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ORIGINAL ARTICLE

Psychosocial factors and glycemic control in insulin-naïve and insulin-experienced people with type 2 diabetes: a path analysis model

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Abstract The purpose of this study was to compare the status of psychosocial factors and glycemic control in insulin-naïve and insulin-experienced people with type 2 diabetes (T2D). In this observational study on people with T2D, demographic, self-care behavior, resources, and affective variables as well as health-related quality of life were assessed and compared in insulin-naïve and insulin-experienced considering the number of oral glucose-lowering drugs (OGLDs). Measured variable path analysis was used to test the association among variables and their effect on HbA1c in both groups. In total, 215 insulin-naïve and 165 insulin-experienced patients were recruited in this study. The mean duration of diabetes was 11.7 ± 7.0 years in insulin-experienced and 6.8 ± 5.4 years in insulin-naïve ($p < 0.001$). The mean hemoglobin A1c (HbA1c) was significantly higher in insulin-experienced subjects irrespective of the number of OGLDs [68 ± 20 mmol/mol (8.4 ± 1.8%) vs. 56 ± 16 mmol/mol (7.3 ± 1.4%); $p < 0.001$]. Moreover, insulin-experienced subjects had significantly higher level of diabetes-related distress (2.2 ± 0.9 vs. 1.9 ± 0.8), depression (9.5 ± 5.5 vs. 8.1 ± 5.1), anxiety (18.3 ± 12.0 vs. 15.1 ± 10.5), and lower knowledge of insulin use considering the results of 9-item insulin-use subscale of Michigan diabetes knowledge test (mean 3.9 ± 1.8) compared to insulin-naïve subjects ($p < 0.05$). Higher levels of distress, depression, and anxiety are found in insulin-experienced people with T2D. Therefore, one should be aware that, at the time of insulin need/initiation, people with T2D have reached a more vulnerable state and this should be taken into consideration when implementing a complex insulin initiation plan.

Keywords Diabetes, type 2 · Psychosocial · Glycemic control

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Introduction

The benefit of good glycemic control on diabetes-related complications is obvious in people with type 2 diabetes (T2D) [1]. Timely and effective treatment should be considered to bring patients to glycemic and other metabolic targets. However, achieving glycemic target is difficult. Several studies showed that only half of patients achieved hemoglobin A1c (HbA1c) target [2, 3], while 9% had very poor control [3]. Although lifestyle modifications and oral glucose-lowering drugs (OGLDs) are essential in management of the disease, long-term glycemic control is difficult to achieve and ultimately there is a need for initiation of insulin treatment [4]. Delay in insulin initiation or intensification [3] may be due to patient and physician reluctance [5] and/or fear of hypoglycemia [6] as well as weight gain [7] are possible causes. On the other hand, many patients remain under poor glycemic control even years after they received their first insulin prescription [4].

Considering that insulin is the most effective glucose-lowering agent, it is necessary to understand why patients with T2D who are on insulin are still unable to achieve good glycemic control [8, 9]. Hence, the aim of this study was to compare the status of psychosocial factors and glycemic control in insulin-naïve and insulin-experienced people with T2D in routine clinical practice.

Methods

We performed a non-interventional, observational study of patients with T2D, aged 30 years or above with diabetes duration of 6 months or more. A detailed description of the design, eligibility criteria, and questionnaires has been published previously [10]. Briefly stated, patients were excluded if they had severe diabetes-related complications, active psychosis, a history of substance use, dementia, or if they were pregnant.

People coming for regular clinic visits were recruited in the study. The project and its goals were explained for every eligible patient. All patients signed the informed consent. Patients were asked to complete the questionnaires during the following 7 days. Four categories of variables were assessed to explore their associations with type of treatment:

1. *Demographic variables* including age, gender, duration of diabetes, type of treatment, smoking, body mass index (BMI), abdominal circumference, and hip circumference.
2. *Self-care behavior variables* comprised of total daily calorie intake long form of international physical activity questionnaire (IPAQ) and self-management profile for type 2 diabetes (SMP-T2DM).

Calorie intake was assessed using a single 24-h recall. Detailed questions were asked about all foods and beverages consumed during the previous day.

IPAQ covers four domains of physical activity including occupational-related, transportation, household/gardening, and leisure-time activities. According to the scoring system, physical activity levels were categorized as inactive, minimally active, or health enhancing physically active [11].

SMP-T2DM consisted of 18 items on five self-care domains scoring between 0 and 7. Higher scores indicated better self-management [12].

3. *Resources variables* consisting of family social support questionnaire (FSSQ), brief Michigan diabetes knowledge test (DKT), and patient assessment of care for chronic conditions (PACIC).

FSSQ consisted of 79 questions with higher scores indicating higher levels of social support [13].

DKT comprised of 23 items to assess general knowledge of diabetes [14].

PACIC-5A consisting of 26 items on 6 domains was used to assess patient physician relationship [15].

4. *Affective variables* including WHO-5 well-being index, patient health questionnaire (PHQ-9), beck anxiety inventory, and diabetes distress scale (DDS).

WHO-5 including 5 items was used to assess emotional well-being. Higher scores was attributed to higher level of well-being [16].

PHQ-9 was comprised of 9 items to assess level of depression [17].

Beck anxiety inventory consisted of 21 multiple choice questions to assess level of anxiety [18].

DDS included 17 items. A mean item score of < 2 was interpreted as little or no distress, 2–2.9 as moderate, and ≥ 3 as high distress [19].

Health-related quality of life was also assessed using self-administered EQ-5D questionnaire [20], which contains questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In addition, patients were asked to rate a state of ill health on a visual analog scale from 0 to 100, with 0 representing being worst imaginable health and 100 representing best imaginable health.

A calibrated digital scale (Seca gmbh & co. kg. Germany) was used for weight measurement. Height measurement was done with a stadiometer (Seca gmbh & co. kg. Germany) calibrated before each measurement. A trained nurse assessed abdominal and hip circumferences using a cloth tape. The midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the mid-axillary line was defined as waist, and

the hip was measured at the level of the greater femoral trochanters.

Systolic and diastolic blood pressure (BP) measurements were obtained from each patient (the right arm) in the sitting position, using a standard mercury sphygmomanometer (Erkameter 3000, ERKA, Bad Tolz, Germany) (Korotkoff I and V) with a cuff of appropriate size. Blood pressure was measured by the same trained nurse after the patient had rested for ≥ 10 min.

Blood samples were obtained after an overnight fast of at least 12 h for measurement of fasting blood sugar (FBS) using a glucose analyzer (YSI 2700 Select, YSI, Inc., Yellow Springs, OH), HbA1c using ion exchange chromatography (DS5 Analyzer, Drew Scientific limited, Cumbria, UK). Triglyceride (TG), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), creatinine (Cr), and blood urea were measured using an autoanalyzer (Liasys, AMS, Italy).

Statistical analysis

STATA (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP.) and IBM SPSS for Windows Version 19 (IBM Corp., Armonk, NY, USA) were used to perform statistical analyses. In the first step, patients were divided into two groups, i.e., insulin-experienced and insulin-naïve. Sub-group analyses were then conducted in each group considering the number of OGLDs received (no/one, or ≥two). Percentage estimates and 95% confidence intervals (CI) were calculated for each item. Quantitative values were expressed as means ± standard deviation (SD), and qualitative values were expressed as percentages. Normal assumptions were checked by looking at the normal curve or frequency histogram as well as Kolmogorov-Smirnov test. In the case of normal distribution, we used parametric statistical test while we used non-parametric statistical, in the case of non-normal distribution or inequality in the variances of variables. Levene's test was used to assess the equality of variances considering the number of OGLDs. When the variances were equal, the statistical significance of differences between the groups was determined using two-way analysis of variance. In the case of inequality of variances, Mann-Whitney test was used.

All statistical analyses were two-sided and a probability value of $p \leq 0.05$ was considered significant. Measured variable path analysis (MVPA), a form of structural equation modeling, was used to test the relationships among variables and their effect on HbA1c as the indicator of glycemic control using Mplus Version 6.12. The parameter estimation method was maximum likelihood. The χ^2 tests were reported, but model fit was primarily evaluated with root mean square error of approximation (RMSEA) [21]. It tests how well an estimated model fits the data structure. A significant χ^2 test suggests that the data fit the model well, while RMSEA values less than 0.1 indicate adequate model fit [22]. Variables included in the path model were normally distributed.

Results

The study population was comprised of 165 (43.5%) insulin-experienced and 215 (56.5%) insulin-naïve subjects. Baseline characteristics were the same between patient sub-groups except for diabetes duration that was longer in insulin-experienced (11.7 ± 7.0 vs. 6.8 ± 5.4 years, $p < 0.001$, Table 1). Although there was 0.76 kg/m^2 difference in BMI between insulin-experienced and insulin-naïve patients, the difference was not statistically significant (28.8 ± 4.6 vs. 28.0 ± 4.0 kg/m^2, $p = 0.11$). However, there was significant difference in waist circumference, with insulin-experienced having larger waist circumference than insulin-naïve patients (99.6 ± 11.2 vs. 97.2 ± 10.0 cm, $p = 0.01$, Table 1).

In both insulin-experienced and insulin-naive patients, metformin was the most frequently prescribed OGLD (87.8 and 96.2%, respectively). Among 215 insulin-naïve, 83 (38.6%) were receiving one OGLD, and 132 (61.4%) were on two or more OGLDs. In the insulin-experienced group, 124 (75.1%) were under treatment with no or one OGLD, and 41 (24.8%) were receiving two or more OGLDs (Table 1). The time lag for insulin initiation was 8.1 ± 5.9 years considering the different types of insulin regimens. The mean dose of insulin was 0.56 ± 0.3 IU/kg/day. Eighty patients (48.2%) were on premixed or split-mixed insulin regimens. Basal insulin only was reported in 25.3% of the participants and basal plus rapid acting insulin in another 23.5%.

There were statistically significant differences in measures of blood glucose control (HbA1c) between insulin-naïve and insulin-experienced considering concomitant OGLD use [56 ± 16 mmol/mol (7.3 ± 1.4%) vs. 68 ± 20 mmol/mol (8.4 ± 1.8%), $p < 0.001$] (Table 2).

Behavioral and psychosocial factors

There were no obvious differences regarding total daily calorie intake (1890.5 ± 1275.8 vs. 1886.6 ± 510.3 Kcal, $p = 0.09$) or physical activity (median: 2448 (16702) vs. 2580 (17622) MET-min/week, $p = 0.78$) between insulin-naïve and insulin-experienced. Moreover, no statistical difference was reported in "number of days during the past week (last 7 days) missing taking diabetes medications as prescribed" between the two groups (0.4 ± 1.2 days in insulin-naïve vs. 0.5 ± 1.5 days in insulin-experienced, $p = 0.6$). However, insulin-experienced had significantly higher level of distress (2.2 ± 0.9 (moderate) vs. 1.9 ± 0.8 (little or no), $p = 0.01$), depression (9.5 ± 5.5 (moderate) vs. 8.07 ± 5.1 (mild), $p = 0.03$), and anxiety

Table 1 Baseline patient characteristics in study population

	Insulin-naïve			Insulin user			*P* value
	No or one OGLD	Two or more OGLDs	All	No or one OGLD	Two or more OGLDs	All	
N (%)	83 (38.6)	132 (61.4)	215	124 (75.15)	41 (24.85)	165	
Gender (female), %	11.5	15.5	27.1	18.9	0.07	26.3	0.04
Age (years)	53.69 ± 8.89	55.17 ± 7.64	54.59 ± 8.16	55.21 ± 7.81	54.02 ± 7.90	54.91 ± 7.83	0.58
Diabetes duration (years)	4.67 ± 5.04	8.19 ± 5.15	6.83 ± 5.38	11.94 ± 7.26	10.93 ± 6.02	11.69 ± 6.97	0.00
Weight (kg)	74.19 ± 12.66	76.82 ± 12.96	75.80 ± 12.88	76.76 ± 13.02	76.51 ± 15.15	76.70 ± 13.53	0.32
BMI (kg/m^2)	27.71 ± 4.33	28.18 ± 3.77	28.00 ± 3.99	28.77 ± 4.71	28.71 ± 4.49	28.76 ± 4.65	0.11
Hip circumference (cm)	101.93 ± 9.43	102.01 ± 7.57	101.98 ± 8.32	103.73 ± 8.69	102.88 ± 8.70	103.52 ± 8.67	0.13
Waist circumference (cm)	95.08 ± 10.37	98.48 ± 9.51	97.16 ± 9.97	99.85 ± 11.20	99.02 ± 11.46	99.64 ± 11.24	0.01
Systolic BP (mmHg)	119.46 ± 17.13	122.44 ± 16.27	121.28 ± 16.63	127.10 ± 18.82	128.54 ± 18.38	127.45 ± 18.66	0.000
Diastolic BP (mmHg)	79.04 ± 9.38	78.75 ± 8.38	78.86 ± 8.76	81.12 ± 8.33	82.19 ± 8.44	81.39 ± 8.35	0.007
Time since insulin initiation (months)	N/A	N/A	N/A	45.78 ± 42.48	25.45 ± 27.07	40.86 ± 40.18	0.00

BMI body mass index, *BP* blood pressure, *OGLDs* oral glucose-lowering drugs

(18.3 ± 12.02 (very low) vs. 15.1 ± 10.5 (very low), $p = 0.03$) compared to insulin-naïve patients.

Considering the results of "the diabetes knowledge test," although knowledge was not significantly different in insulin-experienced compared to insulin-naïve regarding the 14-item general test (7.8 ± 1.8 vs. 7.7 ± 2.02, $p = 0.93$), the mean level of knowledge of insulin use was low in insulin-experienced considering the results of 9-item insulin-use subscale (3.9 ± 1.8). Among participants, no one could give correct answer to the questions on "necessary action when having the flu" or "skipping one time of insulin injection". Only 21 (12.7%) and 24 (14.5%) of insulin-experienced patients could give a correct answer to the questions on "ketoacidosis signs" or "time to initiate reaction of intermediate insulin." Table 3 shows behavioral and psychosocial factors in study population.

Effects of variables on HbA1c in insulin-naïve and insulin-experienced people: a path analysis model

Duration of diabetes, BMI, total daily calorie intake, physical activity, self-management profile, family social support, diabetes knowledge, patient physician relationship, well-being index, depression, anxiety, diabetes distress, utility, and VAS score were included in the model. The estimated MVPA with parameters and statistical significance of individual paths are shown in Figs. 1 and 2.

Table 2 Metabolic control by pre-study therapy

	Insulin-naïve			Insulin user			*P* value
	No or one OGLD	Two or more OGLDs	All	No or one OGLD	Two or more OGLDs	All	
FBG (mg/dl)	135.12 ± 36.41	144.33 ± 36.38	140.79 ± 36.58	151.32 ± 55.88	145.22 ± 49.60	149.80 ± 54.30	0.51
HbA1c (%)	6.94 ± 1.15	7.57 ± 1.54	7.33 ± 1.43	8.39 ± 1.86	8.34 ± 1.84	8.38 ± 1.85	0.00
TG (mg/dl)	154.89 ± 25.60	154.28 ± 29.99	154.52 ± 28.33	159.23 ± 37.76	154.49 ± 31.79	158.05 ± 36.32	0.63
Total Chol (mg/dl)	139.93 ± 68.01	139.59 ± 64.46	139.72 ± 65.68	136.90 ± 64.65	136.71 ± 58.06	136.85 ± 62.89	0.68
LDL (mg/dl)	85.06 ± 15.79	82.13 ± 18.98	83.26 ± 17.84	86.45 ± 23.19	84.97 ± 21.83	86.08 ± 22.80	0.37
HDL (mg/dl)	38.60 ± 9.04	38.60 ± 9.21	38.60 ± 9.12	39.88 ± 9.77	37.54 ± 8.57	39.60 ± 9.51	0.72

All data are shown as mean ± standard deviation

FBG fasting blood glucose, *HbA1c* hemoglobin A1c, *TG* triglyceride, *Total Chol* total cholesterol, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein

Table 3 Behavioral and psychosocial factors in study population

		Insulin-naïve			Insulin user			*P* value
		No or one OGLD	Two or more OGLDs	All	No or one OGLD	Two or more OGLDs	All	
Self-care behavior variables	Total daily calorie intake	2072.46 ± 1896.77	1776.59 ± 615.52	1890.50 ± 1275.83	1903.19 ± 524.69	1836.95 ± 467.28	1886.63 ± 510.35	0.09
	Physical activity (median)	2793 (16,702)	2069.5 (15,264.5)	2448 (16,702)	2559 (17,622)	2655 (10,591)	2580 (17,622)	0.78
	Self-management	75.04 ± 12.02	72.31 ± 11.97	73.33 ± 12.03	69.64 ± 12.82	73.93 ± 9.77	70.69 ± 12.25	0.06
Resources variables	The family social support	3.18 ± 0.65	3.23 ± 0.43	3.21 ± 0.52	3.22 ± 0.45	3.21 ± 0.42	3.22 ± 0.44	0.79
	Diabetes knowledge (14-item general test)	7.60 ± 1.92	7.87 ± 1.70	7.77 ± 1.78	7.64 ± 2.09	7.75 ± 1.80	7.67 ± 2.02	0.93
	Patient physician relationship	2.46 ± 1.01	2.39 ± 0.80	2.42 ± 0.89	2.70 ± 0.83	2.56 ± 0.86	2.67 ± 0.83	0.03
Affective variables	Well-being	49.41 ± 21.69	51.54 ± 19.24	50.72 ± 20.19	46.95 ± 21.03	47.90 ± 18.23	47.19 ± 20.31	0.20
	Depression	8.21 ± 5.54	7.98 ± 4.88	8.07 ± 5.13	9.65 ± 5.63	8.97 ± 5.07	9.49 ± 5.49	0.03
	Anxiety	14.32 ± 9.18	15.65 ± 10.88	15.15 ± 10.48	18.67 ± 12.36	17.00 ± 10.96	18.27 ± 12.02	0.03
	Diabetes distress	1.87 ± 0.86	1.99 ± 0.83	1.95 ± 0.84	2.19 ± 0.92	2.14 ± 0.97	2.18 ± 0.93	0.01
HRQoL	Utility	0.83 ± 0.14	0.81 ± 0.15	0.82 ± 0.14	0.74 ± 0.28	0.77 ± 0.23	0.75 ± 0.27	0.18
	VAS	68.91 ± 20.67	70.63 ± 17.13	69.97 ± 18.54	62.32 ± 27.11	67.74 ± 23.73	63.62 ± 26.38	0.055

All data are shown as mean ± standard deviation

HRQoL health-related quality of life, *VAS* visual analog scale

Insulin-naïve

The estimated model (Fig. 1) demonstrated a good fit, χ^2 (df = 23, N = 215) = 45.32, P = 0.003, RMSEA = 0.067. As shown in Fig. 1, there was only significant positive direct effect from duration of diabetes (β = 0.19, t value = 0.007) to HbA1c.

Insulin-experienced

The estimated model in insulin-experienced people also showed a good model fit, χ^2 (df = 12, N = 165) = 18.48, p = 0.10, RMSEA = 0.057). As demonstrated in Fig. 2, there was only significant positive direct effect from anxiety (β = 0.71, t value < 0.001) to HbA1c.

Discussion

In this study, as expected due to either duration or complexity of disease, a higher level of HbA1c was found in insulin-experienced compared to insulin-naïve independent of type and dose of concomitant OGLDs received. Moreover, the results also revealed higher level of distress, depression, and anxiety as well as low knowledge about insulin use in this group of people with T2D; therefore, the level of knowledge and distress in those eligible for insulin initiation must be considered for this treatment to be truly effective.

Insulin as the most effective glucose-lowering drug is a medical requirement in the treatment of patients with diabetes in the case of pancreatic β cell failure [3, 23]. However, several studies have shown that people who are on insulin still fail to achieve glycemic targets [8, 24, 25]. In the "A1chieve study," there was no difference in relation to the glycemic control between insulin-naïve and prior insulin users; HbA1c:[80 ± 19 mmol/mol (9.5 ± 1.7%) vs. 79 ± 20 mmol/mol (9.4 ± 1.8%)] [4]. Delaying insulin initiation or intensification in real clinical practice where both patients and many physicians are reluctant to initiate insulin in the face of disease progression results in poor glycemic control in people with T2D [26–28]. Fear of hypoglycemia, needle phobia, anticipated pain, and weight gain are concerns about insulin injection [29, 30] that still continue even after patients initiate insulin use [8] resulting in insulin non-adherence [31] and overindulge in eating to prevent hypoglycemia [32].

In our study, non-adherence to treatment was not an issue as there was no difference between the two groups considering "missing taking diabetes medications." Meanwhile, two third of insulin-experienced group were receiving basal plus at least one injection of rapid/short acting insulin; therefore, insulin therapy has been moved toward more intensified regimen. The other important finding of this study was the higher level of diabetes-related distress in the insulin-experienced group.

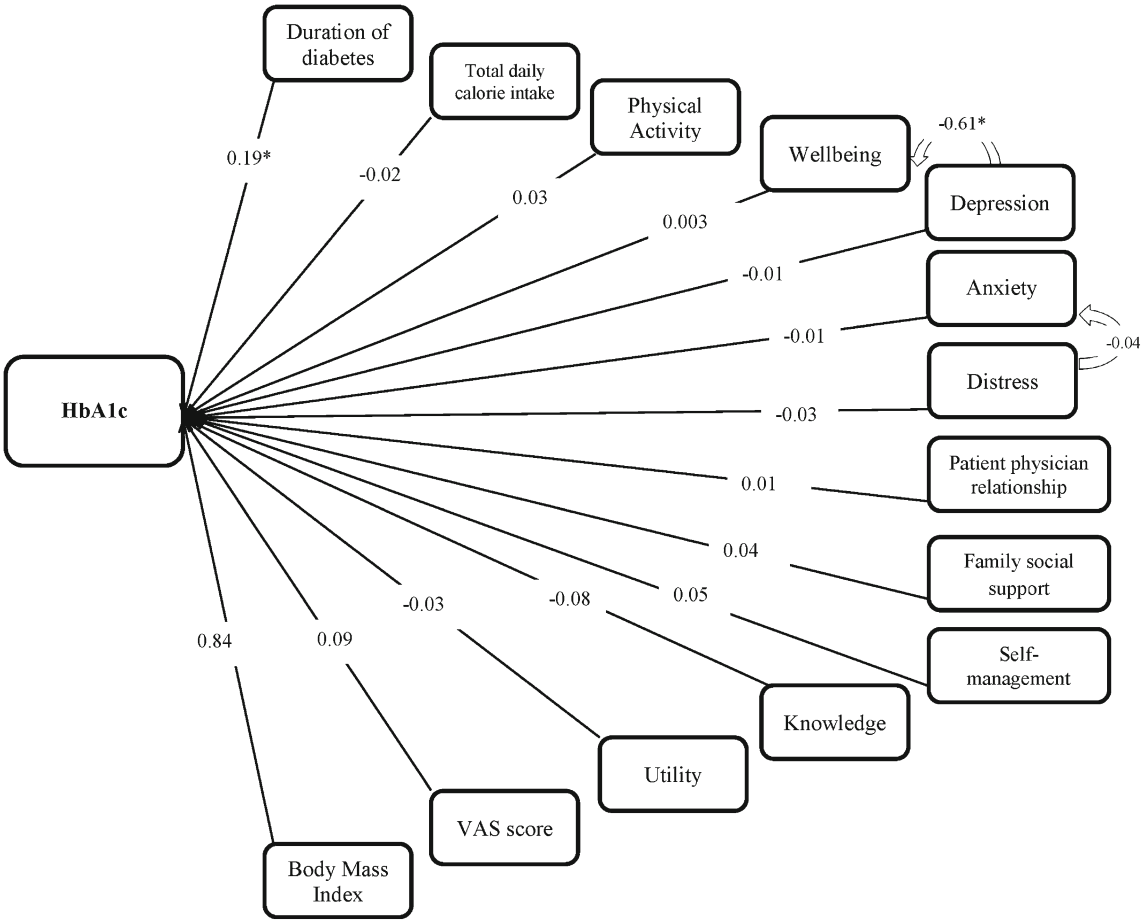

Fig. 1 Measured variable path analysis in insulin-naïve

The efforts to control persistent hyperglycemia may lead to distress as a consequence of anger, disappointment, and loss of motivation affecting diabetes self-management [8]. In a study conducted by Tong et al., it was revealed that insulin-experienced subjects ascribe persistence of poor glycemic control to different factors, namely, psychosocial and emotional problems, treatment-related factors, and lack of knowledge about glycemic goals [8]. Comorbid major depression occurs in about 10–15% of patients with diabetes [33], which complicates diabetes medication non-adherence [34, 35] and increases the risk of diabetes complications [36] and hyperglycemia [37]. Consequently, depression may result in poor self-care behaviors including adherence to diet, exercise, and medication prescriptions [35]. Moreover, Makine et al. found that negative appraisal of insulin therapy is significantly associated with higher levels of depression and diabetes-related emotional distress [38]. In a study conducted by Holmes-Truscott et al., it was revealed that greater psychological resistance to insulin treatment is due to broader diabetes-related distress and its treatment. Hence, reducing diabetes-related distress by explaining disease progression and loss of β cell function in diabetes may lessen patients concern regarding insulin therapy [39].

Low knowledge of insulin use was also a reason for poor glycemic control in insulin-experienced subjects in the current study. The participants were not well informed about insulin use, more specifically the terms ketoacidosis, insulin reaction, and necessary action when having the flu or missing an insulin injection. Consistent with the results of our study, Murata et al. reported poor knowledge of ketoacidosis and insulin reaction among the majority of veterans in the USA [40]. Seemingly, poor knowledge of insulin use may increase the risk of its related complications (ketoacidosis, insulin reaction, and hypoglycemia) which may consequently result in poor glycemic control [41]. This poor level of knowledge might potentiate the burden of diabetes-related distress and poor glycemic control [42, 43]. Therefore, providing training programs to educate people with T2D, more specifically insulin-experienced subjects or those about to initiate insulin treatment, in addition to psychological counseling to overcome the fears and minimize or prevent psychological insulin resistance is warranted [24].

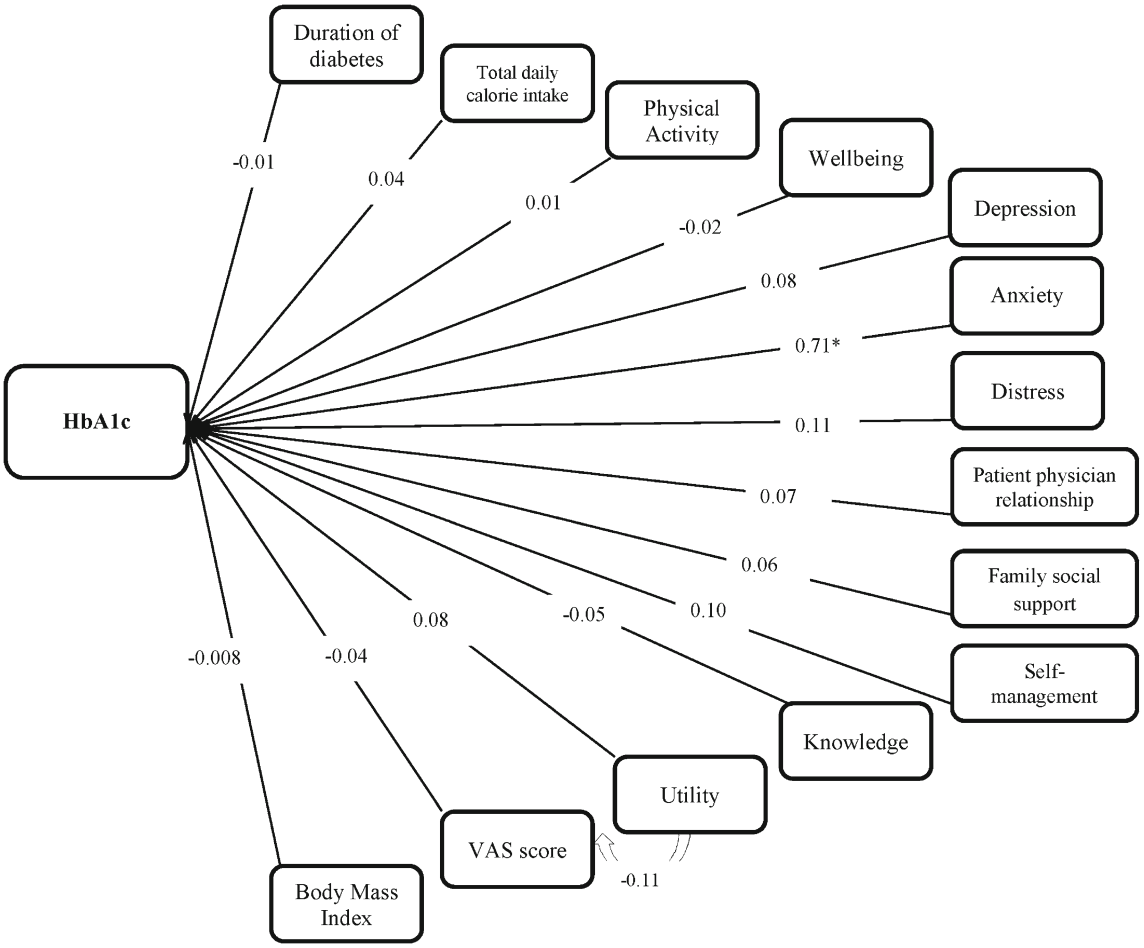

Fig. 2 Measured variable path analysis in insulin users

In this study, we also used measured variable path analysis to assess these associations and their effects on glycemic control in insulin-naïve and insulin-experienced people. The findings demonstrated that longer duration of diabetes was directly associated with worse glycemic control in the insulin-naïve group, while in insulin-experienced people anxiety was the only variable associated with poorer glycemic control. Consistent with our results, Camara et al. have shown that a higher level of anxiety is associated with a higher HbA1c level in people with T2D [44].

This was the first study in a non-western population to explore the relationships between type of treatment and key psychosocial and behavioral factors. However, there were some limitations in this study. A major limitation was the size of the study and the fact that findings might not be generalizable to a greater public, either geographically or ethically.

Moreover, any causal effect could not be shown between type of treatment and psychosocial factors due to the design of the study. In addition, we did not have enough data on timely insulin initiation and intensification, although two-thirds of insulin-experienced group were receiving basal plus rapid/short acting insulin.

Conclusion

Our findings demonstrated that glycemic control was not good in this group of insulin-experienced people. Psychosocial problems might directly or indirectly lead to poor glycemic control despite insulin use. In addition, both physicians and patients' barriers to insulin therapy, namely, low knowledge of insulin use may be the other reason. Thus, health care providers should consider psychosocial factors and help patients to overcome their concerns regarding insulin treatment. Furthermore, there should be appropriate diabetes educational programs to raise patients' knowledge and skills.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol was approved by the ethics committee of the Iran University of Medical Sciences, and the study procedures were carried out in accordance with the principles of the Declaration of Helsinki. The project and its goals were explained for every eligible patient and all patients signed the informed consent.

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