

CHINESE MEDICAL SCIENCES JOURNAL

ORIGINAL ARTICLE

Clinical Characteristics of 261 Cases of Hospitalized Patients with Type 1 Diabetes Mellitus[△]

Jing Yang^{1,2}, Mei-cen Zhou², Kai Feng², Ou Wang², Hua-bing Zhang²,
Wei Li², Fan Ping², Jing Yang³, and Yu-xiu Li^{2*}

¹First Clinical Medical College, Shanxi Medical University, Taiyuan 030001, China

²Department of Endocrinology, Key Laboratory of Endocrinology of the Ministry of Health, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China

³Department of Endocrinology, First Hospital of Shanxi Medical University, Taiyuan 030001, China

Key words: type 1 diabetes mellitus; adult-onset type 1 diabetes mellitus; islet function; islet-related autoantibody; hospitalization time

Objective To retrospectively analyze the clinical characteristics of 261 cases of hospitalized patients with type 1 diabetes mellitus (T1DM) in Peking Union Medical College Hospital (PUMCH).

Methods Clinical data of 261 cases of hospitalized patients diagnosed with T1DM in the Department of Endocrinology at PUMCH from January 2007 to December 2014 were analyzed retrospectively. All patients were divided into the T1DM antibodies positive group ($n=180$) and negative group ($n=81$) according to the results of immunohistochemistry, in which 123 newly diagnosed T1DM patients were divided into the adult onset group (>18 years, $n=58$) and non-adult onset group (≤ 18 years, $n=65$) according to the onset age of T1DM, respectively. The clinical characteristics from different groups were compared.

Results In 261 patients, the average age was 26.6 ± 15.4 years, the average disease duration was 49 (1-480) months, the positive rate of antibodies to glutamic acid decarboxylase antibody was 58.8% (153/260). The level of 2-hour postprandial C peptide and the positive rate of T1DM antibodies in the non-adult onset group were higher than those in the adult onset group (0.98 vs. 0.52 ng/ml, $P=0.002$ and 80.4% vs. 62.5%, $P=0.048$). The age of onset in the T1DM antibodies positive group was smaller than that in the T1DM antibodies negative group (19.7 ± 11.4 vs. 24.7 ± 15.6 years, $P=0.04$), while the incidence of ketosis in the T1DM antibodies positive group was higher than that in the T1DM antibodies negative group (48.3% vs. 34.2%, $P=0.035$). With the progress of the disease, the fasting C peptide level of the T1DM antibodies positive group decreased more rapidly. Compared with the single time hospitalized patients, multiple

hospitalized patients had a lower incidence of diabetic retinopathy (8.2% vs. 22.4%, $P=0.032$), a lower hemoglobin A_{1c} level ($8.04\% \pm 2.10\%$ vs. $9.56\% \pm 2.64\%$, $P<0.001$) and fasting blood glucose level (8.7 ± 3.1 vs. 10.9 ± 4.2 mmol/L, $P<0.001$).

Conclusions Compared with the non-adult onset T1DM patients, the islet function of adult onset patients was even worse. In the T1DM antibodies positive patients, the islet β cell function decreased more rapidly, so the antibodies could not only clarify the diagnosis of T1DM and also predict prognosis of the islet β cell function. In the management of T1DM patients, regular hospital revisits contributed to get better glycemic control and reduced the occurrence of diabetic complications.

Chin Med Sci J 2016; 31(2):69-75

TYPE 1 diabetes mellitus (T1DM) which is an autoimmune disease characterized by destruction of pancreatic islet β cell leads to absolute insulin deficiency and hyperglycemia. According to the International Diabetes Federation (IDF), the prevalence of T1DM is increasing worldwide at the rate of 3%-5% per year.¹ China has a large number of T1DM patients, although the incidence rate of the disease is relatively low.² The onset ages of T1DM were mostly at childhood or teenage, whereas the adult-onset T1DM was becoming more and more common nowadays.³⁻⁵ However fewer studies have focused on the population with adult-onset T1DM. In this study, we retrospectively analyzed the clinical data of 261 cases of hospitalized patients diagnosed with T1DM in the Department of Endocrinology at Peking Union Medical College Hospital (PUMCH) from January 2007 to December 2014, and summarized the clinical characteristics of T1DM, as well as explored the islet β cell function in T1DM, especially in patients with adult onset and islet-related antibodies positive.

PATIENTS AND METHODS

Patients

We searched the document system by the term "type 1 diabetes mellitus" at PUMCH from January 2007 to December 2014 and found 349 cases of hospitalized patients diagnosed with T1DM in the Department of Endocrinology. Studies excluded 36 patients without clinical data, 28 patients without the results of islet-related antibodies, 11 patients in pregnancy, and 13 patients diagnosed with type 1B diabetes mellitus. Finally, the clinical data of 261 cases, including 210 cases with a one-time inpatient record and 51 cases with more than one inpatient record, were retrospectively analyzed.

All patients were divided into the T1DM antibodies positive group ($n=180$) and negative group ($n=81$) according to the results of immunohistochemistry, in which

123 newly diagnosed patients were divided into the adult onset group (>18 years, $n=58$) and non-adult onset group (≤ 18 years, $n=65$) according to the onset age of T1DM, respectively. Individual with disease duration less than 1 year was diagnosed as the newly diagnosed T1DM.

Clinical measurements

The general demographic characters were recorded, including T1DM onset age, disease duration, the incidence of diabetic ketoacidosis (DKA), family history of diabetes, complications including diabetes microvascular and macrovascular diseases. The first time inpatient medical records were taken as the baseline data for patients with multiple hospitalizations.

The laboratory examination included hemoglobin A_{1c} (HbA_{1c}), fasting blood glucose (FBG), fasting C peptide (FCP), postprandial 2-hour C peptide (2h CP), cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and T1DM antibodies such as glutamic acid decarboxylase antibody (GADA), islet cell cytoplasmic antibodies (ICA), insulin auto antibody (IAA), insulinoma-associated 2 molecule antibody (IA-2A). The C peptide level was determined using chemiluminescent quantitative immunoassay kit (Siemens, Japan). ICA antibody was measured by indirect immunofluorescence (Euroimmun, Germany), and IAA, GADA, IA-2A antibodies were measured by an enzyme-linked immunosorbent assay (Euroimmun). TC, TG, LDL-C, HDL-C levels were determined using Beckmen AU automatic biochemical analyzer (Beckmen, USA).

Statistical analysis

Statistical analyses were performed using SPSS software, version 22.0 (Chicago, IL, USA). Continuous variables were presented as means $\pm$ standard deviation. Parameters not normally distributed were presented as median (minimum, maximum). Categorical data were analyzed using χ^2 test. The significance of the mean differences was tested by t

test. All P values were two-sided, and $P<0.05$ was considered statistically significant.

RESULTS

Clinical characteristics of T1DM patients

Among the 261 T1DM patients, the average of hospitalization age was 26.6 ± 15.4 years, the age of onset was 22.5 ± 14.3 years, the average disease duration was 49 (1-480) months, body mass index (BMI) was 19.8 ± 3.3 kg/m², and 44 (16.8%) cases had a family history, 109 (41.8%) cases had DKA onset, 153 (58.8%) cases had GADA antibody positive (Table 1). The 51 multiple hospitalized patients took the first hospitalized data as the baseline data.

Comparison of clinical characteristics between the adult onset group and non-adult onset group

Among the 123 newly diagnosed patients, the percentage of urban residents in the adult onset group was more than that in the non-adult onset group ($P=0.011$). The systolic blood pressure, diastolic blood pressure, and BMI in the non-adult onset patients were significantly lower than those in the adult onset group (all $P<0.001$). The 2-h CP in the non-adult onset group was higher than that in the adult onset group ($P=0.002$). The positive rate of ICA in the non-adult onset group was higher than that in the adult onset group ($P=0.027$), and there was no significant difference in IAA, IA-2A and GADA between the two groups. There was no significant difference in the therapy methods on T1DM patients between the two groups. (Table 2)

Comparison of clinical characteristics between the islet-related antibodies positive group and antibodies negative group

The average age, the onset age and the disease duration in the antibody positive group were significantly lower than those in the negative group (all $P<0.05$). The family history, systolic blood pressure, diastolic blood pressure, BMI, TC, HDL-C, LDL-C between the two groups were not significantly different (all $P>0.05$). The patients in the antibodies positive group were more susceptible to ketosis than those in the negative group ($P=0.035$), but the incidence of DKA between the two groups was not significantly different ($P=0.314$). (Table 3)

All patients were divided into subgroups according to the disease duration and antibodies as following: (1) short disease duration group (< 1 years): 91 patients in the antibodies positive subgroup, 32 patients in the antibodies

Table 1. Clinical characteristics of T1DM patients ($n=261$)

Items	Values
Sex (female/male, n)	132/129
Urban residents (%)	78.5
Age [§] (yrs)	26.6 ± 15.4
Onset age [§] (yrs)	22.5 ± 14.3
BMI [§] (kg/m ²)	19.8 ± 3.3
Diabetes duration (months)	49
Systolic blood pressure [§] (mm Hg)	109 ± 16
Diastolic blood pressure [§] (mm Hg)	70 ± 10
HbA1c [§] (%)	10.2 ± 2.8
FCP (ng/ml)	0.3 (0-1.4)
2-h CP (ng/ml)	0.57 (0-2.43)
ICA (%)	31.2 (76/243)
GADA (%)	58.8 (153/260)
IAA (%)	13.9 (24/172)
IA-2A (%)	40.9 (27/66)
TC [§] (mmol/L)	4.54 ± 1.05
TG [§] (mmol/L)	1.05 ± 0.85
HDL-C [§] (mmol/L)	1.51 ± 0.58
LDL-C [§] (mmol/L)	2.59 ± 0.95
DKA (%)	41.8
Ketosis (%)	41.8
Family history (%)	16.8
Diabetic retinopathy (%)	13.1
Diabetic nephropathy (%)	8.2
Diabetic peripheral neuropathy (%)	14.3
Diabetic autonomic neuropathy (%)	5.7
Hypertension (%)	6.1
Dyslipidemia (%)	13.9

§: Plus-minus values are means $\pm$ SD.

T1DM: type 1 diabetes mellitus; BMI: body mass index; HbA1c: hemoglobin A1c; FCP: fasting C peptide; 2-h CP: postprandial 2-hour C peptide; ICA: islet cell cytoplasmic antibodies; GADA: glutamic acid decarboxylase antibody; IAA: insulin antibody; IA-2A: insulinoma-associated 2 molecule antibody; TC: total cholesterol; TG: triglyceride; HDL-C: high density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; DKA: diabetic ketoacidosis.

negative subgroup; (2) middle disease duration group (1-5 years): 54 patients in the antibodies positive subgroup, 22 patients in the antibodies negative subgroup; (3) long disease duration group (>5 years): 35 patients in the antibodies positive subgroup, 27 patients in the antibodies negative subgroup. The FCP in the antibodies positive subgroup was lower than that in the antibodies negative subgroup both in the short disease duration [0.33 (0-0.95) vs. 0.51 (0-1.1) ng/ml, $P=0.015$] and the long disease duration groups [0.05 (0-0.1) vs. 0.14 (0-0.5) ng/ml, $P=0.049$]. And as disease progressed, the positive rate of FCP decreased rapidly.

Comparison of clinical characteristics between the

multiple hospitalized group and single hospitalized group

Totally, 51 T1DM patients (24 males, 27 females) had more than one hospitalized records, whose the last hospitalizing data was taken and compared with 98 patients (49 males, 49 females) in 210 of single hospitalized patients. There was no significant difference in the disease duration between the multiple hospitalized group and single hospitalized group ($P=0.291$). The occurrence of retinopathy, HbA1c and FBG levels were lower in the multiple hospitalized group than those in the single hospitalized group (all $P<0.05$). The incidence of other diabetic complications in the single hospitalized group was higher than that in the multiple hospitalized group, but there was no significant difference (all $P>0.05$). (Table 4)

Table 2. Comparison of clinical characteristics between the adult onset group and non-adult onset group in newly diagnosed T1DM patients

Groups	<i>n</i>	Sex (female/male)	Urban residents (%)	Age [§] (yrs)	Onset age [§] (yrs)	Diabetes duration (months)	BMI [§] (kg/m ²)
Non-adult onset group	65	32/33	68.7	12.1±3.9	11.8±3.9	3.6 (1-12)	17.7±2.6
Adult onset group	58	25/33	88.1	33.4±13.3	33.3±13.8	3.7 (1-12)	20.6±3.0
<i>P</i> value		0.922	0.011	<0.001	<0.001	0.609	<0.001
Groups	<i>n</i>	Systolic pressure [§] (mm Hg)	Diastolic pressure [§] (mm Hg)	HbA1c [§] (%)	FCP (ng/ml)	2-h CP (ng/ml)	ICA [% (<i>n</i>)]
Non-adult onset group	65	100±13	64±9	11.5±3.0	0.49 (0-1.1)	0.98 (0-2.59)	49.2 (32/65)
Adult onset group	58	112±15	73±9	10.7±2.7	0.34 (0-1.4)	0.52 (0-2.43)	30.1 (18/56)
<i>P</i> value		<0.001	<0.001	0.181	0.181	0.002	0.027
Groups	<i>n</i>	GADA [% (<i>n</i>)]	IAA [% (<i>n</i>)]	IA-2A [% (<i>n</i>)]	Autoantibodies positive ^a [% (<i>n</i>)]	TC [§] (mmol/L)	TG [§] (mmol/L)
Non-adult onset group	65	64.6 (42/65)	14.0 (7/50)	68.2 (15/22)	80.4 (41/51)	4.4±0.98	0.90±0.67
Adult onset group	58	62.1 (36/57)	12.1 (4/33)	42.8 (6/14)	62.5 (30/48)	4.3±0.92	1.06±0.61
<i>P</i> value		0.625	0.927	0.163	0.048	0.679	0.068
Groups	<i>n</i>	HDL-C [§] (mmol/L)	LDL-C [§] (mmol/L)	DKA (%)	Ketosis (%)	Family history (%)	Hypertension prevalence (%)
Non-adult onset group	65	1.51±0.48	2.4±0.9	44.6	46.2	9.8	0
Adult onset group	58	1.37±0.45	2.5±0.8	48.3	43.1	14.0	6.9
<i>P</i> value		0.138	0.566	0.440	0.685	0.466	0.118
Groups	<i>n</i>	Hyperlipemia prevalence (%)	Therapy methods (%)				
			Multiple daily injection	Premixed insulin	Insulin pump		
Non-adult onset group	65	7.8	87.2	8.5	4.3		
Adult onset group	58	17.2	95.8	0	4.2		
<i>P</i> value		0.338		0.118			

§: Plus-minus values are means±SD.

^aat last one autoantibodies was positive.

Table 3. Comparison of clinical characteristics in T1DM patients between antibodies positive group and antibodies negative group

Group	<i>n</i>	Sex (female/male)	Urban residents (%)	Age [§] (yrs)	Onset age [§] (yrs)	Diabetes duration (months)	BMI [§] (kg/m ²)
Antibodies positive group	180	91/89	77.8	23.2±13	19.7±11.4	41(1-480)	19.6±3.3
Antibodies negative group	81	35/46	77.8	30.4±16	24.7±15.6	68(1-408)	20.2±2.9
<i>P</i> value		0.55	0.86	0.01	0.04	0.014	0.216
Group	<i>n</i>	Systolic pressure [§] (mm Hg)	Diastolic pressure [§] (mm Hg)	HbA1c [§] (%)	FCP (ng/ml)	2-h CP (ng/ml)	TC [§] (mmol/L)
Antibodies positive group	180	108.7±15.0	69.6±10.0	10.2±2.9	0.2 (0-1.4)	0.4 (0-1.97)	4.4±1.0
Antibodies negative group	81	109.1±16.8	68.9±9.5	9.5±2.7	0.2 (0-1.1)	0.3 (0-1.76)	4.6±1.0
<i>P</i> value		0.945	0.655	0.079	0.645	0.209	0.128
Group	<i>n</i>	TG [§] (mmol/L)	HDL-C [§] (mmol/L)	LDL-C [§] (mmol/L)	Family history (%)	DKA (%)	Ketosis (%)
Antibodies positive group	180	0.96±0.69	1.49±0.54	2.48±0.90	19.0	39.1	48.3
Antibodies negative group	81	1.10±1.70	1.61±0.63	2.66±0.82	13.6	44.6	35.2
<i>P</i> value		0.026	0.133	0.117	0.345	0.314	0.035

§: Plus-minus values are means±SD.

Table 4. Comparison of clinical characteristics in T1DM patients between the multiple hospitalized group and the single hospitalized group

Group	<i>n</i>	Sex (female/male)	Urban residents (%)	Onset age [§] (yrs)	Diabetes duration (months)	HbA1c [§] (%)	FBG [§] (mmol/L)
Multiple hospitalization group	51	27/24	90.2	25.4±15.7	48 (8-600)	8.04±2.10	8.7±3.07
Single hospitalization group	98	49/49	73.4	24.3±12.2	60 (10-480)	9.56±2.64	10.9±4.2
<i>P</i> value		0.733	0.017	0.781	0.291	<0.001	<0.001
Group	<i>n</i>	FCP (ng/ml)	2-h CP (ng/ml)	Diabetic retinopathy (%)	Diabetic nephropathy (%)	Diabetic peripheral neuropathy (%)	Diabetic autonomic neuropathy (%)
Multiple hospitalization group	51	0.06 (0-0.91)	0.085 (0-1.82)	8.2	10.2	16.3	6.1
Single hospitalization group	98	0.10 (0-1.00)	0.055 (0-2.14)	22.4	12.2	25.5	13.3
<i>P</i> value		0.795	0.646	0.032	0.715	0.208	0.19

§: Plus-minus values are means±SD.

FBG: fasting blood glucose.

DISCUSSION

There were 261 cases in this study and the average age was 26.6±15.4 years, the adult patients accounted for 51.9% as a big part in T1DM, which was consistent with Zhao *et al'* study.⁶ The present study showed that the islet

β cell function in the adult onset group was worse than that in the non-adult onset group. This result was not consistent with previous findings. Poudel *et al'*⁷ indicated that the β-cell function in the adult onset group was better than that in the child onset group. The presence of residual β cells at different stages of T1DM has been reported by a large number of studies.⁸⁻⁹ In China, Shao¹⁰ reported that islet β

cell function in patients with adult onset T1DM was better, but Zhang *et al*¹¹ showed that C peptide in the newly diagnosed adult onset T1DM patients was lower. The opposite results might cause by the difference of population distribution, which the patients in Zhang *et al*'s study mostly came from the north, but patients in Shao's study from the southern regions, then the northern patients at diagnosis appeared worse islet β function. The present studies were retrospective study, involving the effect of regional differences on the islets function was less, so more studies and large sample prospective study are needed to confirm. The percentage of urban residents in the adult onset group was 88.1%, which was higher than that in the non-adult onset group. It indicated that adult onset T1DM patients might be affected by regional variation or higher living standards.

Islet-related antibodies play an important role in the diagnosis of T1DM, about 90% of newly diagnosed T1DM patients were antibodies positive reported by Canivell *et al*.¹² In this study, the antibody positive rate was 69.2% in the T1DM patients, which was similar to previous studies.¹³⁻¹⁴ This study found that along with the extension of the disease duration, the islet β cell function in the antibody positive group decreased more faster, which indicated that islet-related antibodies could not only help to clarify the type of diabetes but also predict the islet β cell function. Yang *et al*¹⁵ showed that the titer of GADA could predict the β cell function in latent autoimmune diabetes patients. Similar to this study, the clinical progress of the antibodies positive patients was more quickly, which could be interpreted that antibodies led to β cell function declined rapidly. Ling *et al*¹⁶, Qrtqtist *et al*¹⁷ and Boettler *et al*¹⁸ all suggested GADA was the mark of β cell damage.

In this study, blood glucose control was better in the multiple hospitalized patients than that in the single hospitalized patients, and the incidence of retinopathy was lower. Although there were no significant differences in the incidences of diabetes complications, the incidence of T1DM complications in multiple hospitalized patients was lower. At present, it lacked researches on the effect of multiple hospitalizations on T1DM patients. Due to the long disease duration and complicated disease condition, diabetic patients were prone to suffer from slack mood and heavy psychological burdens,¹⁹⁻²⁰ and these factors made the patients not follow the doctor's advice, which would cause a series of serious adverse consequences. Hospitalized times or long-term outpatient follow-up could improve patient's compliances, maintain better blood glucose level, thereby reducing the occurrence of complications of diabetes. It was recommended that T1DM patients should

be managed, such as regular outpatient follow-up.

This study had some limitations. First, this study was a retrospective study, therefore some data were missing. Second, the major limitation of this study was its small sample number. So the results need further large sample prospective study to confirm.

In conclusion, the islet β cell function of adult onset T1DM patients was worse, but the antibodies positive rate was relatively low, so it was important to detect C peptide in adult onset patients. The decline of islet β cell function in the islet-related antibodies positive patients was quicker, indicating that the islet-related antibodies could not only clarify the diagnosis, and also predict the islet β cell function. In the management of T1DM patients, multiple hospitalization or long-term clinic follow-up could help to maintain better blood glucose control and reduce the occurrence of diabetic complications.

REFERENCES

1. Forlenza GP, Rewers M. The epidemic of type 1 diabetes: what is it telling us? *Curr Opin Endocrinol Diabetes Obes* 2011; 18:248-51.
2. Chinese Diabetes Society. China guideline for type 1 diabetes diagnosis and treatment. Beijing: People's Medical Publishing House; 2012.
3. Nitiyanant W, Tandhanand S, Mahtab H, et al. The Diabcare-Asia 1998 study-outcomes on control and complications in type I and type 2 diabetic patients. *Curr Med Res Opin* 2002; 18:317-27.
4. Mbanya JC, Motala AA, Sobngwi E, et al. Diabetes in sub-Saharan Africa. *Lancet* 2010; 375:2254-66.
5. Li J, Yan J, Luo G, et al. Clinical analysis of 3159 cases type 1 diabetes mellitus in Guangdong province. *Chin J Diabetes Mellitus* 2013; 3:96.
6. Zhao L, Lu Z, Yang G, et al. Clinical characteristic analysis of 742 hospitalized cases with type 1 diabetes mellitus. *Chin J Diabetes Mellitus* 2013; 5:89-93.
7. Poudel A, Savari O, Striegel DA, et al. Beta-cell destruction and preservation in childhood and adult onset type 1 diabetes. *Endocrine* 2015; 49:693-702.
8. Pipeleers D, Chintinne M, Denys B, et al. Restoring a functional beta-cell mass in diabetes. *Diabetes Obes Metab* 2008; 10:54-62.
9. Tsai EB, Sherry NA, Palmer JP, et al. The rise and fall of insulin secretion in type 1 diabetes mellitus. *Diabetologia* 2006; 49:261-70.
10. Shao H. Islet autoantibodies and HLA gene heterogeneity of type 1 diabetes onset at different ages. Changsha: Central South University; 2010.

11. Zhang S, Sun Q, Feng K, et al. Clinical, biochemical, and immunological characteristics of newly diagnosed nonobese diabetic patients aged 18-45 years in China. *J Diabetes Complications* 2012; 26:40-3.
12. Canivell S, Gomis R. Diagnosis and classification of autoimmune diabetes mellitus. *Autoimmun Rev* 2014; 13:403-7.
13. Liu L, Deng H, Weng JP, et al. Prevalence of diabetes autoantibodies in Chinese adult patients with type 1 diabetes mellitus and its relation with beta cell function. 50th European Association for the Study of Diabetes Annual Meeting, Vienna, September 15-19, 2014.
14. Hu LP, Gu P, Zhao M. The clinical significance of serum autoantibodies to pancreatic islet in one thousand and four hundreds patients with diabetes. *J Mod Lab Med* 2006; 21:15-7.
15. Yang L, Zhou ZG, Huang G, et al. Six-year follow-up of pancreatic beta cell function in adults with latent autoimmune diabetes. *World J Gastroenterol* 2005; 11: 2900-5.
16. Ling Z, De Pauw P, Jacobs-Tulleneers-Thevissen D, et al. Plasma GAD65, a marker for early β -cell loss after intraportal islet cell transplantation in diabetic patients. *J Clin Endocrinol Metab* 2015; 100:2314-21.
17. Ortqvist E, Brooks-Worrell B, Lynch K, et al. Changes in GAD65Ab-specific antiidiotypic antibody levels correlate with changes in C-peptide levels and progression to islet cell autoimmunity. *J Clin Endocrinol Metab* 2010; 95:E310-8.
18. Boettler T, Pagni PP, Jaffe R, et al. The clinical and immunological significance of GAD-specific autoantibody and T-cell responses in type 1 diabetes. *J Autoimmun* 2013; 44:40-8.
19. Jones A, Olsen MZ, Perrild HJ, et al. The psychological impact of living with diabetes: descriptive findings from the DAWN2 study in Denmark. *Prim Care Diabetes* 2016; 10:83-6.
20. Hapunda G, Abubakar A, van de Vijver F, et al. Living with type 1 diabetes is challenging for Zambian adolescents: qualitative data on stress, coping with stress and quality of care and life. *BMC Endocr Disord* 2015; 18:15-20.