

Individualized Glycemic Control in Type 2 Diabetic Patients in Iran: A Multi-Center Data Analysis

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Abstract

Background: Clinical guidelines and expert committees have recently suggested that the hemoglobin A1C (HbA1c) should be individualized based on various criteria. Data regarding the achievement of individualized glycemic targets in type 2 diabetes mellitus (T2DM) patients is scant in Iran. We intended to provide information found on real-world outcomes from the perspective of an individualized recommendation.

Methods: A cross-sectional analysis was conducted in 15 diabetes centers in Iran between 2013-2017. Two steps cluster sampling selection was used to recruit 1591 patients with T2DM. Considering Ismail-Beigi's individualized strategy, the study population was categorized into five treatment intensities of HbA1c: most intensive ($\leq 6.5\%$), intensive (6.5–7.0%), less intensive (~7.0%), not intensive (7.0–8.0%), and moderated (~8.0%). The percentage of patients who met their group individualized glycemic targets was estimated as the degree of achievement of each treatment intensity.

Results: The cumulative incidence rate of early microvascular, advanced microvascular, and macrovascular complications was 53%, 25%, and 34%, respectively. Besides, 78% [77.6-79%] of patients did not achieve individualized glycemic targets.

Conclusion: The outcome showed poor individualized glycemic control and a high incidence of diabetes complications. Considering individualized HbA1c targets for Iranian patients with T2DM is an urgent need.

Kew Words: anxiety stress fear; Covid-19; hospitalization recurrence;

Introduction

The foremost step in managing type 2 diabetes mellitus (T2DM) is targeting glycemic goals. [1,2], In Iran, the golden target of hemoglobin A1C (HbA1c) for managing T2DM is $<7.0\%$, the same as the American Diabetic Association (ADA) guideline recommendation. [3,4] Patients with poorly controlled blood glucose are endangered with an increased risk of atherosclerotic cardiovascular disease (CVD) and microvascular disease. [5] A secondary prospective cohort analysis [6] and a comprehensive review⁷ have proposed the optimization treatment strategies to prevent diabetes complications. Moreover, in the last decade, clinical guidelines and expert committees have recommended that HbA1C should be individualized based on various criteria, including duration of diabetes, diabetic complications, socio-economic characteristics, comorbid conditions, life expectancy, and history of hypoglycemia. [8-10] According to Ismail-Beigi and others, the glycemic target (HbA1c) range for T2DM patients should be individualized based on age, diabetes duration, macrovascular and microvascular complications, and propensity for

hypoglycemia. ¹¹ Furthermore, careful consideration must be given to each patient's capacities, desires, values, living situations, support systems, cognitive status, overall prognosis, and life expectancy. Consequently, glycemic targets should not be viewed as tight goals; they should be flexible and adaptable to changes based on patients' health and living conditions. [12] The result of a patient-level Monte Carlo-based Markov model also showed that individualized control was a cost-saving scenario and would generate more Quality Adjusted Life Years (QALYs) than uniform intensive control (HbA1c level $<7\%$) for the US T2DM population from a health care sector perspective. [13]

Iranian diabetic patients are expected to reach 5.2 million in 2025. [14] A previous study reported that Iranian patients with T2DM exert a significant burden on the healthcare system. ¹⁵ Additionally, the Iranian diabetes population has a high prevalence of long-standing diabetes and microvascular complications. [7] Analyzing the real-world outcome of the traditional guideline is vital before calling for any amendment in the

treatment of T2DM. To the best of our knowledge, this study is the first evaluation in Iran to compare the real-world health outcome (HbA1c results) from the perspective of a personalized strategy.

Materials and Methods

Study Design

Clinical data extraction was performed from paper and electronic records at 15 diabetes centers (public, semi-public [centers related to the social security insurance organization], and private centers) in five provinces in Iran including Tehran, Isfahan, Yazd, Mazandaran, and Kurdistan.

Two-stage cluster sampling was applied to recruit the required sample size: 1) province selection (clusters) and 2) diabetes-center selection in the clusters. Subjects were selected by a random sampling method based on the patient identification number. The entire population was included since the center's statistical population was small.

Subjects were eligible for inclusion in our study if they received diabetic routine care, regular glycemic control visits, laboratory investigations, and antidiabetic medications for at least five years. Written informed consent was taken from those aged 18 or older if they were willing/able to participate in the study.

Ethics approval was obtained from the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.PSRC.REC.1396.1991).

Individualized Strategy

We defined individualized HbA1C targets according to the Ismail-Beigi methodology by considering multi-variables, including HbA1C, duration of diabetes, age, and history of microvascular and macrovascular complications.

Duration of diabetes is defined as the difference between the patient's age and the age of diabetes diagnosis. The short duration was determined as five to ten years; while over ten years was taken as a long duration, and advanced age was considered for subjects aged 75 or older. Macrovascular

complications are regarded as the diagnosis of the following: heart failure, angina, myocardial infarction, and stroke. Advanced microvascular complications are defined as having one or more of the following: receipt of nephrology care (dialysis in the past 12 months), macroalbuminuria (the ratio of albumin to creatinine >300 with CACR test), blindness, severe neuropathy, and amputation.

Treatment intensities (HbA1C targets) were defined based on the chosen individualized recommendations as: most intensive ($\leq 6.5\%$), intensive (6.5–7.0%), less intensive ($\sim 7.0\%$), not intensive (7.0–8.0%), and moderated ($\sim 8.0\%$). The patients were assigned to each treatment intensity, then the percentage of T2DM patients who met their treatment intensity' targets was extracted. Finally, the result of the individualized target was compared with the uniform conventional target (HbA1c < 7%) as a reference to stick to the current recommendations guideline.

Statistical Analysis

Statistical analysis was performed using the STATA software version 14 for Windows (Stata Corp., College Station, TX, US). Based on the results of normality tests, continuous variables (i.e., duration of disease, glycemic indices) are presented either as mean \pm SD, and categorical outcomes (i.e., meeting the preset glycemic targets) are demonstrated as proportions (95% confidence interval [95% CI]) or mean \pm SEM.

Results

Patient Characteristics

In total, 1591 patients with T2DMs were included in this study. Patient characteristics are shown in **table 1**. The mean age was 60, and 58% of patients were women. The mean HbA1C in all patients for five years (2013–17) was 7.56, and 33% had a short disease duration. The cumulative incidence rates of macrovascular, microvascular, and advanced microvascular complications were 34%, 53%, and 25% over five years, respectively. The results showed an increase of 11.5% in the incidence rate of macrovascular complications and 19.43% in early microvascular complications over the period.

Variable	Category	N (%) N=1591	
Sex	Women	925 (58.11)	
	Men	666 (41.86)	
Age (year)	20-44	111 (7)	
	45-65	986 (62)	
	66-75	382 (24)	
	>75	111 (7)	
Diabetes Duration	Short diabetes duration	522 (32.81)	
	Long diabetes duration	1069 (67.19)	
Macrovascular complications	Prevalence	Five-years	183 (11.5)
	Incidence rate	2013	491 (30.86)
		2017	674 (42.36)
Early microvascular complications	Prevalence	Five -years	309 (19.43)

Variable		Category	N (%) N=1591
	Incidence rate	2013	749 (47.07)
		2017	1058 (66.50)
Advanced microvascular complications	Prevalence	Five-years	180 (11.32)
	Incidence rate	2013	313 (19.67)
		2017	493 (30.99)
HbA1c (mean±SD)		Five-years	7.56±1.22
		2013	7.58±1.38
		2017	7.58±1.39

Individualization of Glycemic Targets

Table 1: Clinical and demographic information of type 2 diabetes patients

Using Ismail-Beigi and colleagues strategy and including clinical information, the study population were stratified and simplified in the five treatment intensities (HbA1c target). [11] **Table 2** shows the percentage of the study population from 2013 to 2017 including in each of the five treatment intensities. We calculated the number of patients in each group who had met the group target and the average of the studied population who were in individualized targets. The details of the data are presented in **table 3**.

Treatment intensity (HbA1c target)	Number of patients in each category N (%)				
	2013	2014	2015	2016	2017
Most intensive ($\leq 6.5\%$)	151 (9.54)	137 (8.65)	110 (6.95)	93 (5.87)	85 (5.37)
Intensive (6.5%–7.0%)	410 (25.90)	357 (22.55)	326 (20.59)	295 (18.64)	241 (15.22)
Less intensive (7.0%)	309 (19.52)	338 (21.35)	368 (23.25)	393 (24.83)	425 (26.85)
Not intensive (7.0%–8.0%)	551 (34.81)	578 (36.51)	579 (36.58)	576 (36.39)	573 (36.20)
Moderated (8.0%)	162 (10.23)	173 (10.93)	200 (12.63)	226 (14.28)	259 (16.36)

Meeting Individualized Targets

Table 2: Patients in each treatment intensity category

Treatment intensity (HbA1c target)	The percentages of degree of achievement of individualized HbA1c targets*				
	2013	2014	2015	2016	2017
Most intensive ($\leq 6.5\%$)	25.17	26.28	24.55	18.28	12.94
Intensive (6.5%–7.0%)	17.80	15.97	19.94	15.93	14.94
Less intensive (7.0%)	12.30	13.31	17.12	17.81	20.71

Treatment intensity (HbA _{1c} target)	The percentages of degree of achievement of individualized HbA _{1c} targets*				
	2013	2014	2015	2016	2017
Not intensive (7.0%–8.0%)	32.12	29.93	34.89	33.85	35.43
Moderated (8.0%)	12.35	8.67	11.00	7.96	8.49
The degree of achievement	21.86	20.59	23.94	21.92	22.74
Patient percentages on conventional target ($\leq 7\%$)	32	34	34	31	31

*Percentage of patients who meet HbA_{1c} targets in each Treatment Intensity.

Twenty-one percent of patients (21.8 and 22.7% from 2013 to 2017) met the individualized glycemic targets. At the same time, about 32% (32 and 31% from 2013 to 2017) of the study population were within the target for uniform conventional recommendation ($<7\%$, 53 mmol/mol) (**table 3**).

Discussion

Achievement of individualized HbA_{1c} target levels showed that only one-fifth of patients with T2DM who regularly received diabetic treatment, were adequately controlled (21.88% [22.4-21%]). However, a study in the US¹⁶ showed that 29% and 30% of T2DM patients were out of the target control based on ADA guidelines and the Ismail-Beigi strategy,¹¹ respectively.

Another study conducted by Coons and colleagues reported that the level of glycemic control would be different from targets recommended by traditional guidelines if considering the age and comorbidities of each patient. It accentuated that more studies should be done to develop a methodology to individualize the HbA_{1c} in Canada.¹⁷ These crucial factors regarding traditional guidelines and individualized recommendations bring burning questions about the goal of diabetes translational and quality improvement studies. Studies show that the prevalence of major microvascular complications of T2DM patients in Iran is high.¹⁸ Besides, cardiovascular complications related to diabetes are more frequent in Iran than in other Eastern Mediterranean and Middle Eastern countries.¹⁹ In the same vein, our result showed an increase of 11.5% in the incidence rate of macrovascular complications and 19.43% in early microvascular complications over the study period (**table 1**).

On the other hand, the Iranian diabetes guideline, similar to the ADA guideline, recommends that the HbA_{1c} should be less than 7% for managing T2DM.⁵ However, several studies reported that most patients with T2DM did not reach this target.^{20,21} It is reasonably expected that this inadequate glycemic control will increase diabetes complications, decrease the patient's quality of life, and intensify the disease burden for the patients and the healthcare system. Therefore, we suggest that diabetes guidelines be re-evaluated from various health-related facets, and individualized strategy is one of them.

The data regarding the achievement of individualized HbA_{1c} targets in T2DM patients is scarce in Iran. We intended to provide information illustrating the pharmaceutical health outcome from the perspective of an individualized strategy proposed by Ismail-Beigi and others.¹¹

The central goal of recommendations to individualize glycemic targets (HbA_{1c}) is to increase the health outcomes in the diabetes population. In fact, individualized recommendations encourage more intensive glycemic control for younger T2DM patients with fewer comorbidities to prevent macrovascular and microvascular complications in the long-term and more

relaxed glycemic control for elderly patients and those with the risk of hypoglycemia or those with multiple comorbidities.^{4, 22, 23} Moreover, as part of selecting wisely, the American Geriatric Society has warned about intensive glycemic control in older patients with diabetes by prescribing medications other than metformin.²⁴ Overtreatment in elders means using glucose-lowering medicines (except metformin) to achieve a tight HbA_{1c} target that might surge the risk of hypoglycemia.^{25, 26} Studies showed that older patients with T2DM might have more restricted HbA_{1c} $<7\%$ than younger patients,²⁷ which illustrates overtreatment in some elders according to individualized recommendations.²⁵

Comparing our results with international evidence depicts the need for emergency amendments to Iranian diabetes management and a strong recommendation for considering individualized HbA_{1c} targets. Nevertheless, it is clear that all required conditions for implementing the individualized strategy for managing diabetes, including education, financial resources, and healthcare facilities, must be considered in advance.

Our study had several strengths and limitations. We could declare that this study reflected the outcomes of real-world ongoing clinical practices as the data were collected randomly at the patient level from diabetic clinics. Despite these merits, our study had some limitations. The range of hypoglycemic episodes in over-treated patients was not assessed, as they were not documented in patients' clinical information.

Conclusion

The outcome showed poor individualized glycemic control and a high incidence of diabetes complications in the population with T2DM in Iran. Considering individualized HbA_{1c} targets for Iranian patients with T2DM is an urgent need.

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Authors' Contribution

AS, YB, MD, AA, AE, SY: the conception and design of the work, interpretation of the data, drafting of the article. All authors approved the present version of the manuscript. All authors agreed on being accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest:

None declared.

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