

Journal of Acute Disease



journal homepage: www.jadweb.org

doi: 10.4103/2221-6189.254430

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Long-term diabetes-related severe complications among individuals with T2DM in Jazan, Saudi Arabia

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ARTICLE INFO

ABSTRACT

Article history: Received 29 December 2018 Revision 25 January 2019 Accepted 4 March 2019 Available online 20 March 2019

Keywords: T2DM Diabetes Complications Jazan **Objective:** To explore the patterns and prevalence of complications of type 2 diabetes mellitus (T2DM) in Jazan region. Methods: A cross-sectional study was conducted with a sample (n=281) of the Jazan population attending Jazan Diabetes Centre. A structured questionnaire was used for data collection, and the statistical analysis was performed using SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA) software. Results: The prevalence of one or more complications due to T2DM was 42.7%, which was significantly increased with age, BMI and T2DM duration. The prevalence also differed significantly according to gender and participation in exercise (P<0.05 for all factors). The prevalence of cardiovascular complications was found to be 7.1%, higher among males (9.4%) than females (4.1%), although the difference was not significant (P>0.05). The prevalence of retinopathy was estimated as 32.4% and significantly differed according to gender, age groups, participation in exercise and BMI categories (P value < 0.05 for all). The multivariate logistic regression analysis suggested that the most important independent predictors of T2DM complications were T2DM duration (11-15 years) (P=0.028, OR=3.54) and having T2DM for more than 15 years (P=0.013, OR=5.38). Conclusions: This study reveals a high prevalence of long-term complications among T2DM patients attending Jazan Diabetes center. T2DM prevention and proper T2DM management strategies are strongly needed to minimize the burden of the disease due to T2DM complications.

1. Introduction

Type 2 diabetes mellitus (T2DM) is considered as one of the most important growing global public health concerns[1]. Recent estimates and projections of WHO suggested that approximately 150 million people are classified as patients with diabetes globally. Moreover, this figure will increase dramatically (103.8%) by the year 2040 for Middle East and North Africa[2,3], and with a large variation between developed and developing countries. Obviously the bulk of cases are located in developing countries.

The long-term complications of diabetes involve the development

of nephropathy, retinopathy, and neuropathy and increased risk of cardiac, peripheral arterial and cerebrovascular disease, which furtherly are associated with increasing cases of disability and premature death^[4,5]. Furthermore, the metabolic dysregulation associated with diabetes mellitus (DM) causes secondary pathophysiologic changes in multiple organ systems that place a tremendous burden on the patients and their families^[6]. The impact of diabetic complications extends from affecting patients and their families to the health care system and macro economy of their

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How to cite this article: Ageely H. Long-term diabetes-related severe complications among individuals with T2DM in Jazan, Saudi Arabia. J Acute Dis 2019; 8(2):72-77.

country[7,8].

Numerous studies have been conducted in Saudi Arabia and have documented an ever-high prevalence of DM in the Saudi community[9-12]. The high prevalence of diabetes is associated with rapid economic development, urbanization and changes in lifestyle modes in this rich country.

Assessing the pattern of complications and their related factors is very important to implement health educational programs and to generate policy initiatives that help in reducing the individual and social burden of diabetes.

Although there are some studies in Jazan focused on different aspects of DM, no previous effort has documented the different types of complications^[13-15]. Hence, this study intended to explore the patterns and prevalence of complications of T2DM in Jazan region.

2. Materials and methods

2.1. Ethics

Ethical aspects of this study were conducted in accord with the general guidelines of the Saudi Bio and medical ethics governance in the KSA. Study protocols and instruments were institutionally approved. An ethical approval (approval # 1760- Jazan Hospital IRB, H-10-Z068) was obtained from the Jazan Ethical Committee. All patients read, understood and signed an informed written consent.

2.2. Study design and location

This observational cross-sectional study was conducted in Jazan town (also called Gizan and Jizan), the provincial capital of Jazan region that is located in the southwestern part of the Kingdom of Saudi Arabia. It is bounded to the north by the Asir region, south by the State of Yemen, east by the Asir region and the State of Yemen, and west by the Red Sea.

2.3. Participants, recruitment and sampling procedure

Participants were recruited during the period from 1 July to 31 August 2017 when patients attended the Jazan Diabetic Centre. Eligibility criteria included: (1) age 18 years and above; (2) diagnosis as T2DM at least six months before the survey; (3) medical records at the centre. Patients who consented to participate in the study were asked to answer the questionnaire. A random sampling of 324 patients was calculated using a prevalence of T2DM (12%) based on a national study^[13], 95% confidence interval, error not more than 5%, and a 25% non-response rate. Systematic random sampling was used to select the study participants.

2.4. Data collection and study instrument

The data were collected by "face-to-face" interviews using a standardized questionnaire. Only the following severe complications were included: cardiovascular conditions, nephropathy, cerebrovascular disease, neuropathy, and diabetic foot. Problems that developed after the proper diagnosis of T2DM and could be attributed to diabetes were considered in this study. Cardiovascular morbidity included angina, chronic heart failure, myocardial infarction, other related heart diseases, and peripheral vascular disease. Patients were first asked about the different complications, and then their data were extracted from the medical records.

2.5. Statistical analysis

Data analysis involved descriptive statistics as well as inferential statistics. Simple tabulation and frequencies were utilized to give a general overview of the data, and numerical data were presented in the form of means. Student's *t* test was used to compare numerical data. The *chi*-square test or Fisher's exact test was used to evaluate the proportion differences among sub-groups. Crude odds ratios were obtained by univariate analysis to determine the association of each variable with T2DM. All statistical tests were two-sided, and P<0.05 was considered to indicate statistical significance. The statistical analysis was performed using SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA) software.

3. Results

A total of 281 people with T2DM were included (for a rate of 86.8%, for practical reasons). The mean HbA1c and BMI values among the study participants were 9.24 kg/m² and 28.79 kg/m² respectively. The main sociodemographic and health indicators of the participants showed that the majority of the study participants (42.0%) were in the age group of 45-59 years. Acording to mode of living the distribution of T2DM patients showed that 44.3% of them were from rural areas and 55.7% from urban areas. The marital status distribution showed that 79.0% of them were married, while only 10.0% of them were single. The physical activity distribution showed that only 36.5% of them were exercising regularly. Levels of HbA1c were not significantly associated with all variables shown in Table 1 (P>0.05 for all). Further, there were no significant associations between BMI and the rest of the table factors, except for educational levels.

Table 1

Sociodemographic characteristics and complication risk factors of the T2DM patients.

Variables	$n^{\#}$	%	Mean HbA1c Mean BM	
			(%)	(kg/m^2)
Gender (n=281)				
Male	160	56.9	9.22	27.22
Female	121	43.1	9.25	30.74
Age groups (n=281)				
Less than 45 years	83	29.5	8.92	28.80
45-59 years	118	42.0	9.46	29.25
60 years and more	80	28.5	9.17	28.09
Marital status (n=281)				
Single	28	10.0	10.01	25.84
Married	222	79.0	8.96	29.09
Divorced	4	1.4	9.87	30.03
Widowed	27	9.6	9.80	29.15
Educational Level (n=277))			
Illiterate	85	30.7	9.38	29.92
Can read and write	21	7.6	9.70	25.46
Primary	18	6.5	8.85	32.14
Intermediate	22	7.9	9.75	28.43
Secondary	64	23.1	9.46	27.12
University and above	67	24.2	8.64	29.21
Residence (n=273)				
Rural	121	44.3	9.30	28.32
Urban	152	55.7	9.23	29.20
Tobacco Use (n=280)				
Yes	34	12.1	10.26	28.40
No	246	87.9	9.16	28.86
Khat use $(n=278)$				
Yes	45	16.2	10.21	27.51
No	233	83.8	9.17	29.07
Any Exercise (n=263)				
Yes	96	36.5	8.79	27.92
No	167	63.5	9.42	29.24
T2DM Duration (n=274)				
1-5 years	82	29.9	9.08	29.05
6-10 years	85	31.0	9.13	29.57
11-15 years	55	20.1	9.83	28.40
16-20 years	22	8.0	8.59	26.81
More than 20 years	30	10.9	9.94	27.59
Overall	281	100	9.24	28.79

Some categories do not add to 281 due to different responses.

Table 2 displays the prevalence of the severe complications according to some selected characteristics. The prevalence of cardiovascular complications was found to be 7.1% among the study participants and was higher among males (15, 9.4%) than among females (5, 4.1%) but without a significant difference (P<0.05). Cardiovascular complications varied between different age groups and BMI categories significantly (P<0.05 for both). The overall prevalence of retinopathy was estimated as high as 32.4% and differed significantly according to gender, age group, exercise participation and BMI category (P<0.05 for all). Foot disease was significantly higher among females than males and increased with BMI (P<0.05 for both). The proportion of study participants with at least one complication was 42.7% and differed significantly according to gender, age group, exercise participation and BMI category (P<0.05 for all factors).

Table 3 illustrates the factors associated with coronary artery disease (CAD) complication among T2DM subjects. Age 45-59 years was found to be significantly associated with increased risk of CAD among T2DM patients (P=0.027, OR=10.15), followed by T2DM duration (more than 20 years), which were also found to be significant predictor risk factors for the development of CAD among T2DM patients (P=0.027, OR=12.46).

Table 3

Factors associated with CAD complication among T2DM subjects.

Variables	Estimate	SE	OR (95% CD)	P value
Age groups				
Less than 45 years (reference)				
45-59 years	2.318	1.048	10.15(1.30-79.20)	0.027
60 years and more	1.894	1.092	6.65(0.78-65.52)	0.083
T2DM Duration			· · · · ·	
1-5 years (reference)				
6-10 years	1.622	1.107	5.06 (0.58-44.30)	0.143
11-15 years	2.624	1.076	13.79(1.60-113.69)	0.015
16- 20 years	1.350	1.435	3.86(0.23-64.26)	0.347
More than 20 years	2.523	1.141	12.46(1.33-116.52)	0.027
HbA1c	0.196	0.155	1.23(0.90-1.65)	0.205
Triglyceride	0.005	0.002	1.01(1.00-101.00)	0.033
Cholesterol-total	-0.004	0.005	1.00(0.97-1.01)	0.464

The duration of T2DM and the increase in age were the best predictors for the development of retinopathy. HbA1c was also found to be positively associated with retinopathy (P=0.045, OR=1.16) (Table 4).

Table 4

Factors associated with retinopathy complication among T2DM subjects.

Variables	Estimate	SE	OR (95% CI)	P value
Age groups				
Less than 45 years (reference)				
45-59 years	0.912	0.337	2.49(1.27-4.82)	0.007
60 years and more	0.974	0.361	2.65(1.31-5.37)	0.007
T2DM duration				
1-5 years (reference)				
6-10 years	0.652	0.363	1.92(0.94-3.91)	0.072
11-15 years	0.857	0.395	2.36(1.07-5.12)	0.030
16- 20 years	1.599	0.511	4.95(1.82-13.47)	0.002
More than 20 years	0.871	0.470	2.39(0.95-6.00)	0.064
HbA1c	0.154	0.077	1.16(1.00-1.36)	0.045
Triglyceride	0.003	0.002	1.00(1.00-1.01)	0.065
Cholesterol-total	0.003	0.003	1.00(0.99-1.01)	0.216

Regarding foot disease, duration of T2DM was found to be the most important predictor, as shown for 11-15 years (P=0.032, OR=5.83), 16-20 years (P=0.005, OR=11.77) and more than 20 years (P=0.003, OR=12.17). Although an association was found between HbA1c and CAD and foot diseases (OR=1.23 and 1.04, respectively), the difference was not significant (P=0.205 and 0.640, respectively). Triglyceride was also found to be a predictor for CAD and foot disease (P= 0.033 and 0.003)(Table 5).

Table 2

Distribution of common chronic complications according to some selected characteristics [n(%)].

Parameter	Characteristic	n	Cardiovascular disease	Retinopathy	Nephropathy	Foot disease	Overall
Gender	Male	160	15(9.4)	20(12.5)	3(1.9)	8(5.0)	36(22.5)
	Female	121	5(4.1)	71(58.7)	4(3.3)	21(17.4)	84(69.4)
	χ^2		2.865	67.090	0.596	11.360	61.994
	P value		0.091	0.000 1	0.440	0.001	0.000 1
Age groups	Less than 45 years	83	1(1.2)	16(19.3)	1(1.2)	7(8.4)	25(30.1)
	45-59 years	118	13(11.0)	44(37.3)	2(1.7)	13(11.0)	58(49.2)
	60 years and more	80	6(7.5)	31(38.8)	4(5.0)	9(11.3)	37(46.3)
	χ^2		7.121	9.288	2.917	0.456	7.788
	P value		0.028	0.010	0.233	0.796	0.020
Any exercise	Yes	96	3(3.1)	23(24.0)	1(1.1)	6(6.3)	32(33.3)
	No	167	13(7.8)	66(39.5)	5(3.0)	22(13.2)	81(48.5)
	χ ²		2.316	6.594	1.020	3.072	5.724
	P value		0.128	0.010	0.313	0.088	0.017
BMI categories	Underweight	4	0(0.0)	2(50.0)	0(0.0)	2(50.0)	3(75.0)
	Normal weight	73	2(2.7)	15(20.5)	0(0.0)	7(9.6)	18(24.7)
	Overweight	85	9(10.6)	28(32.9)	2(2.4)	6(7.1)	39(45.9)
	Obese	108	7(6.5)	45(41.7)	3(2.8)	12(11.1)	56(51.9)
	χ^2		4.202	9.251	2.053	8.090	15.436
	P value		0.024	0.026	0.561	0.004 4	0.001
Overall prevalence		281	20(7.1)	91(32.4)	7(2.5)	29(10.3)	120(42.7)

Table 5

Factors associated with foot disease complication among T2DM subjects.

Variables	Estimate	SE	OR (95% CI)	P value
T2DM duration				
1-5 years (reference)				
6-10 years	1.111	0.832	3.04(0.59-15.51)	0.182
11-15 years	1.764	0.822	5.83(1.16-29.23)	0.032
16- 20 years	2.465	0.878	11.77(2.10-65.79)	0.005
More than 20 years	2.499	0.836	12.17(2.37-62.66)	0.003
HbA1c	0.046	0.098	1.04(0.86-1.27)	0.640
Triglyceride	0.006	0.002	1.01(1.00-1.01)	0.003
Cholesterol-total	0.007	0.004	1.01(1.00-1.02)	0.066

The results of the univariate and multivariate logistic regression analyses for the potential risk factors of T2DM complications among the study participants are shown in Table 6. Univariate analysis revealed that the increase in age and the T2DM duration were associated with a significant risk for having at least one T2DM complication (P<0.05 for all). The multivariate logistic regression analysis suggested that the most important independent predictors of

Table 6

Univariate and multivariate logistic regression analyses for T2DM complication-related factors among study participants

Variables		Univariate		Multivariate		
	Estimate	OR (95% CI)	P value	Estimate	OR (95% CI)	P value
Age groups						
>45 years (reference)						
45-59 years	0.808	2.24(1.24-4.05)	0.007	0.106	1.11(0.35-3.50)	0.856
60 years and more	0.691	2.00(1.05-3.79)	0.035	0.598	1.82(0.66-5.20)	0.265
T2DM duration						
1-5 years (reference)						
6-10 years	0.60	1.82(0.95-3.50)	0.073	0.612	1.84 (0.70-4.83)	0.213
11-15 years	1.33	3.80(1.84-7.84)	0.000	1.264	3.54(1.15-10.90)	0.028
More than 15 years	1.19	3.27(1.24-8.64)	0.017	1.682	5.38(1.43-20.23)	0.013
HbA1c	0.16	1.17(0.99-1.37)	0.053	0.107	1.11(0.98-1.00)	0.382
Triglyceride	0.00	1.00(1.00-1.01)	0.085	0.004	1.00(0.99-1.01)	0.165
Cholesterol-total	0.00	1.03(0.99-1.00)	0.301	0.005	1.00(0.99-1.01)	0.267

T2DM complications among our samples were T2DM duration (11-15 years) (P=0.028, OR=3.54), and having T2DM for more than 15 years (P=0.013, OR=5.38).

4. Discussion

With the increase of prevalence of DM currently, we are facing an increase in the long-term complications of DM, a development considered a major public health problem. All types of DM are associated with the development of diabetes-specific complications. The aim of this study was to explore the patterns and prevalence of long-term complications of T2DM in Jazan region. The present study was designed to fill the gap regarding this important issue in Jazan, southwest Saudi Arabia.

The present study revealed that overall, 120 (42.7%) participants with T2DM had at least one diagnosed severe complication, which indicates that severe complications of T2DM exert a huge burden on the health care system in Saudi Arabia. This estimate is much lower than most studies conducted in the KSA[16] and studies conducted in Arab countries[17,18] and globally[19-21].

This study also found that cardiovascular conditions constituted a predominant chronic condition among T2DM patients in Jazan over other morbidities. Studies carried out in the KSA[22] and elsewhere also pointed to cardiovascular conditions as the predominant severe complication of T2DM[21,23].

The present study revealed a prevalence of diabetic retinopathy higher than that of studies conducted in the KSA[22] and Arab countries[18]. Regarding the prevalence of foot diseases, it was found that its prevalence was higher than in most of the global studies[19,20,24]. These differences may be attributed to data collection methods and the study scales.

The link between high glycemic control and the high prevalence of DM complications in patients with T2DM is well established elsewhere[18,20,25]. Our findings reinforce the well-known phenomenon that T2DM complications are strongly related to duration of diabetes as the multivariate analyses results suggested that the most important independent predictor of T2DM complications among our sample was T2DM duration, a welldocumented fact in most clinical literature[19,20,24,26].

This study was based on a cross-sectional study design; thus, its results should be interpreted in this context regarding the different associations described. In addition, the study was based on a single diabetic center, which may affect the generalizability of the study results. Despite these limitations, the findings from this study are useful for policymakers planning the development of diabetes services in Saudi Arabia.

In conclusion, this study revealed a high prevalence of long-term complications among T2DM patients attending the Jazan Diabetes Center. The associations between severe complications and age and the duration of T2DM were well documented. T2DM prevention and proper management of T2DM strategies are strongly needed to minimize the burden of disease due to T2DM complications.

Conflict of interest statement

The author reports no conflict of interest.

Acknowledgments

The author would like to thank the Jazan Diabetes Centre for the use of the medical dataset. In addition, the author would like to thank all study participants who participated in this study.

References

- World Health Organization. *Global report on diabetes*. Geneva, Switzerland: World Health Organization; 2016.
- [2] Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010; 87(1): 4-14.
- [3] Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract* 2017; **128**: 40-50.
- [4] International Diabetes Federation. *IDF diabetes atlas*. 6th ed. Brussels, Belgium: International Diabetes Federation; 2013.
- [5] IDF Diabetes Atlas Group. Update of mortality attributable to diabetes for the IDF Diabetes Atlas: estimates for the year 2011. *Diabetes Res Clin Pract* 2013; **100**(2): 277-279.
- [6] Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *Lancet* 2014; **383**(9922): 1068-1083.
- [7] American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care* 2013; 36(4): 1033-1046.
- [8] Alhowaish AK. Economic costs of diabetes in Saudi Arabia. J Family Community Med 2013; 20(1): 1-7.
- [9] Alqurashi KA, Aljabri KS, Bokhari SA. Prevalence of diabetes mellitus in a Saudi community. Ann Saudi Med 2011; 31(1): 19-23.
- [10]Khaild Al-Rubeaan. National surveillance for type 1, T2DM diabetes and prediabetes among children and adolescents: a population-based study (SAUDI-DM). *J Epidemiol Commun Health* 2015; **69**(11): 1045-1051.
- [11]Al-Baghli NA, Al-Ghamdi AJ, Al-Turki KA, Al Elq AH, El-Zubaier AG, Bahnassy A. Prevalence of diabetes mellitus and impaired fasting glucose levels in the Eastern Province of Saudi Arabia: results of a screening campaign. *Singapore Med J* 2010; **51**(12): 923-930.
- [12]Al-Rubeaan K, Al-Manaa HA, Khoja TA, Ahmad NA, Al-Sharqawi AH, Siddiqui K, et al. Epidemiology of abnormal glucose metabolism in a country facing its epidemic: SAUDI-DM study. *J Diabetes* 2015; 7(5): 622-632.
- [13]Bani IA. Prevalence, knowledge, attitude and practices of diabetes mellitus among Jazan population, Kingdom of Saudi Arabia (KSA). J Diabetes Mellitus 2015; 5(02): 115.
- [14]Solan YM, Kheir HM, Mahfouz MS, Al-Faify AA, Hakami DT, Al Faifi MA, et al. Diabetic foot care: Knowledge and practice. J Endocrinol Metabol 2017; 6(6): 172-177.
- [15]Badedi M, Solan Y, Darraj H, Sabai A, Mahfouz M, Alamodi S, et al. Factors associated with long-term control of T2DM diabetes mellitus. J Diabetes Res 2016; 2: 1-8.
- [16]Khan AR, Lateef ZN, Fatima S, Al Yousuf SA, Afghan SZ, Al Marghani S. Prevalence of chronic complication among type 2 diabetics attending primary health care centers of Al Ahsa district of Saudi Arabia: a cross sectional survey. *Clob J Health Sci* 2014; 6(4): 245-253.

- [17]Hajat C, Harrison O, Al Siksek Z. Weqaya: a population-wide cardiovascular screening program in Abu Dhabi, United Arab Emirates. *Am J Public Health* 2012; **102**(5): 909-914.
- [18]Jelinek HF, Osman WM, Khandoker AH, Khalaf K, Lee S, Almahmeed W, et al. Clinical profiles, comorbidities and complications of type 2 diabetes mellitus in patients from United Arab Emirates. *BMJ Open Diabetes Res Care* 2017; 5(1): e000427.
- [19]Djrolo F, Paraïso NM, Diarra O, Makoutode M. Diabetes complications and associated factors in type 2 diabetic patients in Cotonou. *J Diabetes Mellitus* 2014; 4(04): 311.
- [20]Liu Z, Fu C, Wang W, Xu B. Prevalence of chronic complications of type 2 diabetes mellitus in outpatients-a cross-sectional hospital based survey in urban China. *Health Qual Life Outcomes* 2010; 8(1): 62.
- [21]Morgan CL, Currie CJ, Stott NC, Smithers M, Butler CC, Peters JR. The prevalence of multiple diabetes-related complications. *Diabet Med* 2000; 17(2): 146-151.

- [22]Shi W, LI X, LI J. The morbidity of chronic diabetic complication with logistic analysis of related potential factor. *Chin J Epidemiol* 2004; **25**(1): 60-64.
- [23]Ammari F. Long-term complications of type 1 diabetes mellitus in the western area of Saudi Arabia. *Diabetologia Croatica* 2004; 33(2): 59-63.
- [24]McNeely MJ, Boyko EJ: Diabetes-related comorbidities in Asian Americans: results of a national health survey. J Diabetes Complications 2005; 19(2): 101-106.
- [25]Albasheer OB, Mahfouz MS, Solan Y, Khan DA, Muqri MA, Almutairi HA, et al. Depression and related risk factors among patients with type 2 diabetes mellitus, Jazan area, KSA: A cross-sectional study. *Diabetes Metab Syndr* 2017; **12**(2): 117-121.
- [26]Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; **321**(7258): 405-412.