Diabetes & Metabolism 48 (2022) 101389

Available online at ScienceDirect www.sciencedirect.com

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Original article

Prevalence and risk of diabetic complications in young-onset versus late-onset type 2 diabetes mellitus

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ARTICLE INFO

Article History:
Received 3 March 2022
Revised 8 September 2022
Accepted 14 September 2022
Available online 19 September 2022

Keywords:
Young-onset diabetes
Late-onset diabetes
Type 2 diabetes mellitus
Microvascular complications

ABSTRACT

Aims: To compare the prevalence and risk of diabetic complications between people with young-onset and late-onset type 2 diabetes mellitus (T2DM).
Methods: In this observational study, 10,447 people with T2DM had at least one study of diabetic complications: retinopathy, neuropathy, chronic kidney disease (CKD), carotid artery plaque. We use odds ratios to compare complications between young-onset T2DM (YOD) and late-onset T2DM (LOD).
Results: We compare 1,791 people with YOD (diagnosed < 40 years) and 8,656 with LOD (diagnosed ≥ 40 years). The YOD had a higher prevalence of these complications than the LOD ($p < 0.011$) after adjustment for confounding factors. Further adjustment for diabetes duration greatly attenuated the odds ratios however, neuropathy remained significantly more frequent in people with YOD (adjusted odds ratio: 1.39, 95% confidence interval: 1.13−1.71, $p = 002$). In cluster analysis on the 2,126 study participants who were diagnosed with T2DM within the previous two years, 47% of the YOD group were in the severe insulin-deficient diabetes cluster in comparison to 23% LOD; 28% and 44% respectively were in the mild age-related diabetes.
Conclusion: People with YOD had a higher prevalence of complications than those with LOD, but this was mostly attributed to a longer duration of diabetes. However, the prevalence of neuropathy remained significantly higher even after adjusting for factors including the duration of diabetes.

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent metabolic diseases worldwide, and its complications have become a great health burden globally [1]. As the onset age of T2DM is decreasing, the prevalence of T2DM among young adults is increasing annually [2]. The increase in the prevalence of young-onset T2DM (YOD) emerges as a clinical challenge, and YOD could be related to a high risk of diabetic complications. Several studies showed an increased risk of macrovascular complications in individuals with YOD than those with late-onset T2DM (LOD) or type 1 diabetes mellitus (T1DM): higher all-cause, cardiovascular disease, stroke, ischemic heart disease mortalities [3−5]. The longer duration of diabetes in YOD has been suggested as the primary mechanism underlying the increased risk of macrovascular complications compared with that in LOD [6]. In addition, beta-cell deterioration over time seems to be more rapid in people with YOD than in those with LOD, suggesting its aggressive phenotype [7].

At the onset of T2DM in adolescence, the risk of microvascular complications steadily increased over time, and more than 60% developed one or more complications when they reached early adulthood [8]. The incidence of microvascular complications is higher in YOD than in those with T1DM, as seen in the SEARCH study [9]. However, the data examining whether the risk of microvascular complications is higher in YOD than in LOD remain inconclusive. Chan et al. reported that YOD is associated with an increased risk of nephropathy and end-stage renal disease (ESRD); however, the increased risk was mostly attributed to the longer duration of diabetes [10]. The odds of developing retinopathy was reported to increase [11] or decrease [12] with the duration of diabetes. The prevalence of neuropathy was reported to be lower in YOD than LOD [13]. However, the effect of YOD on microvascular complication is largely unknown due to the limited number of studies and their inconsistent results.

In this study, we aimed to investigate the effect of YOD versus LOD on the prevalence of diabetic complications: diabetic retinopathy, neuropathy, CKD, carotid artery plaque in Korean people with T2DM.

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https://doi.org/10.1016/j.diabet.2022.101389
1262-3636/

In addition, based on a recent study which reported a new classification of diabetes [14], we performed cluster analysis to characterize YOD versus LOD, in people diagnosed with T2DM in the past two years. The incidence of retinopathy and CKD were also studied, comparing YOD and LOD according to age at examination and duration of diabetes.

Methods

Study population

This longitudinal observational study was conducted using data from the Seoul Metabolic Syndrome Cohort, that enrolled 12,599 people with diabetes mellitus from November 1997 to September 2016 at Huh's Diabetes Center. A total of 10,447 people with T2DM who underwent a complete medical survey including the recording of the duration of diabetes, laboratory tests, and one or more complication studies completed within 6 months after the time of enrollment were included in the present study. T2DM was diagnosed according to the judgment of the endocrinologist based on the fasting and 2 hour plasma glucose values during a 75 g oral glucose tolerance test or HbA1c criteria according to the American Diabetes Association guideline and Korean Diabetes Association guidelines at the time [15,16]. Considering the possibility of type 1 diabetes (T1DM) or latent autoimmune diabetes in adults (LADA), we excluded people with low C-peptide levels (< 0.6 ng/mL). Glutamic acid decarboxylase antibody (GADA) was measured only for those who were highly suspected for T1DM or LADA. We excluded people who were clinically suspected of having LADA disease with positive GADA (≥ 1 by immune radiometric assay) results. In this study, YOD was defined as T2DM diagnosed at < 40 years of age, based on age strata used for the estimated world diabetes prevalence by the International Diabetes Federation and previous studies [6,10,17]. This study was approved by the ethics committee of Inha University Hospital (2021−09−034).

Measurements and definitions of clinical and laboratory parameters

Baseline medical information such as medical and family history, smoking and alcohol consumption, physical activity level per month, and medication use were collected. Anthropometric measurements included weight, height, and waist circumference. Venous blood samples were collected from participants after 8 h of fasting. Laboratory parameters including glycated hemoglobin (HbA1c), total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), blood urea nitrogen, and creatinine were measured using routine laboratory methods. The estimated glomerular filtration rate (eGFR) was assessed using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [18]. Homeostasis Model Assessment (HOMA2) values were calculated with the HOMA calculator to estimate β-cell function (HOMA2-β) and insulin resistance (HOMA2-IR) based on C-peptide concentrations (University of Oxford, Oxford, UK) [19]. Body mass index (BMI) was calculated as weight divided by height in meters squared (kg/m^2). Regular alcohol consumers were defined as individuals who drank twice a month or more, while ever-smokers were defined as individuals who had ever smoked five or more packs of cigarettes. "Time of enrolment" was defined as the year of the baseline work-up.

Definitions of diabetic complications

Diabetic retinopathy was diagnosed when fundoscopic results showed any of the following abnormal findings: cotton wool spots, microaneurysms or hemorrhage, hard exudate, neovascularization, fibrovascular proliferation, and vitreous hemorrhage. Diabetic neuropathy was identified among those who met the respective diagnostic criteria (>2 standard deviations (SD) from the normal mean values) on the basis of the results of nerve conduction velocity (NCV) tests using Neuroscreen Plus (Jaeger-Toennis, Freiburg, Germany) [20−22]. Chronic kidney disease (CKD) was defined as an eGFR of < 60 mL/min/1.73 m^2. The common carotid arteries were examined by high-resolution ultrasonography (LOGIQ7; GE Healthcare, Chicago, IL, USA). Carotid artery plaque was considered present if any one of the following criteria was met: (1) carotid intima-media thickness of 1.5 mm or higher, (2) protrusion of atherosclerosis in the lumen of the artery with ≥ 50% thickness compared with the surrounding area, (3) presence of distinct areas of hyperechogenicity [23,24].

The risk of incident or new-onset retinopathy was evaluated in people who had two or more annual fundoscopy including the baseline examination. In people who underwent three or more annual eGFR examinations, new-onset CKD was diagnosed when an eGFR of < 60 mL/min/1.73 m^2 was confirmed twice or more, consecutively.

Statistical analysis

The baseline characteristics of the study participants are presented as mean ± SD or as numbers (percentages) for categorical variables. Continuous variables were compared between YOD and LOD using independent t-tests, categorical variables using the χ^2 test. After stratifying the groups by age, the prevalences of diabetes complications in each age group were compared using χ^2 tests. Multivariable logistic regression was performed to compare the risk of having diabetic complications in the two study groups adjusting sequentially for age, sex, BMI, systolic blood pressure (SBP), HbA1c, LDL-C, time of enrolment, smoking, alcohol consumption, and duration of diabetes. Those with missing data in any of the above variables were excluded in the multivariable logistic regression. The adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were determined.

We used Kaplan-Meier analysis to plot the cumulative incidence of retinopathy and CKD by age and by diabetes duration, stratified by YOD versus LOD. The log rank test was used to compare YOD and LOD cumulative incidences.

To explore the characteristics of the YOD and LOD groups, a new method of classification of diabetes through cluster analysis [14] was applied. Only people diagnosed with T2DM in the two previous years were included for cluster analysis. BMI, age at onset of diabetes, HbA1c, HOMA2-β and HOMA2-IR were chosen as model variables. People with extreme outlying values (>5 SD from the mean) were excluded, providing a total of 2126 for cluster analysis. Each variable was standardized, to a mean of zero, variance of 1. K-means clustering was performed with a k value of 4. Since people with T1DM and LADA were excluded from this study population in advance, a severe autoimmune diabetes subgroup could not be identified, as in the study of Ahlqvist et al. [14]. Therefore, people were classified into four groups. (cluster 1, severe insulin-deficient diabetes (SIDD); cluster 2, severe insulin-resistant diabetes (SIRD); cluster 3, mild obesity-related diabetes (MOD); and cluster 4, mild age-related diabetes (MARD).

Evaluation of clusterwise cluster stability was performed by resampling the dataset with 2000 runs [25]. In the resampled data, the Jaccard similarities of the original clusters to the most similar clusters were calculated. In general, stable clusters should have Jaccard similarity greater than 0·75.

A p value of < 0.05 was considered statistically significant; all analyses were performed with the IBM SPSS statistical software for Windows (version 26.0; IBM, Armonk, NY, USA), and "fpc" package in R program (version 4.2.1; https://www.r-project.org/).

Results

Baseline characteristics

From the Seoul Metabolic Syndrome Cohort data, a total of 10,447 people (5323 [51.0%] men and 5124 [49.0%] women) with T2DM were enrolled. Among them, 1791 were diagnosed with T2DM before the age of 40 years and were classified as the YOD group, while the other 8656 were diagnosed at the age of 40 years or older and were classified as the LOD group. The study flowchart is shown in supplementary Figure 1. The average age of the whole population was 57.9 ± 10.8 years, and the average duration of diabetes 8.0 ± 7.5 years.

The baseline characteristics of study participants according to the age of onset of T2DM are shown in Table 1. The distribution of enrolment year is shown in Supplementary Table 1. Those with YOD were younger and had a longer duration of diabetes compared with those with LOD. No significant difference was observed in BMI between the two groups. HbA1c, triglyceride, HOMA2-IR and eGFR were significantly higher and HOMA2-β was lower in people with YOD than in those with LOD. The YOD group had significantly lower SBP and HDL-C level compared to the LOD group. The percentage who received insulin therapy was higher in the YOD group. With regard to health-related behaviors, the YOD were more likely to smoke and consume alcohol than the LOD group. Those with YOD were less frequently treated with statins. The YOD group had a significantly higher prevalence of diabetic retinopathy and neuropathy than those with LOD, but a lower prevalence of carotid artery plaque and CKD.

Table 1
Baseline characteristics of the study participants with YOD and those with LOD.

Study population *N* = 10,447	YOD *N* = 1791	LOD *N* = 8656	*p*-value
Age, years	45.4 ± 10.6	60.5 ± 8.8	<0.001
Female, n (%)	650 (36.3)	4474 (51.7)	<0.001
Age of diabetes diagnosis, years	33.8 ± 4.9	53.3 ± 8.6	<0.001
Duration of diabetes, years	11.6 ± 9.6	7.2 ± 6.8	<0.001
DM duration, quartile			<0.001
< 2 years	294 (16.4)	2111 (24.4)	
≥ 2 to < 5 years	334 (18.6)	2289 (26.4)	
≥5 to < 10 years	373 (20.8)	2288 (26.4)	
≥ 10 years	790 (44.1)	1968 (22.7)	
Body weight, kg	69.0 ± 21.3	64.4 ± 10.7	<0.001
BMI, kg/m^2	24.6 ± 3.8	24.4 ± 3.1	0.031
Waist circumference, cm	84.2 ± 10.0	83.9 ± 8.7	0.217
Systolic BP, mmHg	130.0 ± 17.3	135.2 ± 18.2	<0.001
Diastolic BP, mmHg	89.9 ± 227.5	87.5 ± 156.6	0.591
HbA1c,%	8.9 ± 2.1	8.1 ± 1.8	<0.001
HOMA2-IR	1.75 ± 0.92	1.69 ± 0.81	0.012
HOMA2-beta (%)	44.7 ± 30.4	59.2 ± 31.7	<0.001
Total cholesterol, mmol/L	**5.1 ± 1.2**	**5.1 ± 1.1**	0.089
Triglyceride, mmol/L	1.9 ± 1.6	**1.7 ± 1.2**	<0.001
HDL-C, mmol/L	1.27±0.33	1.30±0.38	0.014
LDL-C, mmol/L	3.0 ± 1.0	3.0 ± 1.0	0.190
eGFR EPI, mL/min/1.73 m^2	95.2 ± 23.0	84.7 ± 18.7	<0.001
Diabetes medications			<0.001
Without medication	478 (26.7)	2304 (26.6)	
One OAD only	280 (15.6)	2011 (23.2)	
Two OADs	422 (23.6)	2262 (26.1)	
Three OADs	203 (11.3)	1058 (12.2)	
Four or more OADs	46 (2.6)	201 (2.3)	
OADs plus insulin	217 (12.1)	537 (6.2)	
Insulin only	145 (8.1)	283 (3.3)	
Regular alcohol consumption, n/total (%)	740/1434 (51.6)	2340/6516 (35.9)	<0.001
Ex-smoker, n/total (%)	356/1397 (25.5)	1793/6357 (28.2)	<0.001
Current smoker, n/total (%)	442/1397 (31.6)	1022/6357 (16.1)	<0.001
Statin use, n (%)	242/1769 (13.7)	1329/8563 (15.5)	0.050
Diabetic complications			
Carotid artery plaque, n/total (%)	590/1542 (38.3)	4047/7468 (54.2)	<0.001
Diabetic retinopathy, n/total (%)	205/1649 (12.4)	538/7856 (6.8)	<0.001
CKD, n/total (%)	135/1762 (7.7)	812/8450 (9.6)	0.010
Neuropathy, n/total (%)	522/1470 (35.5)	1745/6638 (26.3)	<0.001

Data are expressed as mean ± SD or n (%). LOD, late-onset type 2 diabetes mellitus; YOD, young-onset type 2 diabetes mellitus; DM, diabetes mellitus; BMI, body mass index; BP, blood pressure; HbA1c, glycated hemoglobin; HOMA2-IR, homeostatic model assessment 2 for insulin resistance; HOMA2-beta, homeostatic model assessment 2 for beta-cell function; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; OAD, oral antidiabetic agent; CKD, chronic kidney disease.

Diabetic complications in YOD versus LOD

The prevalence of diabetic complications was also investigated according to age group (Table 2). The prevalences of diabetic retinopathy, CKD and neuropathy were significantly higher in people with YOD than in those with LOD from 40 years of age onward. The prevalences of carotid artery plaque were higher in those with YOD only after 50 years of age.

After adjusting for multiple variables: age, sex, BMI, SBP, HbA1c, LDL-C, time of enrolment, smoking, alcohol consumption, YOD was significantly associated with increased prevalences of diabetic retinopathy, CKD, neuropathy, and carotid artery plaque compared with LOD (aOR: 2.39, 95% CI: 1.90–3.00; aOR: 2.91, 95% CI: 2.21–3.83; aOR: 2.73, 95% CI: 2.29–3.25; and aOR: 1.23, 95% CI: 1.05–1.44, respectively; Table 3). Further adjustment for the duration of diabetes in model 5 attenuated the differences in the prevalences of diabetic complications. The higher prevalences of diabetic retinopathy, CKD and carotid artery plaque were no longer statistically significant in the YOD group compared with the LOD group (aOR: 0.98, 95% CI: 0.0.75–1.30; aOR: 1.30, 95% CI: 0.93–1.80; and aOR: 0.85, 95% CI: 0.70–1.02, respectively). The effect size of diabetic neuropathy in the YOD group compared to the LOD was reduced, but remained statistically significant (aOR: 1.39, 95% CI: 1.13–1.71). Considering the age difference between the groups, which is inevitable based on the definition, only people with YOD aged 40 years and older and those with LOD were included in an additional analysis, and similar results were confirmed (Supplementary Table 2). Additionally, we changed the order of adjustment level to confirm the effect of diabetes duration. When diabetes duration was adjusted at Model 2, the association between YOD and diabetic complication was attenuated early (Supplementary Table 3).

We further investigated whether the DM onset age was associated with diabetic complications (Supplementary Table 4). In the crude model, an increase in DM onset age was associated positively with CKD and carotid plaque, possibly because CKD and carotid plaque are closely related with aging. However, after adjusting for multiple variables including age, an increase in DM onset age was associated with lower prevalences of diabetic complications. To confirm the interaction between the YOD versus LOD variable and age or the duration of diabetes, each of the relevant interaction variables was additionally evaluated. In neuropathy, both interactions between the YOD versus LOD variable and age and the duration of diabetes were statistically significant. (all $p < 0.05$, Supplementary Table 5).

The cumulative incidence of retinopathy and CKD were assessed, according to age and duration of diabetes, using long-term follow up data and Kaplan Meier survival analysis (Fig. 1). We analyzed the 2917 T2DM who did not have retinopathy at the initial workup and who had more than one follow-up fundoscopy results. The median follow-up duration was 6.3 years. (Fig. 1a) In addition, the data from 5589 T2DM who did not have CKD at the initial evaluation and who underwent additional serum tests twice or more were analyzed. The median follow-up duration was 7.1 years (Fig. 1b). The cumulative incidences of both retinopathy and CKD were higher in the YOD group at all ages (all $p < 0.001$ respectively.) According to the diabetes duration (Fig. 1c and d), the cumulative incidences of retinopathy

Table 2
Prevalence of diabetic complications in study participants with LOD and those with YOD, stratified by age groups.

	Prevalence of diabetic retinopathy (n = 9505)			Prevalence of CKD (n = 10,212)			Prevalence of neuropathy (n = 8108)			Prevalence of carotid artery plaque(n = 9010)		
	YOD (n = 1649)	LOD (n = 7856)	*p value*	YOD (n = 1762)	LOD (n = 8450)	*p value*	YOD (n = 1470)	LOD (n = 6638)	*p value*	YOD (n = 1542)	LOD (n = 7468)	*p value*
< 30 years	5/67 (7.5)	0		0/74 (0)	0		8/38 (21.1)	0		3/48 (6.3)	0	
30–39 years	29/472 (6.1)	0		1/514 (0.2)	0		70/363 (19.3)	0		71/424 (16.7)	0	
40–49 years	64/547 (11.7)	40/904 (4.4)	<0.001	24/571 (4.2)	21/980 (2.1)	0.02	167/504 (33.1)	102/718 (14.2)	<0.001	176/517 (34.0)	270/862 (31.3)	0.296
50–59 years	82/408 (20.1)	164/2688 (6.1)	<0.001	62/437 (14.2)	87/2833 (3.1)	<0.001	184/408 (45.1)	444/2290 (19.4)	<0.001	224/403 (55.6)	1114/2494 (44.7)	<0.001
60–69 years	21/132 (15.9)	259/3070 (8.4)	0.003	37/141 (26.2)	355/3301 (10.8)	<0.001	77/135 (57.0)	775/2613 (29.7)	<0.001	101/131 (77.1)	1824/2966 (61.5)	<0.001
≥70 years	4/23 (17.4)	75/1194 (6.3)	0.032	11/25 (44.0)	349/1336 (26.1)	0.045	16/22 (72.7)	424/1017 (41.7)	0.004	15/19 (78.9)	839/1146 (73.2)	0.575

CKD, chronic kidney disease; LOD, late-onset type 2 diabetes mellitus; YOD, young-onset type 2 diabetes mellitus.

Table 3
Odds ratio of having diabetic complications in people with YOD (compared with LOD).

	Diabetic retinopathy (n = 6776)OR (95% CI)	p value	CKD (n = 7126)OR (95% CI)	p value	Neuropathy (n = 6074)OR (95% CI)	p value	Carotid artery plaque (n = 6571)OR (95% CI)	p value
Model 1	2.68 (2.14–3.35)	<0.001	2.98 (2.27–3.90)	<0.001	3.05 (2.57–3.61)	<0.001	1.31 (1.12–1.54)	0.001
Model 2	2.66 (2.12–3.32)	<0.001	3.14 (2.39–4.12)	<0.001	3.03 (2.55–3.58)	<0.001	1.32 (1.13–1.54)	0.001
Model 3	2.45 (1.95–3.07)	<0.001	3.04 (2.32–4.00)	<0.001	2.78 (2.34–3.31)	<0.001	1.26 (1.07–1.47)	0.005
Model 4	2.39 (1.90–3.00)	<0.001	2.91 (2.21–3.83)	<0.001	2.73 (2.29–3.25)	<0.001	1.23 (1.05–1.44)	0.011
Model 5	0.98 (0.75–1.30)	0.911	1.30 (0.93–1.80)	0.121	1.39 (1.13–1.71)	0.002	0.85 (0.70–1.02)	0.087

Model 1 = adjusted for age and sex; Model 2 = Model 1 + BMI; Model 3 = Model 2 + systolic BP, HbA1c; Model 4 = Model 3 + LDL-C, time of enrolment, smoking and alcohol consumption; Model 5 = Model 4 + diabetes duration.
CKD, chronic kidney disease; OR, odds ratio; CI, confidence interval; YOD, young-onset type 2 diabetes mellitus; LOD, late-onset type 2 diabetes mellitus; BMI, body mass index; BP, blood pressure; HbA1c, glycated hemoglobin, LDL-C, low-density lipoprotein-cholesterol.

increased with T2DM duration, similarly in both groups whereas for CKD it was higher in the LOD group ($p = 0.437$; $p < 0.001$).

Cluster analysis

We performed cluster analysis on the 2126 study participants who were diagnosed with diabetes within the two years before inclusion in the study, 265 had YOD and 1861 LOD. The study participants were grouped into four clusters (Supplementary Figure 2). Cluster 1 labelled as severe insulin-deficient diabetes (SIDD) was characterized by early-onset diabetes, poor glucose control, and severe insulin secretory dysfunction. Cluster 2, labelled as severe insulin resistant diabetes (SIRD), was characterized by severe insulin resistance with relatively preserved insulin secretory function.

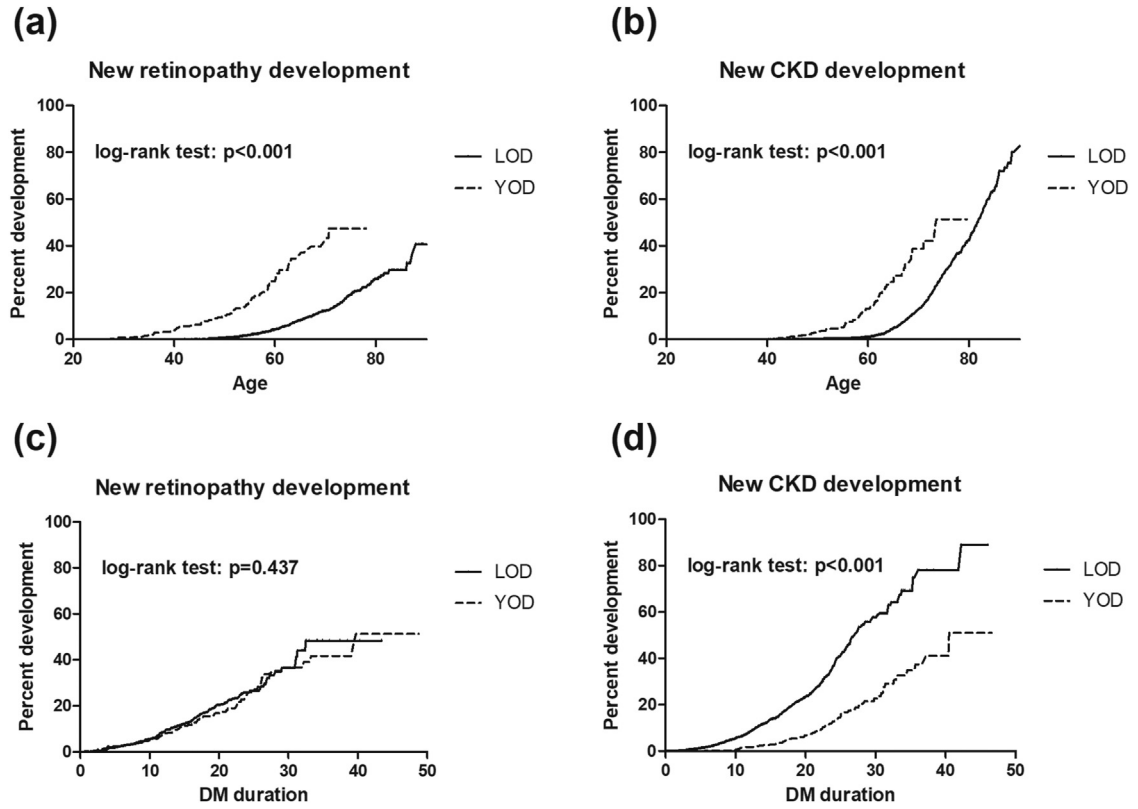

Fig. 1. Kaplan–Meier plot of retinopathy and CKD development in people with YOD and LOD based on age (a, b) and diabetes duration (c, d)
Log-rank test was performed for the comparison of the YOD and LOD incidence curves.
CKD, chronic kidney disease; YOD, young-onset type 2 diabetes mellitus; LOD, late-onset type 2 diabetes mellitus; DM, diabetes mellitus.

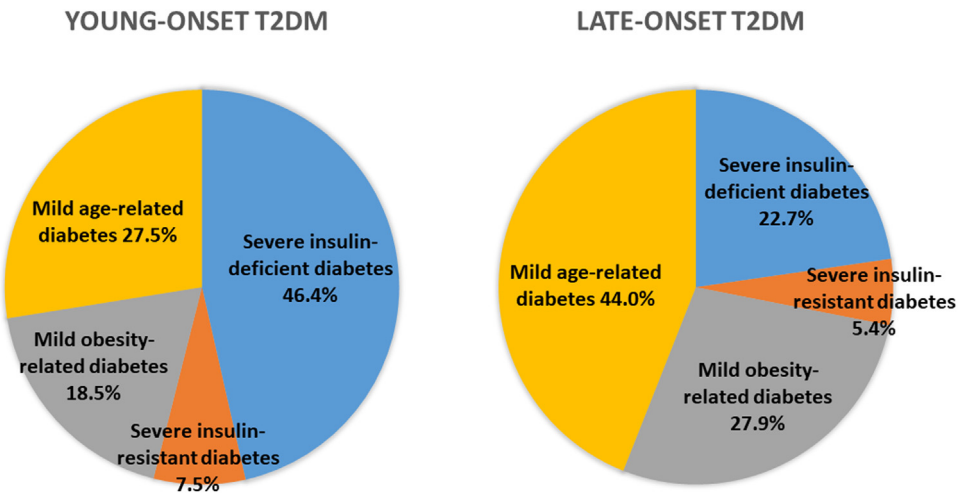

Fig. 2. Distribution of people with YOD and LOD according to the cluster classification.
YOD, young-onset type 2 diabetes mellitus; LOD, late-onset type 2 diabetes mellitus; SIDD, severe insulin-deficient diabetes; SIRD, severe insulin-resistant diabetes; MOD, mild obesity-related diabetes; MARD, mild age-related diabetes.

Cluster 3, labelled as mild obesity (MOD) was characterized by relatively high BMI. Cluster 4, labelled as mild age-related diabetes (MARD), was characterized by later onset diabetes with mild insulin resistance and mild insulin secretory dysfunction.

Fig. 2 shows the distribution of people according to the cluster classification in YOD versus LOD. The percentage in the SIDD subgroup was highest in the YOD 46%, in contrast to only 23% in the LOD, whereas 44% and 23% respectively, were classified as MARD.

The prevalences of diabetic complications in each cluster are shown in Supplementary Table 6. The prevalences of retinopathy and CKD were significantly different between clusters (all $p < 0.05$). The prevalence of retinopathy was highest in SIDD group, and the prevalence of CKD was highest in SIRD group.

As a result of checking clusterwise cluster stability, the Jaccard similarity mean of each cluster was all over 87%, ensuring cluster stability.

Discussion

The increasing prevalence of YOD has been reported in a number of studies conducted in different ethnic groups including Asian populations [2,26]. In South Korea, the prevalence of diabetes in individuals aged 30–39 years increased from 3.1% in 2014 to 3.7% in 2018 [27]. This increasing prevalence of YOD suggests that more attention should be paid to its clinical manifestation and management. The results of the current study reveal that people with YOD are at increased risk of developing diabetic microvascular complications, which is mostly attributable to long duration of diabetes.

Several studies investigated the differences in the risks of microvascular complications in people with YOD and those with T1DM. The prevalences of retinopathy (9.1% vs 5.6%), peripheral neuropathy (17.7% vs 8.5%), and diabetic kidney disease (19.9% vs 5.8%) were significantly higher in young adults with T2DM than in those with T1DM [9]. In addition, some ophthalmological evidence suggested that the retinal complications occurring in people with YOD might be more aggressive than those with young-onset T1DM [28,29]. However, whether these microvascular complications are more prevalent in people with YOD than in those with LOD remains inconclusive due to the limited number of studies and their inconsistent results [10,12,30,31]. Converse results were sometimes derived depending on whether the age and the duration of diabetes were adjusted [11,12]. In this study, we evaluated the prevalences of microvascular complications: diabetic retinopathy, CKD, neuropathy in people with YOD. YOD was associated with high odds ratios for the prevalence of diabetic retinopathy, CKD, and neuropathy. The effect sizes were markedly decreased after adjustment for the duration of diabetes. From the results, we may suggest that the increased prevalences of diabetic microvascular complications in people with YOD are mostly attributable to the prolonged duration of diabetes.

The importance of disease duration on vascular complication is also well described in other studies. Nanayakkara et al. reported that for every 1 year increase in the duration of diabetes in people aged < 60 years, the aORs of macrovascular and microvascular disease increased by 2% and 11%, respectively [32]. Individuals with a longer duration of diabetes are exposed to prolonged hyperglycemia, which can result in oxidative stress, vascular damage, and beta-cell exhaustion [33] leading to various kinds of vascular complications.

However, in this study, the increased odds ratio of having neuropathy in the YOD versus the LOD remained statistically significant after adjustment for the duration of diabetes. Interactions between the YOD / LOD variable and both age and also the duration of diabetes were significant. This suggests the possibility of high neuropathy risk in the YOD group, especially at younger age and early in the diagnosis of T2DM. In addition, a decrease in T2DM onset age was associated with higher prevalence of diabetic complications after adjusting for multiple variables including age at baseline. This finding implies that YOD itself may have unfavorable effects on the progression of microvascular complications other than the duration of diabetes. The rate of beta-cell exhaustion is reported to be more rapid in people with YOD than in those with LOD [22]. The decline of beta-cell function assessed by oral glucose tolerance test was 20%–35% per year in young adults with T2DM, while it was 7% per year in individuals with LOD [34–36]. In this regard, individuals with YOD could also have worse glycemic control with higher HbA1c levels and a shorter time to start insulin treatment [37,38]. Our study also showed poor glycemic control in people with YOD. Those with YOD had significantly higher HbA1c levels and lower insulin secretory function represented by HOMA-β, and a higher percentage who received insulin therapy compared with those with LOD. Considering the characteristics of people with YOD with insulin secretion dysfunction, we further performed cluster analysis to determine whether similar results are obtained for YOD and LOD in the new classification of diabetes. Interestingly, 46.6% of YOD were in the SIDD cluster compared to only 22.7% of the LOD. It suggests that a deficiency in insulin secretion is prominent at the time of diabetes development in the YOD group.

Lifestyle and adherence to treatment can also attribute to a higher risk of complications in individuals with YOD than in those with LOD. Although those with YOD have more aggressive phenotype than

those with LOD, their adherence to treatment tends to be poorer than that of individuals with LOD [39]. In a study by Yang et al., the overall clinical attendance rate of people with T2DM continued to increase from 2009 to 2017; however, the clinic attendance rate of those with YOD was only approximately half of that of the LOD [39]. A study in Australia also showed that young people with T2DM had a twofold increased odds of not following self-care practices including dietary advice, taking regular medications, and self-monitoring of blood glucose levels [40]. This low compliance in young people may lead to an increased risk of diabetic complications. In this study, T2DM with YOD were more likely to smoke and consume alcohol than those with LOD. In addition, despite their increased risk of developing diabetic complications, people with YOD were less likely to receive statin treatment than those with LOD.

YOD is also associated with higher risk of macrovascular complications than LOD. Hillier et al. reported that the risk of myocardial infarction in people with YOD was 14 times higher than that in age-matched controls, while the disease risk in people with LOD was less than 4-fold higher than that in age-matched controls [5]. Higher mortality rates and reduced life expectancy were also reported in people with YOD than in those with LOD or the general population [3,41,42]. In this study, we analyzed the prevalence of carotid artery plaque, which is closely associated with cardiovascular and cerebrovascular accidents [43,44]. The YOD has higher prevalences of carotid artery plaque than those with LOD in the age groups of 50–59 and 60–69 years. After adjusting for multiple confounding factors including age, the odds ratios of carotid artery plaque were increased in the YOD group compared to the LOD group. However, considering that the odds ratio was not statistically significant after adjustment for the duration of diabetes, a higher risk of progression of atherosclerosis in the YOD group than in the LOD group is mainly explained by the longer duration of diabetes. The effect of diabetes duration on vascular complications in people with YOD was also reported in previous studies. Chan et al. reported that the risk of cardio-renal events was higher in YOD than in those with LOD for any given age group; however, the association between cardio-renal events and YOD was not significant after further adjustment for diabetes duration [10].

Our study has several strengths and limitations. To date, there are a limited number of studies that compare the prevalences and the risks of microvascular complications, especially diabetic neuropathy, between the YOD and LOD populations. Most of the previous studies focused on evaluating the effect of YOD and T1DM on microvascular complications [4,45,46]. We assessed the different microvascular complications including diabetic retinopathy, CKD, and neuropathy in YOD and LOD. We also analyzed the long-term risk of developing diabetic retinopathy and CKD. This study has several limitations as well. First, because GADA was measured only when T1DM was highly suspected, those with LADA might not have been completely excluded. Second, there have been changes in diagnostic criteria and treatment guidelines over the long enrolment period, and these changes could have been a bias in the analysis. Therefore, in the final analysis, the year of enrolment was additionally added as an adjustment variable, but the possibility of insufficient correction may still remain. Third, the adjustments on metabolic indicators that may have changed during the study period may not be sufficient and not all participants were screened for all complications. Additionally, adjustment level and the presence of missing data could have affected the results. However, we confirmed the results after adjusting for multiple variables, modifying the adjustment levels (Supplementary Table 3). Lastly, we could not collect data on neuropathic symptoms, which is relevant to individual well-being. In this study, diabetic neuropathy was defined based on the NCV, and NCV has limitations in that it only assesses large fibers [47]. However, NCV is an objective method to evaluate the risk of developing diabetic neuropathy, which makes the study results reliable [47].

In summary, YOD is associated with higher prevalences of microvascular complications than LOD and this association is mainly due to the prolonged diabetes duration. However, the prevalence of neuropathy was significantly higher after adjusting for factors including the duration of diabetes. The characteristics of YOD itself may also contribute to an increase in microvascular complication risk. These findings emphasize the importance of paying close attention to YOD and its complications. However, further studies are warranted to provide a better understanding and management strategies for YOD.

Author contribution

Conceptualization: YC, HSP, and SHK
Methodology: YC, BWH, SHS, DHS, and SHK
Data curation: YC, DHS, SHA, SH and SHK
Statistical analysis: YC and YJS
Investigation: YC, HSP, and SHK
Writing and Editing: YC, HSP, YJS and SHK
Supervision, SHK.

Declaration of Competing Interest

The authors declare no conflicts of interest

Acknowledgements

We would like to thank Editage (www.editage.co.kr) for English language editing.

Funding

This work was supported by INHA UNIVERSITY HOSPITAL Research Grant.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.diabet.2022.101389.

References

[1] van Dieren S, Beulens JW, van der Schouw YT, Grobbee DE, Neal B. The global burden of diabetes and its complications: an emerging pandemic. Eur J Cardiovasc Prev Rehabil 2010;17(Suppl 1):S3–8. doi: 10.1097/01.hjr.0000368191.86614.5a.
[2] Magliano DJ, Sacre JW, Harding JL, Gregg EW, Zimmet PZ, Shaw JE. Young-onset type 2 diabetes mellitus - implications for morbidity and mortality. Nat Rev Endocrinol 2020;16:321–31. doi: 10.1038/s41574-020-0334-z.
[3] Huo L, Magliano DJ, Rancière F, Harding JL, Nanayakkara N, Shaw JE, et al. Impact of age at diagnosis and duration of type 2 diabetes on mortality in Australia 1997–2011. Diabetologia 2018;61:1055–63.
[4] Constantino MI, Molyneaux L, Limacher-Gisler F, Al-Saeed A, Luo C, Wu T, et al. Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. Diabetes Care 2013;36:3863–9. doi: 10.2337/dc12-2455.
[5] Hillier TA, Pedula KL. Complications in young adults with early-onset type 2 diabetes: losing the relative protection of youth. Diabetes Care 2003;26:2999–3005. doi: 10.2337/diacare.26.11.2999.
[6] Huo X, Gao L, Guo L, Xu W, Wang W, Zhi X, et al. Risk of non-fatal cardiovascular diseases in early-onset versus late-onset type 2 diabetes in China: a cross-sectional study. Lancet Diabetes Endocrinol 2016;4:115–24. doi: 10.1016/S2213-8587(15)00508-2.
[7] Viner R, White B, Christie D. Type 2 diabetes in adolescents: a severe phenotype posing major clinical challenges and public health burden. Lancet 2017;389:2252–60. doi: 10.1016/S0140-6736(17)31371-5.
[8] Today Study Group. Long-term complications in youth-onset type 2 diabetes. N Engl J Med 2021;385:416–26.
[9] Dabelea D, Stafford JM, Mayer-Davis EJ, D'Agostino R, Dolan L, Imperatore G, et al. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. JAMA 2017;317:825–35.
[10] Chan JC, Lau ES, Luk AO, Cheung KK, Kong AP, Yu LW, et al. Premature mortality and comorbidities in young-onset diabetes: a 7-year prospective analysis. Am J Med 2014;127:616–24. doi: 10.1016/j.amjmed.2014.03.018.

[11] Middleton TL, Constantino MI, Molyneaux L, D'Souza M, Twigg SM, Wu T, et al. Young-onset type 2 diabetes and younger current age: increased susceptibility to retinopathy in contrast to other complications. Diabet Med 2020;37:991–9. doi: 10.1111/dme.14238.
[12] Pavkov ME, Bennett PH, Knowler WC, Krakoff J, Sievers ML, Nelson RG. Effect of youth-onset type 2 diabetes mellitus on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. JAMA 2006;296:421–6. doi: 10.1001/jama.296.4.421.
[13] Huang JX, Liao YF, Li YM. Clinical features and microvascular complications risk factors of early-onset type 2 diabetes mellitus. Curr Med Sci 2019;39:754–8. doi: 10.1007/s11596-019-2102-7.
[14] Ahlqvist E, Storm P, Karajamaki A, Martinell M, Dorkhan M, Carlsson A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol 2018;6:361–9. doi: 10.1016/S2213-8587(18)30051-2.
[15] American Diabetes A.. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2021. Diabetes Care 2021;44:S15–33. doi: 10.2337/dc21-S002.
[16] Hur KY, Moon MK, Park JS, Kim S-K, Lee S-H, Yun J-S, et al. 2021 clinical practice guidelines for diabetes mellitus in Korea. dmj 2021;45:461–81. doi: 10.4093/dmj.2021.0156.
[17] Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010;87:4–14. doi: 10.1016/j.diabres.2009.10.007.
[18] Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro III AF, HI Feldman, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
[19] Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care 1998;21:2191.
[20] Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care 2010;33:2285–93. doi: 10.2337/dc10-1303.
[21] Kang ES, Kim HJ, Ahn CW, Park CW, Cha BS, Lim SK, et al. Relationship of serum high sensitivity C-reactive protein to metabolic syndrome and microvascular complications in type 2 diabetes. Diabetes Res. Clin. Pract. 2005;69:151–9.
[22] Cho Y, Seo SH, Seo DH, Ahn SH, Hong S, Huh BW, et al. Differences in complication patterns in subgroups of type 2 diabetes according to insulin resistance and beta-cell function. Sci Rep 2022;12:1–9.
[23] Qi Y, Fan J, Liu J, Wang W, Wang M, Sun J, et al. Cholesterol-overloaded HDL particles are independently associated with progression of carotid atherosclerosis in a cardiovascular disease-free population: a community-based cohort study. J Am Coll Cardiol 2015;65:355–63. doi: 10.1016/j.jacc.2014.11.019.
[24] Lee HH, Cho Y, Choi YJ, Huh BW, Lee BW, Kang ES, et al. Non-alcoholic steatohepatitis and progression of carotid atherosclerosis in patients with type 2 diabetes: a Korean cohort study. Cardiovasc Diabetol 2020;19:81. doi: 10.1186/s12933-020-01064-x.
[25] Hennig C. Cluster-wise assessment of cluster stability. Comput Stat Data Anal 2007;52:258–71.
[26] Xu Y, Wang L, He J, Bi Y, Li M, Wang T, et al. Prevalence and control of diabetes in Chinese adults. JAMA 2013;310:948–59. doi: 10.1001/jama.2013.168118.
[27] Won JC, Lee JH, Kim JH, Kang ES, Won KC, Kim DJ, et al. Diabetes fact sheet in Korea, 2016: an appraisal of current status. Diabetes Metab J 2018;42:415–24. doi: 10.4093/dmj.2018.0017.
[28] Bronson-Castain KW, Bearse Jr. MA, Neuville J, Jonasdottir S, King-Hooper B, Barez S, et al. Early neural and vascular changes in the adolescent type 1 and type 2 diabetic retina. Retina 2012;32:92–102. doi: 10.1097/IAE.0b013e318219deac.
[29] Song SH. Significant retinopathy in young-onset type 2vs. type 1 diabetes: a clinical observation. Int J Clin Pract 2016;70:853–60. doi: 10.1111/ijcp.12789.
[30] Song SH, Gray TA. Early-onset type 2 diabetes: high risk for premature diabetic retinopathy. Diabetes Res Clin Pract 2011;94:207–11. doi: 10.1016/j.diabres.2011.07.030.
[31] Krakoff J, Lindsay RS, Looker HC, Nelson RG, Hanson RL, Knowler WC. Incidence of retinopathy and nephropathy in youth-onset compared with adult-onset type 2 diabetes. Diabetes Care 2003;26:76–81. doi: 10.2337/diacare.26.1.76.
[32] Nanayakkara N, Ranasinha S, Gadowski A, Heritier S, Flack JR, Wischer N, et al. Age, age at diagnosis and diabetes duration are all associated with vascular complications in type 2 diabetes. J Diabetes Complications 2018;32:279–90. doi: 10.1016/j.jdiacomp.2017.11.009.
[33] Robertson R, Zhou H, Zhang T, Harmon JS. Chronic oxidative stress as a mechanism for glucose toxicity of the beta cell in type 2 diabetes. Cell Biochem Biophys 2007;48:139–46. doi: 10.1007/s12013-007-0026-5.
[34] Kahn SE, Lachin JM, Zinman B, Haffner SM, Aftring RP, Paul G, et al. Effects of rosiglitazone, glyburide, and metformin on beta-cell function and insulin sensitivity in ADOPT. Diabetes 2011;60:1552–60. doi: 10.2337/db10-1392.
[35] Matthews DR, Cull CA, Stratton IM, Holman RR, Turner RC. UKPDS 26: sulphonylurea failure in non-insulin-dependent diabetic patients over six years. UK Prospective Diabetes Study (UKPDS) Group. Diabet Med 1998;15:297–303. doi: 10.1002/(SICI)1096-9136(199804)15:4<297::AID-DIA572>3.0.CO;2-W.
[36] Bacha F, Gungor N, Lee S, Arslanian SA. Progressive deterioration of beta-cell function in obese youth with type 2 diabetes. Pediatr Diabetes 2013;14:106–11. doi: 10.1111/j.1399-5448.2012.00915.x.
[37] Hillier TA, Pedula KL. Characteristics of an adult population with newly diagnosed type 2 diabetes: the relation of obesity and age of onset. Diabetes Care 2001;24:1522–7. doi: 10.2337/diacare.24.9.1522.
[38] Mast R, Danielle Jansen AP, Walraven I, Rauh SP, van der Heijden AA, Heine RJ, et al. Time to insulin initiation and long-term effects of initiating insulin in people with type 2 diabetes mellitus: the Hoorn Diabetes Care System Cohort Study. Eur J Endocrinol 2016;174:563–71. doi: 10.1530/EJE-15-1149.
[39] Yang YS, Han K, Sohn TS, Kim NH. Young-onset type 2 diabetes in South Korea: a review of the current status and unmet need. Korean J Intern Med 2021;36:1049–58. doi: 10.3904/kjim.2021.379.
[40] Nanayakkara N, Pease AJ, Ranasinha S, Wischer N, Andrikopoulos S, de Courten B, et al. Younger people with Type 2 diabetes have poorer self-care practices compared with older people: results from the Australian National Diabetes Audit. Diabet Med 2018;35:1087–95. doi: 10.1111/dme.13660.
[41] Færch K, Carstensen B, Almdal TP, Jørgensen ME. Improved survival among patients with complicated type 2 diabetes in Denmark: a prospective study (2002–2010). J Clin Endocrinol Metab 2014;99:E642–E6.
[42] Huo L, Harding JL, Peeters A, Shaw JE, Magliano DJ. Life expectancy of type 1 diabetic patients during 1997-2010: a national Australian registry-based cohort study. Diabetologia 2016;59:1177–85. doi: 10.1007/s00125-015-3857-4.
[43] Wannarong T, Parraga G, Buchanan D, Fenster A, House AA, Hackam DG, et al. Progression of carotid plaque volume predicts cardiovascular events. Stroke 2013;44:1859–65. doi: 10.1161/STROKEAHA.113.001461.
[44] Gomez CR. Carotid plaque morphology and risk for stroke. Stroke 1990;21:148–51. doi: 10.1161/01.str.21.1.148.
[45] Amutha A, Anjana RM, Venkatesan U, Ranjani H, Unnikrishnan R, Narayan KMV, et al. Incidence of complications in young-onset diabetes: comparing type 2 with type 1 (the young diab study). Diabetes Res Clin Pract 2017;123:1–8. doi: 10.1016/j.diabres.2016.11.006.
[46] Dabelea D, Stafford JM, Mayer-Davis EJ, D'Agostino Jr R, Dolan L, Imperatore G, et al. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. JAMA 2017;317:825–35. doi: 10.1001/jama.2017.0686.
[47] Petropoulos IN, Ponirakis G, Khan A, Almuhannadi H, Gad H, Malik RA. Diagnosing diabetic neuropathy: something old, something new. Diabetes Metab J 2018;42:255–69. doi: 10.4093/dmj.2018.0056.