0 (0.02)	1.0 (0.03)	0.0 (−0.1, 0.05)	0.9 (0.02)	0.9 (0.02)	0.0 (−0.05, 0.05)
Systolic BP (mm Hg)	121.3 (0.4)	121.8 (0.6)	−0.5 (−1.4, 1.6)	122.7 (0.4)	123.2 (0.4)	−0.5 (−0.6, 1.8)
Diastolic BP (mm Hg)	74.4 (0.3)	75.8 (0.4)	−1.4 (−2.1, −0.3)***	75.3 (0.2)	76.0 (0.3)	−0.7 (−1.0, 0.4)
Obesity (BMI≥30), no. (%)	288 (16.8)	125 (14.4)	2.4 (−0.5, 5.4)*	930 (37.0)	577 (35.8)	1.2 (−1.8, 4.3)
Smoking (%)						
Never-smoker	1103 (71.3)	577 (71.8)	−4.2 (−4.3, 3.4)	2150 (96.8)	1446 (97.3)	−0.5 (−1.7, 0.6)
Current-smoker	443 (28.7)	227 (28.2)	4.2 (−3.4, 4.3)	72 (3.2)	40 (2.7)	0.5 (−0.6, 1.7)
Education (%)						
Primary or below	1033 (60.5)	529 (62.3)	−1.8 (−5.8, 2.2)	2111 (86.0)	1371 (88.0)	−2.0 (−4.2, 0.08)
Secondary	339 (19.9)	181 (21.3)	−1.5 (−4.8, 1.9)	258 (10.5)	146 (9.4)	1.1 (−0.8, 3.0)
Matriculation or above	335 (19.6)	139 (16.4)	3.3 (0.1, 6.4)	87 (3.5)	41 (2.6)	0.9 (−0.2, 2.0)

Age-adjusted means were calculated using general linear models. Data are express as mean (SE) or number (%). The difference in the means or percentage of the variables between not switched and switched to insulin. PG: plasma glucose.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

Table 4 – Predictors of switch to insulin (Cox's proportional hazard model).

Covariate	Hazard rate	95% CI
Age at diagnosis (year)	0.97	0.96–0.97*
Body mass index (kg/m^2)	1.02	1.01–1.03*
Number of follow-up visit	0.97	0.96–0.97*
HbA1c (%)	1.08	1.1–1.3*
Gender (men = reference)	1.2	1.1–1.3*

CI = confidence interval.
* $P < 0.001$.

oral agent or diet. Women who switched to insulin showed higher FPG and HbA_{1c} levels through the follow-up. Men who switched to insulin showed higher LDL (Table 5).

4. Discussion

In this large retrospective cohort study, patients with type 2 diabetes treated with non-insulin regimen at baseline show 1.7% and 2.7% per year switching to insulin from diet, or oral agent. In most cases this is accompanied by an unfavourable BMI and younger age at diagnosis. The study found that women predominated in switching to insulin. Switching rates were increase with number of follow-up visit and associated with a higher level of HbA_{1c}.

Few studies have assessed rate of switching to insulin in persons with type 2 diabetes and the results are inconsistent. Estimates of rate of switching to insulin will depend upon the methodological factors, the definition of the switching to insulin used, and the composition of the community examined by age and gender, making comparisons between studies of limited values. In the Netherlands study, the cumulative incidence of switching to insulin therapy was 36% over a 4–5 year period [15]. After nine years of follow-up in the United Kingdom Prospective Diabetes Study (UKPDS), 30% of the patients had switched to insulin treatment [16]. In another study, insulin therapy was started in 29.7% of the patients over 2 year period [17]. In a population-based cohort study among elderly persons in Quebec the rate of switching to insulin were 9.7 cases per 1000 patient-years [18]. This rate of insulin initiation seems very low. In the Sweden study, 25% of patients with type 2 diabetes had prescribed insulin within 6 years of starting OADs, and this figure rose to 42% within 10 years, corresponding to an annual rate of insulin initiation of 4% [19]. After 5 years of follow-up in the Australian Fremantle Diabetes Study, 15% of the patients had switched to insulin treatment [20]. The retrospective Scottish study estimated that 5.8% of OADs treatment initiators would start insulin each subsequent year within a median of 1.6 years [21]

Although experimental studies show that insulin therapy can be safe and efficacious in improving glycemic control in type 2 diabetes [22–24], little is known about factors associated with switching from non-insulin to insulin therapy in routine practice. Goddijn studied prospectively a cohort of patients with type 2 diabetes referred by general practitioners to an outpatient department for consideration of insulin therapy. As in our study, she found that switchers had a higher HbA_{1c}. However, in contrast to our finding, their patients had a lower BMI [25]. Ringborg et al. also studied retrospectively a population-based cohort of patients with type 2 diabetes within the Swedish RECAP-DM study for initiation of insulin therapy. As in our study, they also found that switchers had a higher HbA_{1c} [19]. Spoelstra et al. [15] also found patients switched to insulin had a higher HbA_{1c}. However, similar to our finding, their patients had a higher BMI.

We found that switching rates were increase with number of follow-up visit. These patients are more likely to consult a physician on a regular basis and, therefore, are more likely to be offered insulin.

In this study, younger age, a high BMI, being women was associated with the insulin initiation, supporting the results of other studies [21,26] but not all studies [19]. The reason(s) for

Table 5 – Age-adjusted changes over time in subjects who did or did not switched to insulin during mean 9.3 years follow-up period.

Characteristic	Change from baseline to final assessment					
	Men			Women		
	Not switched (n = 1764)	Switched (n = 892)	Difference (95% CI)	Not switched (n = 2587)	Switched (n = 1653)	Difference (95% CI)
Weight (kg)	0.4 (0.14)	−1.5 (0.19)	1.9 (1.5, 2.4)***	0.5 (0.12)	−2.6 (0.15)	3.1 (2.7, 3.4)***
Body mass index (kg/m^2)	0.3 (0.06)	−0.5 (0.08)	0.8 (0.6, 1.0)***	0.4 (0.05)	−0.97 (0.07)	1.3 (1.1, 1.4)***
Fasting glucose (mg/dl)	36.9 (2.33)	41.2 (3.15)	−4.2 (−11.9, 3.5)	17.6 (1.68)	26.9 (2.02)	−8.1 (−13.3, −3.0)***
HbA_{1c} (%)	1.2 (0.11)	1.4 (0.12)	−0.2 (−0.5, 0.1)	0.7 (0.08)	1.15 (0.08)	−0.3 (−0.5, −0.07)***
Cholesterol (mg/dl)	11.5 (1.26)	23.2 (1.70)	−11.8 (−16.8, −7.7)***	12.3 (1.56)	21.6 (1.39)	−8.9 (−12.4, −5.4)***
HDL-cholesterol (mg/dl)	3.5 (0.99)	2.3 (0.91)	1.2 (−1.3, 3.9)	3.3 (1.00)	2.8 (0.79)	0.4 (−2.1, 2.9)
LDL-cholesterol (mg/dl)	9.0 (3.48)	18.6 (3.21)	−9.6 (−19.0, −0.4)*	16.0 (3.32)	18.9 (2.62)	−1.1 (−9.5, 7.3)
Triglyceride (mg/dl)	28.5 (3.54)	44.7 (4.77)	−16.2 (−28.1, −4.9)**	27.1 (3.16)	38.7 (3.78)	−10.7 (−20.3, −1.1)**
Systolic BP (mm Hg)	−8.8 (0.49)	−11.1 (0.68)	2.3 (0.6, 4.0)**	−10.1 (0.41)	−13.1 (0.52)	2.8 (1.51, 4.1)***
Diastolic BP (mm Hg)	−7.6 (0.31)	−6.9 (0.43)	−0.7 (−1.7, 0.3)	−8.2 (0.25)	−8.3 (0.32)	0.2 (−0.6, 1.0)

Data are expressed as mean (SE). The difference in the means of the variables between switched and not switched to insulin.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

this higher rate of switching to insulin in women has not been explored.

In this study, duration of type 2 diabetes was associated with the rate of insulin initiation. Measures of duration of diabetes are subject to error because many individuals with type 2 diabetes remain undiagnosed for years; this error would tend to weaken associations with duration.

Change in body weight was statistically significant in the switched to insulin group. It is somewhat surprising that initiating insulin therapy did not lead to weight increase. This may be explained by the low dose of insulin. It is likely that patients received lifestyle and weight management advices from nutritionists during their visits, which may have improved their lifestyle and eating habits and confound some of the potential weight gain associated with insulin therapy.

The rate of insulin initiation in the present study is lower than those observed in other studies in developed countries [15–17,19–21], but higher than in a population-based cohort study among elderly persons in Quebec, Canada [18]. Lower rates in our study also could have been due to a different patient's preferences, and differences in medical care access and therapy might be one reason. However, this result is difficult to explain because it may also either indicate a low rate of secondary failure of OADs in this population or that diabetes is not being treated aggressively enough. However, most previous studies in developed countries investigate the time between the start of OADs treatment and the initiation of insulin therapy, whereas our patients were not necessarily OADs treatment initiators at baseline and about one-fourth of our patients (24.4%) have received no prior pharmaceutical therapy. The data used in the present study are representative of local treatment practice. However, the individual physicians all make their own decisions and these data should be interpreted in the context of the information source. Fear of needles was predictive of unsatisfactory glycemic control. We were not able to assess whether lower rate of insulin initiation was because of less severe diabetes, better glycemic control, fear of needles, or lesser complications of diabetes, because these clinical data are not captured in the Isfahan Endocrine and Metabolism Research Centre database. Lastly, patient's preferences, perception of health or beliefs about their disease and its treatment were not available in the database.

The strengths of present study include its large size, long follow-up, and sample consisting of both men and women of a wide age range. These real-life data reflect actual treatment pattern and allow for observation of patients over time. Our study was limited by possible selection bias by restricting the study to patients alive during the whole study period. Despite this limitation, the findings here add to our understanding of the rate of switching to insulin in people with type 2 diabetes in Iran. Furthermore, this study provides new data from Iran, a developing country that has been underrepresented in past studies.

In conclusion, the findings of this study illustrate for the first time the switching rates and its predictors to insulin from a non-insulin regimen in patients with type 2 diabetes in Iran. Young age at diagnosis, higher BMI and HbA_{1c} at registration and female gender were identified on multivariate analysis as predictors of switching to insulin. These findings may be taken into account in future treatment decisions.

Acknowledgement

We are grateful to Mr. Majid Abyar for computer technical assistance.

Conflict of interest

The authors declare that they have no conflict of interest.

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