Clinical and Demographic Features among Patients with Type 1 Diabetes Mellitus in Henan, China

Liguo Yang
First Affiliated Hospital of Zhengzhou University
Guangxing Yang
First Affiliated Hospital of Zhengzhou University
Xialian Li (ylg2385182183@163.com)
First Affiliated Hospital of Zhengzhou University

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Abstract

Background

The hallmark of type 1 diabetes (T1D) is the failure of islet cell. However, many studies showed a tendency to heterogeneity in TID. We aimed to investigate the demographic and clinical characteristics in T1D and the differences in young-onset and adult-onset patients.

Methods

This retrospective study was conducted among 1917 patients with T1D. Medical records on patients' demographics, anthropometric measurements, and clinical manifestation were collected. According to the age at onset, it was divided into the young-onset group (<18 years, 234 patients, mean age 11 years) and adult-onset group (≥18 years, 219 patients, mean age 27 years).

Results

The median age of patients at disease onset was 22 yd. The median duration of patients was 3 years. The overall median HbA1c value was 10.3%. Seventeen percent of patients were overweight or obesity. The frequency of overall dyslipidemia was 37.8%. The most frequent dyslipidemia was low high-density lipoprotein-cholesterol (HDL) (29%). The proportion of patients with anti-glutamic acid decarboxylase (GADA), insulin antibody (IAA) and islet cell antibody (ICA) were 28.0%, 6.4% and 21.6%, respectively. Compared with young-onset T1D, adult-onset patients comprised better islet function and glycemic control, higher prevalence of diabetes condition in the male gender (64.4% VS. 51.3%), higher proportion of obesity or overweight (24.6% VS. 9.5%), higher frequency of GADA (33.7% VS. 23.3%), and lower frequency of HDL (8.8% VS. 16.6%). Increasing or decreasing trends of overweight and obesity in this population during the period 2012 to 2018 was not found.

Conclusion

This population was characterized by poor overall blood glucose control, high prevalence of dyslipidemia and low prevalence of GADA, IAA, ICA. Adult-onset patients with T1D are not uncommon and have better clinical manifestations than young-onset patients.

Background

Type 1 diabetes mellitus (T1D) is a chronic autoimmune disease in which endogenous insulin production is severely compromised by an immune-mediated injury of pancreatic β-cells[1, 2]. The estimations of T1D incidence based on population-based registries showed a steady rise in the incidence all over the world during the past 2 decades[3–7]. The exact pathogenesis of T1D is still unclear. George Eisen Barth put forward a conceptional model for the pathogenesis of T1D before 30 years. It held that both environmental risk and genetic susceptibility promote the development of type 1 diabetes. Based on the model, the accelerator and β-cell stress hypothesis proposed that predisposition, insulin resistance related

to the increase of obesity and immunity lead to β-cell insufficiency[8]. However, the rise in incidence is too rapid to be explained by increased transmission of susceptibility haplotypes from one generation to the next. Furthermore, some studies manifested that as time goes on, high-risk HLA genotypes are becoming not so frequent as before in youth with T1D[9, 10]. Therefore, the increasing environmental pressure plays an increasingly important role in the occurring of T1D. There are many environmental factors, such as Obesity, infant and adult diet, vitamin D deficiency, early exposure to islet immune-related viruses (such as enterovirus) and the decline of intestinal microbial diversity. That is still inconclusive.

T1D is one of the most common chronic diseases of childhood. Considerable heterogeneity exists in epidemiological characteristics of T1D based on ethnicity and country[11–13]. Besides, some studies showed that the clinical and immunologic characteristics of T1D differ significantly between Asian and Caucasian populations[2]. T1D commonly occurs in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life[14]. With up to 50% of cases occur in adulthood[15]. A study in China reported 65.3% cases of new onset T1D occurring among adults[16]. Patients of T1D in different age-onset groups have different demographic and clinical characteristics. Previous studies showed that patients presenting with T1D in adulthood are characterized by a longer symptomatic period before diagnosis, a better preserved β-cell function, and a reduced frequency of IAA, compared with young-onset subjects. In contrast to Caucasians, Asian populations have a very low incidence of T1D. The counterbalancing between protective DQB1 and susceptible DRB1 is a factor that may contribute to the low incidence of diabetes in Asians[2].

According to Multinational Project for Childhood Diabetes (DIAMOND) and the Epidemiological Study of Type 1 Diabetes Mellitus in China (T1D China), the Chinese is among populations with the lowest incidence of T1D [6, 17, 18]. However, in China, a region with large population base, a linear increase in diabetes incidence may lead to a substantial increase in the number of patients with T1D. It will eventually bring about a major increase in the estimated health expenditure which have a great economic impact on individuals and their families[19]. Therefore, it is of great value to investigate the situation of hospitalized patients for recognizing and addressing preventable medical problems. Consequently, we aim to investigate demographic, clinical characteristics of patients with T1D, as well as the pattern of being overweight or obesity changes in Henan in recent years.

Materials And Methods

This study consisted of 1917 patients. These patients were diagnosed with T1D when they were admitted to the First Affiliated Hospital of Zhengzhou University during the period 2012 to 2018. All study patients had a documented diagnosis of T1D. In addition, based on the American Diabetes Association (ADA) descriptions of T1D[20] and the World Health Organization (WHO) reports for the classification of diabetes[21], patients should meet at least 1 of the followings: (1) being dependent on insulin when firstly diagnosed, (2) fasting C-peptide levels < 0.10 ng/ml, (3) diabetic ketoacidosis at disease onset, (4) being positive for one or more of diabetes-related autoantibodies. Thirty-five patients diagnosed with diabetes before age 2 years would be excluded from the analysis because they were very likely to have monogenic

diabetes[22]. Fifty patients were excluded from the study because essential information was deficient. The study was carried out in compliance with the declaration of Helsinki. The study was approved by the Ethical Committee of the First Affiliated Hospital of Zhengzhou University (Number: 2020-KY-417). Because this was a retrospective observational study, and de-identified information was used for the analysis, informed consents were waived as part of the Institutional Review Board of the First Affiliated Hospital of Zhengzhou University approval.

We retrospectively evaluated all newly diagnosed patients' medical records and collected the following information: age, gender, height, weight, family history of diabetes, glycosylated hemoglobin (HbA1c) level, fasting plasma glucose (FPG), fasting and 2-h postprandial serum C-peptide level (FCP and 2-h CP), GADA, ICA, IAA, lipid values, proteinuria, and retinopathy. Newly diagnosed patients were grouped according to age at onset: ≥ 18 years (elder- onset group, 219 patients) and 18 years (young-onset group, 234 patients).

Definition

BMI was calculated using the measured weight (kg) divided by the square of measured height (m). Age-specific and sex-specific BMI criteria for overweight and obese categories for children and adolescents aged 2–18 years were derived from the International Obesity Task Force (IOTF definition). For patients aged > 18 years, overweight and obesity were categorized according to current WHO criteria as BMI ≥ 25 to < 30 kg/m^2 and ≥ 30 kg/m^2, respectively. Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults cut-offs points [TC ≥ 6.22 mmol/l (240 mg/dL), TG ≥ 2.26 mmol/l (200 mg/dL), LDL-C ≥ 4.14 mmol/l (160 mg/dL), HDL-C < 1.04 mmol/l (40 mg/dL)]for adults and Experts Consensus for Prevention and Treatment of Dyslipidemia in Children and Adolescents cut-offs points [TC ≥ 5.18 mmol/l (200 mg/dL), TG ≥ 1.70 mmol/l (150 mg/dL), LDL-C ≥ 3.37 mmol/l (130 mg/dL), HDL-C 1.04 mmol/l (40 mg/dL)]for pediatric patients were adopted. Dyslipidemia was defined by the presence of one or more abnormal serum lipid concentration. Retinopathy was defined by hemangioma, exudation, bleeding, or more serious proliferative lesions on one or both sides of the fundus from retinal photographs. Proteinuria was found in urine routine examination.

Laboratory analysis

Patients were required an overnight (at least 8 h) fasting and their venous blood specimens were collected. GADA, ICA, and IAA were measured using fasting serum with radioimmunoassay. GADA values > 1 IU/l, IAA values > 1% and ICA values > 1 IU/ml were considered positive. FPG was measured by a blood glucose meter. HbA1c was measured by automated liquid chromatography with a normal range of 4.1–6.1%. Lipid profiles were tested by an automatic biochemical analyzer. Beta-cell function was estimated by FCP and 2-h CP values that were tested during an oral glucose tolerance test.

Statistical analysis

All statistical analysis was performed with Statistical Product and Service Solutions (SPSS) version 24.0. All P values of less than 0.05 were regarded as being statistically significant. Participants' characteristics

were defined using descriptive statistics. Continuous variables were presented as mean ± SD or median (25th, 75th quartile). The categorical variables were expressed as number of cases and percentage of patients affected n (%). Spearman rank correlation test for nonparametric statistics and chi-square test for categorical variables were used to examine differences in demographic and clinical characteristics between childhood-onset and adult-onset groups.

Results

Clinical and demographic characteristics of all patients

This analysis consisted of 1917 subjects (767 children and adolescents;1150 adults) with a median age of 26(16,38) years (range 2 years to 83 years). As shown in Table 1, 51.7% of cases were male. The median age of patients at disease onset was 21.9 yd. The median duration of patients was 3 years. Among 1917 patients with T1D, HbA1c values were obtainable in 1703 patients. The overall median (interquartile range) HbA1c value was 10.3 (8.21,12.5) %. Height and weight data were obtainable in 1510 patients. Overall, 17% of participants were overweight or obesity. Lipid values were obtainable in 1648 patients. The frequency of dyslipidemia was 37.8%. The most frequent dyslipidemia was low HDL (29%). We observed that 25.2% of patients presented with retinopathy. The proportion of patients with GADA, IAA and ICA were 28.0%, 6.4% and 21.6%, respectively.

Table 1
Clinical and demographic characteristics of all patients

Characteristics	N (%) or Median (IQR) (n = 1917)
Male	991(51.7)
Current age(years)	26(16,38)
Age at onset(years)	21.92(13,32)
Duration(years)	3(1,8)
HbA1c (%)	10.3(8.21,12.5)
OV or OB	213(16.9)
OV	173(13.8)
OB	40(3.2)
Retinopathy	474(25.2)
GAD (+)	328(28.0)
ICA (+)	251(21.6)
IAA (+)	74(6.4)
Dyslipidemia	623(37.8)
High TC	140(8.5)
High TG	185(11.3)
Low HDL	472(29.0)
High LDL	116(7.1)

Comment: Values were presented as numbers of patients(percentages) or median (interquartile range) unless otherwise indicated. OV, overweight; OB, obesity; GADA, anti-glutamic acid decarboxylase; ICA, islet-cell antibodies; IAA, insulin antibodies; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Comparison of characteristics in newly diagnosed young-onset and adult-onset patients

As shown in Table 2, the prevalence of diabetes family histories in young-onset and adult-onset patients were21.46% and 23.39%, separately; but no significant difference was found in two groups. Among these newly diagnosed T1D patients, 17.2% of participants were overweight or obesity. Interestingly, we observed that the adult-onset group had a higher proportion of overweight or obesity (24.6% vs. 9.5%, p = 0.002). The young-onset participants had a higher median HbA1c value than the adult-onset patients

(12.9% vs. 11.7%, p = 0.000). The adult-onset group had significantly higher FCP and 2-h CP (0.41 vs. 0.27 ng/ml, p = 0.000; 0.89 vs. 0.65 ng/ml p = 0.000, respectively) than young-onset patients. The overall frequency of dyslipidemia was 54.7% and was more in adult-onset group (58.2%). The most frequent dyslipidemia was low HDL (47%). The two groups did not differ in TG, HDL, and LDL. However, the frequency of high level of TC in childhood- onset group was significantly higher than the other group (16.6% vs. 8.8%, p = 0.029). The proportions of patients with GADA, IAA and ICA were 28.1%, 2.6% and 22.8%, respectively. The prevalence of GADA in adult-onset group was higher than young-onset group (33.7% vs. 23.3%, p = 0.025).

Table 2
Comparison between young-onset and adult-onset patients with T1D

	Childhood-onset (n = 234)	Adult-onset (n = 219)	p-value
Male (%)	120(51.3)	141(64.4)	0.006
Age at diagnosis(years)	11(7,13)	28(24,37)	0.000
HbA1c	12.9 ± 2.4%	11.7 ± 3.0%	0.000
OV or OB	12(9.5)	32(24.6)	0.002
OV	6(4.8)	23(17.7)	0.001
OB	6(4.8)	9(6.9)	0.597
GADA (+)	49(23.3)	61(33.7)	0.025
ICA (+)	43(20.6)	46(25.4)	0.277
IAA (+)	7(3.3)	3(1.7)	0.351
Dyslipidemia	98(51.3)	106(58.2)	0.212
High TC	31(16.6)	16(8.8)	0.029
High TG	36(18.8)	28(15.4)	0.412
Low HDL	82(42.9)	92(51.4)	0.118
High LDL	14(7.4)	17(9.5)	0.574
Urine acetone bodies	177(77.0)	151(71.9)	0.230
Proteinuria	32(14.0)	28(13.4)	0.890
Diabetes family history	50(21.5)	51(23.4)	0.652
FPG (mmol/l)	6.6 (5.15,7.95)	7.3 (5.55,9.95)	0.051
FCP (ng/ml)	0.27 (0.16,0.47)	0.41 (0.22,0.74)	0.000
2-h CP (ng/ml)	0.65 (0.38,1.09)	0.89 (0.56,1.75)	0.000
TC (mmol/l)	3.97 (3.37,4.85)	4.05 (3.29,4.79)	0.785
TG (mmol/l)	1.03 (0.74, 1.61)	1.18 (0.77,1.87)	0.347
HDL-C (mmol/l)	1.10 (0.92,1.42)	1.02 (0.85,1.2)	0.006

Comments: Values were presented as numbers of patients(percentages), median (interquartile range), or means ± SD unless otherwise indicated. FPG, fasting plasma glucose; FCP, fasting serum C-peptide; 2-h CP, 2-h postprandial serum C-peptide; Other abbreviations are the same as Table 1.

	Childhood-onset (n = 234)	Adult-onset (n = 219)	p-value
LDL-C (mmol/l)	2.34 (1.88,2.89)	2.50 (2,3.313)	0.057

Comments: Values were presented as numbers of patients(percentages), median (interquartile range), or means ± SD unless otherwise indicated. FPG, fasting plasma glucose; FCP, fasting serum C-peptide; 2-h CP, 2-h postprandial serum C-peptide; Other abbreviations are the same as Table 1.

Temporal changes in prevalence of overweight and obesity

The changes in the prevalence of overweight and obesity from 2012 to 2018 according to sex and age at onset were showed in Fig. 1 and Fig. 2. The overall prevalence of overweight or obesity was 15%, 18.8 %,14.7 %, 23.8%, 11.7%, 16.3% and 16.4%, separately (from 2012 to 2018). Figure 1 and Fig. 2 had shown that there were no obvious increasing or decreasing trends of overweight and obesity in this population based on gender or age at onset.

Discussion

In this study, we retrospectively studied demographic and clinical features of T1D and differences between young-onset and adult-onset patients, as well as the trends of prevalence of overweight and obesity. We found that the study patients were characterized by poor blood glucose control, high incidence of dyslipidemia and low detection rate of diabetes-related antibodies. Compared with young-onset T1D, adult-onset patients comprised higher prevalence of diabetes condition in the male gender, higher proportion of obesity and overweight, higher frequency of GADA, better glycemic control and lower frequency of high total cholesterol. To our surprise, no obvious increasing or decreasing trends of overweight and obesity in this population during 2012 and 2018 was observed.

Comparison of Demographic and Clinical Features between this Population and Others

In this analysis, we found that glycemic control was poor among patients with T1D, in whom the median level of HbA1c was 10.3 %. It was similar to the published data from another cross-sectional study in China[23], which showed that mean HbA1c value was > 75 mmol/mol (9.0%). Compared with the reports from India (8.8%), Sweden (8.2%), the United States (8.2%) and Maccabi (8.1%), the median level of HbA1c found in this study was higher[24, 25]. The differences of level of HbA1c values between different studies may be due to ethnicity, clinical characteristics, parental education, and income level.

There are many studies that reported the prevalence of overweight and obesity of T1D, which varies from 21–53.8% in different countries[24, 26–28]. The current study of children, adolescents and adults showed that the prevalence of being overweight or obesity was 16.9%. In contrast to other countries, the prevalence of overweight or obesity among patients with T1D in China was low.

Dyslipidemia is a common concomitant disease of T1D. The overall prevalence of dyslipidemia among patients with T1D in this study was 37.8%, which was higher than that found in Germany at 28.6%[29]. Similarly, an observation has been documented for patients in Korean with prevalence of 37.9%[30]. In contrast, the prevalence in the present study was much lower than that found in Bangladesh, which reported the overall prevalence of dyslipidemia were 65% in children and adolescents; the high TG, high TC, high LDL and low HDL were found in 50%, 66%, 75%, and 48%, respectively[31]. Also, a higher prevalence was found in Brazilian which reported that the prevalence of dyslipidemia in young patients was72.5%[32]. The wide range of prevalence in various studies may be due to multiple genetic factors in different ethnic groups.

The overall prevalence of retinopathy in our data of 25.2% is comparable with the prevalence of 21% reported from a population-based nationwide Swedish cohort with a median age of 21 yd[33]. Unlike our study, some studies showed lower prevalence of 16% in Norway[34], 14% in USA [35]and 11% [36]in Germany. However, unlike the previous studies, our study population included a higher proportion of adult-onset patients and a older age at onset, which may account for the differences.

Since this study is a retrospective analysis, data was limited about IA-2A and Znt8. Therefore, it is a pity that we only analyzed the proportion of GADA, ICA, IAA. We observed that the prevalence of GADA, ICA, IAA in the present study were 28.1%, 22.8% and 2.6%, respectively, which were extremely lower than results reported in previous studies[37–41]. As we know, however, the reported prevalence of these autoantibodies in T1DM may vary greatly depending on disease duration, age of onset, antibody assay method and so on. The exact reason for the low prevalence of islet-related antibodies in this study is unclear. One possibility is that other autoantibodies yet to be included maybe contributory. Another reason is the low genetic susceptibilities in this population. Diabetes-related autoantibodies appeared in people with an increased genetic risk of T1D[42]. A study showed that the frequency of GADA is only 30–40% in Asian T1DM patients[43]. It attributed this difference to the fact that autoimmune-mediated β -cell destruction is less common in Asian patients. Besides, the age of subjects in this study maybe associated with the low prevalence of antibodies. As the age of patients were relatively old, they might have had detectable antibodies in the preclinical stage but have become negative before diagnosis. A study demonstrated that with the increase of the age of onset, the newly diagnosed patients without any islet autoantibodies also increased[44]. Besides, compared with patients over 15 years old at onset, IAA was more common in children under 5 years old who developed T1D[44].

Comparison of clinical features in young-onset and adult-onset patients

It was generally accepted that TID in children were considered to have acute onset with classical symptoms of diabetes, while in adults, the onset of T1D can be more variable and have a better residual beta-cell function. In the analysis of 453 newly diagnosed patients, we observed that elder-onset patients accounted for 48.34 %. It should be noted that elder-onset patients comprised better islet function reflected by FCP and 2-h CP. This result was in line with the results of the Diabetes Control and

Complications Trial study and other subsequent studies[45–47]. Besides, the current study found that patients with the adult-onset group had lower median HbA1c levels at disease onset, which indicated that residual β-cell function was better, clinical manifestation was less severe, or hyperglycemia lasted shorter before diagnosis. Different from the traditional view that autoimmune disease are mostly women, T1D is even characterized by a clear male predominance in diabetes for new cases in Caucasians[48]. Similar to previous findings, we found the male excess in present population. In addition, adult-onset group had higher proportion of male patients than young-onset group, agreeing with other studies in China[23, 49] and Finland[50]. The accelerator hypothesis postulated that the heavier child should develop diabetes at a younger age[51]. We discovered a significant difference in prevalence of overweight and obesity between two subgroups, however, adult-onset patients had higher prevalence of overweight or obesity than young-onset patients. Previous studies had reported similar results. For example, Betts et al. showed no association between BMI SDS at diagnosis and age at onset, but an inverse relationship using BMI SDS at 6 months[52]. As previously reported, studies had shown that the adult patients were most frequently tested positive for GADA[53], which indicated that very young patients tend to mount a weak antibody response to GADA and that the intensity of the GADA response increases with age[50].

Temporal trends in the prevalence of overweight and obesity

Weight change in TID is complex. Factors that may affect weight gain in patients with T1DM include the level of glycemic control, intensive insulin treatment, pattern of treatment, sexuality, the presence of eating disorders and appearance of complications (such as thyroid disease or gastric disease)[24]. Previous studies had shown that T1D had become progressively heavier at disease onset over the past 20 years[54–56]. However, there were no obvious increasing or decreasing trends of overweight and obesity in this population. Weight is associated with Insulin dose. Insulin itself promotes weight gain in that it stimulates lipogenesis, inhibits protein catabolism, and slows basal metabolism. Because of retrospective analysis, we could not get information about insulin dose. It is impossible to explore the relationship between insulin dose and prevalence of overweight or obesity. So, the conclusion needs to be further confirmed by large-scale research.

The limitation of this study is the fact that this study is a retrospective and hospital-based study from one center in Henan province, so the representativeness of the research results is not as good as that of multi-centers. In addition, we cannot fully obtain the clinical data needed for the study.

Conclusion

In conclusion, our data indicated that patients with T1D in this area are characterized by poor overall blood glucose control, high incidence of dyslipidemia and low detection rate of diabetes-related antibodies. In recent years, the prevalence of overweight and obesity in T1D has not increased or decreased linearly. Compared with young-onset patients, adult-onset patients with T1D are not uncommon and have better clinical manifestations at disease onset.

Abbreviations

OV, overweight; OB, obesity; GAD, glutamic acid decarboxylase; ICA, islet-cell antibodies; IAA, insulin antibodies; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FCP, fasting serum C-peptide; 2-h CP, 2-h postprandial serum C-peptide.

Declarations

Competing interests

The authors declare there are no conflicts of interest.

Author’s contributions

YLG and LXL designed the study and drafted the manuscript. YLG and YGX searched the literature, reviewed the literature, screened the record, performed the statistical analysis. All authors contributed to data review and interpretation and manuscript revision. All authors have read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the authors and will be shared upon reasonable request.

Ethics approval

The study was carried out in compliance with the declaration of Helsinki. The study was approved by the Institutional Review Board of the First Affiliated Hospital of Zhengzhou University (Number: 2020-KY-

417). Because this was a retrospective observational study, and de-identified information was used for the analysis, informed consents were waived as part of the Institutional Review Board of the First Affiliated Hospital of Zhengzhou University approval.

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Figures

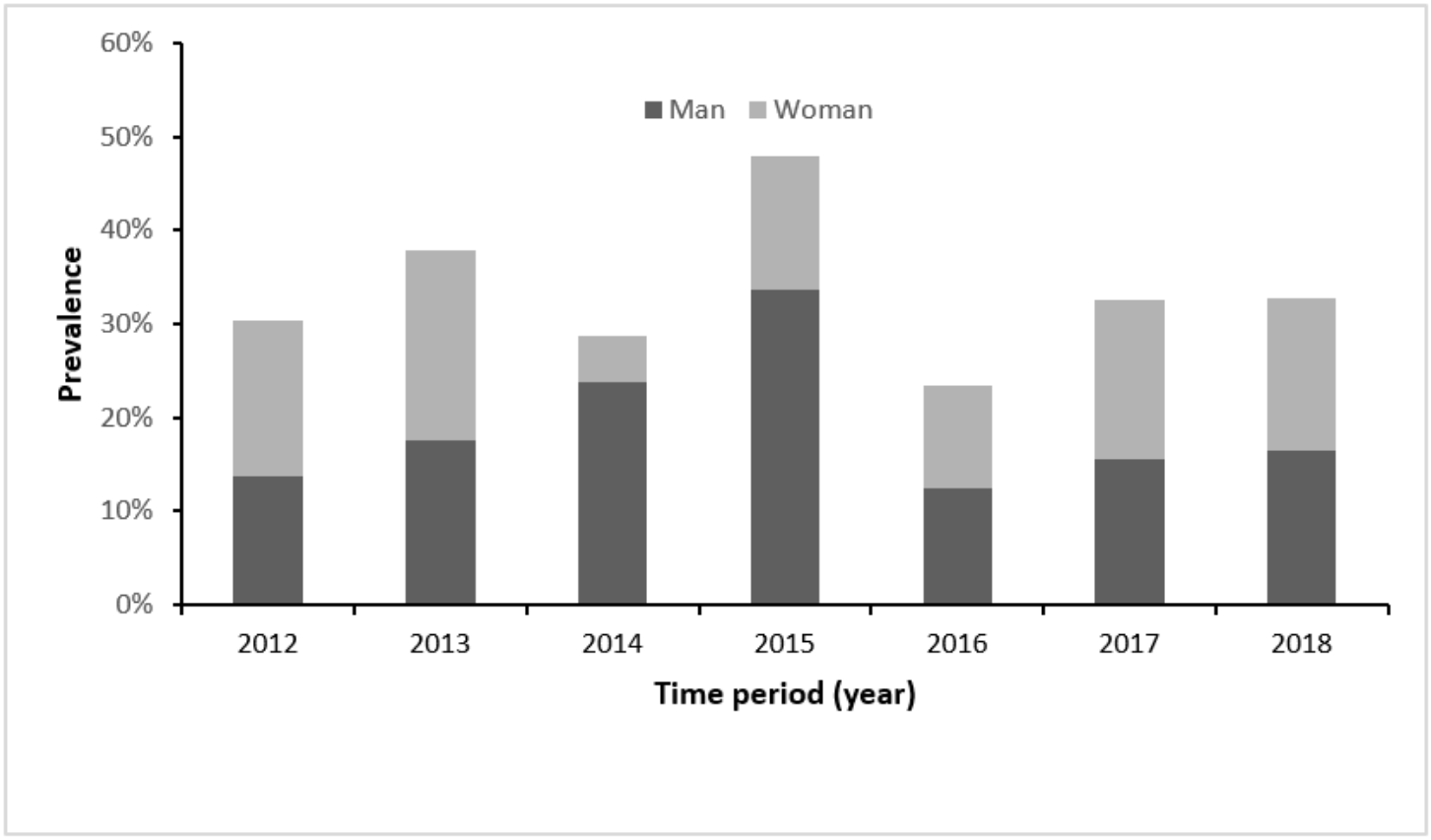

Figure 1

Trends in the prevalence of overweight and obesity among patients by gender (2012-2018).

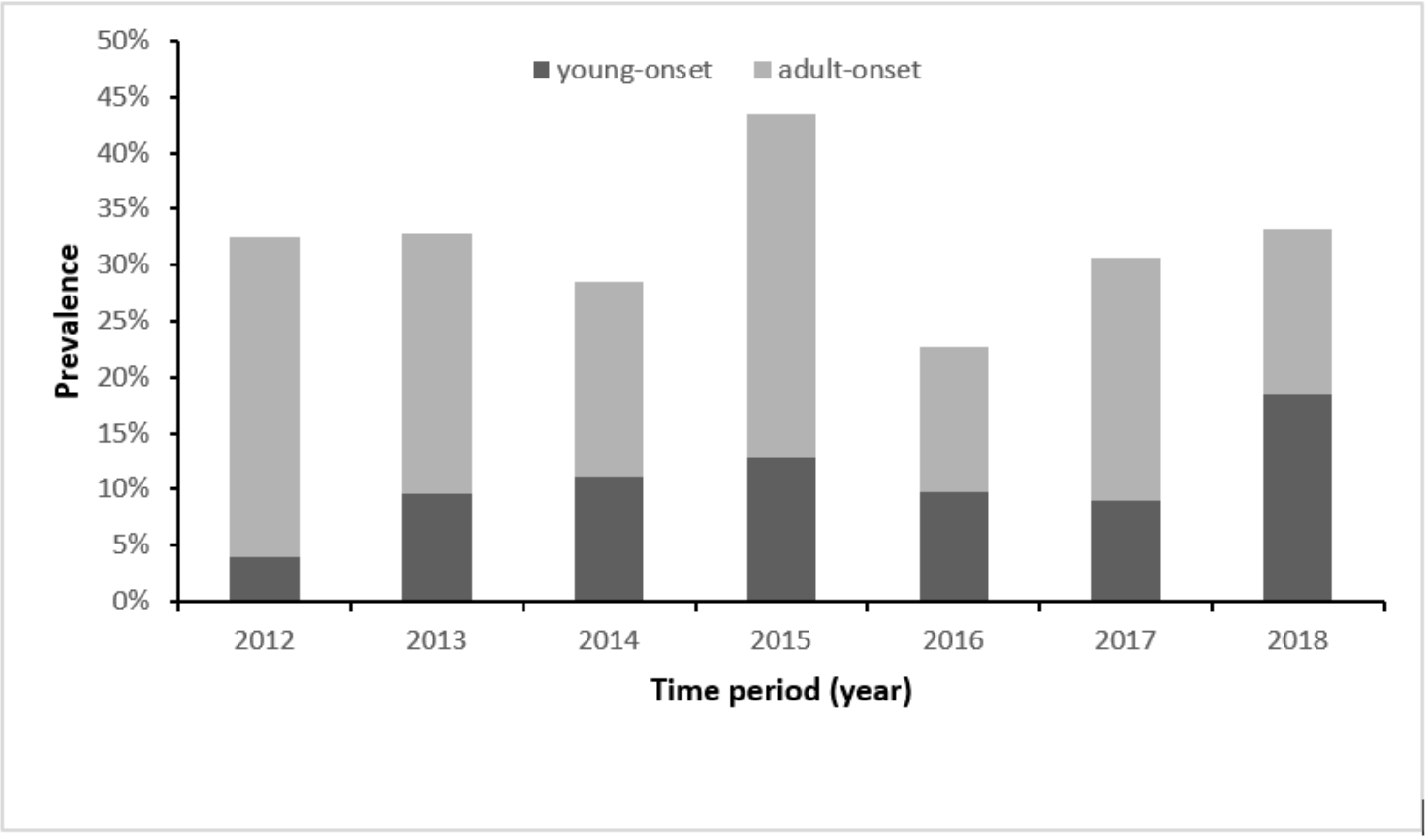

Figure 2

Trends in the prevalence of overweight and obesity among patients by age at onset (2012-2018).