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HbA1c, Systolic Blood Pressure Variability and Diabetic Retinopathy in Asian Type 2 Diabetes

Running Head: HbA1c variability and DR

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ABSTRACT

Objective: To examine the association of hemoglobin A1c (HbA1c) and systolic blood pressure (SBP) variability with diabetes-specific moderate retinopathy in Asians with type 2 diabetes.

Methods: We conducted a retrospective study of 172 moderate diabetic retinopathy [DR] cases and 226 controls without DR matched for age, sex and ethnicity. Serial HbA1c and SBP (range of 3-6 readings) over 2 years prior to photographic screening of DR were collected. Intrapersonal mean and standard deviation (SD) of HbA1c (iM-HbA1c and iSD-HbA1c) and SBP (iM-SBP and iSD-SBP) were derived. Moderate DR was assessed from digital retinal photographs and defined as level >43 using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale.

Results: Cases of moderate DR had higher iM-HbA1c (8.2% vs. 7.3%, p=0.001), iSD-HbA1c (1.22 versus 0.64, p=0.001), iM-SBP (136.8 vs. 129.6 mm Hg, p=0.001) and iSD-SBP (13.3 vs. 11.1, p=0.002) than controls. In the multivariable regression model adjusted for age, gender, ethnicity, duration of diabetes, SBP and HbA1c variables, iM-HbA1c and iM-SBP were significantly associated with moderate DR [OR 1.80 (95% CI 1.37-2.36) and OR 1.03 (95% CI 1.01-1.05) respectively]. iSD-HbA1c and iSD-SBP were not associated with moderate DR. When stratified by HbA1c < 7%, only iSD-SBP remained significantly associated with moderate DR (1.11 [1.01-1.21]).

Conclusion: In a cohort of Asian patients with type 2 diabetes, both higher mean HbA1c levels and SBP, but not their variability, were associated with moderate DR. Among those with good glycemic control, wider variability of SBP is associated with moderate DR.

Key points

1. The significant finding (s) of the study:

In a cohort of Asian patients with type 2 diabetes, both elevated mean glycated haemoglobin (HbA1c) levels and systolic blood pressure (SBP), but not their variability, were associated with moderate diabetic retinopathy (DR).

2. This study adds:

In a sample of Asian patients with type 2 diabetes, HbA1c and SBP variability were not associated with DR.

Keywords

Blood pressure; Diabetes mellitus; Diabetic Retinopathy; Glycated hemoglobin

Introduction

Diabetic retinopathy (DR), the most common microvascular complication of diabetes mellitus,[1] is the leading cause of blindness in working adults globally.[2] Diabetes-related visual impairment places a significant burden on society,[3] with healthcare and economic burdens further compounded by the resulting decline in quality of life.[2] Well-established risk factors for DR include chronic hyperglycemia,[4-6] or HbA1c, and high systolic blood pressure (SBP).[1;5;7] However, diabetic patients may have a wide variation in their long-term glycemic control despite having similar average HbA1c values.[8] HbA1c variability is defined as changes in glycemia over longer periods of time (month to month or quarterly) that lead to a change in their values from one clinic visit to the next,[9] respectively, contrary to within-day glucose fluctuations as a consequence of meals.

Several recent studies have investigated the association between variability in HbA1c and micro- and macrovascular complications. In type 1 diabetes, while HbA1c variability increased the risk for DR and diabetic nephropathy (DN) over and above that of mean HbA1c values alone,[10-12] within-day glucose fluctuations did not confer additional risk in the development of microvascular complications.[13] In type 2 diabetes, studies have consistently suggested that HbA1c variability remains significantly associated with the development of DN.[12;14-17] However, the role of HbA1c variability in the development of DR in type 2 diabetes is less consistent, with reports of increased HbA1c variability serving as predictors of cardiovascular and chronic kidney disease, but not of DR.[15;16;18]

Similar to glycemic variability, blood pressure (BP) variability has also been shown to be associated with adverse outcomes in diabetic patients. In a recent clinical trial, besides maximum SBP, Hata et al found that visit-to-visit variability in systolic blood pressure (SD of SBP) contribute to macrovascular (cardiovascular events) and microvascular events (DR and diabetic neuropathy) in a multi-centre Western study of Type 2 diabetic patients,[19] explained partially by arterial stiffness[20] and abnormal autonomic function.[21] However, to our knowledge, no study has examined the association of BP variability with DR in Asian patients.

Determining if variability of HbA1c and SBP values is associated with DR in Asians with type 2 diabetes might help to reduce diabetic complication as physicians could educate their patients to maintain glycemic control consistently. Therefore, we aimed to determine if HbA1c and SBP variability as assessed retrospectively from regular and consecutive HbA1c and SBP values obtained during a 2-year period preceding the onset of moderate DR were independently associated with diabetes-specific moderate DR.

Methods

Study population

We performed a retrospective case-control study using the data obtained from the database of patients with type 2 diabetes, who had undergone retinal screening at a public primary care clinic (polyclinic) at Outram district in southern Singapore from 2012 to 2013. Type 2 diabetes was defined as a fasting plasma glucose of ≥7 mmol/L (126 mg/dL), a 2-hour plasma glucose of ≥ 11.1mmol/L (200mg/dL) after a 75-g oral glucose tolerance test (OGTT), or a random plasma glucose >11.1mmol/L (200mg/dL) in the presence of symptoms, all of which must be confirmed on repeat measurement

with the same test the subsequent day. All patients with type 2 diabetes with at least one dilated fundus photographic examination and three to six consecutive 4-monthly HbA1c and BP values (lesser readings are attributed to a non-compliance to the scheduled 4-monthly clinic visits) in 2 years prior to their first retinal screening done at the polyclinic were considered eligible for inclusion in the study. This inclusion criterion leads to more reliable estimates of the HbA1c variability, as only patients with regular centre attendance are included. Both cases and controls were selected from the same database. Cases were patients who were found to have a first prevalence of moderate or worse DR on screening (n=172). Moderate DR was chosen as the target outcome as it has been shown to be more specific to diabetes, whereas mild DR is less specific for diabetes.[22;23]

Controls were patients with type 2 diabetes but without DR found on screening and on follow-up with the polyclinic within the same duration as the cases. We recruited them in a ratio of 1 case to 2 controls initially (n=344) matched for age, gender and race. After excluding those with missing information, we were left with 226 controls. The study adhered to the provisions of the Declaration of Helsinki for research involving human subjects and was approved by the SingHealth Institutional Review Board.

Assessment of outcome - DR

Digital retinal photographs were taken following the Early Treatment for Diabetic Retinopathy Study (ETDRS) protocol.[24] 2-field photographs (1 optic-disc centered and macular centered each) using a non-mydriatic 45^0 digital retinal camera (Canon CR-DGi with a 10-D SLR back; Canon, Tokyo, Japan) were obtained for each subject on each visit. Images were graded for DR by a standardised team of trained graders blinded

to the subject characteristics. Subjects were considered to have DR if any of the following lesions were present in any eye: microaneurysms, haemorrhages, cotton wool spots, intraretinal microvascular abnormalities, hard exudates, venous beading, and new vessels. For each eye, retinopathy severity score was assigned according to modified Airlie House Classification System.[25] Based on the severity score of the worse eye, any-DR was defined as a severity score of level 15 and above and moderate or worse DR, as a severity score of level 43 and above. Kappa statistic for inter-rater variability was calculated**.**

Assessment of HbA1c (%) mean and variability

HbA1c was analysed centrally based on the DCA Vantage Hemoglobin A1c assay analyser (DCA Vantage, Siemens Medical Solution Diagnostics, Cergy-Pontoise, France), which is a HbA1c-specific mouse monoclonal antibody adsorbed onto latex particles. HbA1c values were converted to the Diabetes Control and Complications trial (DCCT)-aligned reference HbA1c. The range of HbA1c values reported by the analyser is from 2.5% to 14.0%. Average HbA1c and HbA1c variability was calculated for each patient as the intrapersonal mean (iM-HbA1c) and standard deviation [SD] (iSD-HbA1c) respectively for three to five consecutive HbA1c values obtained during the 2-year period preceding enrolment into the study.

Assessment of SBP mean and variability

Hypertension was defined as repeated average SBP measurements >135 mmHg or diastolic BP (DBP)>85 mm Hg or the use of antihypertensive medications. BP was measured twice (5 minutes apart) in a seated position after the person had rested for at least 5 minutes using a standardised automated sphygmomanometer (Six00 series Aneroid Desk Sphygmomanometer, Accoson, UK). The mean of 2 SBP and DBP

recordings as measured during each visit of the participants at the study site (polyclinic) was used as the SBP and DBP values for each visit. Mean SBP and SBP variability was calculated for each patient as the intrapersonal mean (iM-SBP) and SD (iSD-SBP) respectively for three to five consecutive 3-monthly SBP values obtained during the 2-year period preceding enrolment. Hypertension was defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg, and/or on antihypertensive treatment.

Measurement of other risk factors for DR and complications

Information on socio-demographic and lifestyle factors of subjects was collected retrospectively from the polyclinic's electronic health records based on a standardised protocol. These included age, gender, ethnicity, body-mass index (BMI) calculation, known history of hypertension, hyperlipidaemia, previously documented major events of cardiovascular disease (CVD) such as myocardial infarction and stroke, chronic kidney disease (CKD), known diabetes duration and current diabetic status and treatment (diet only, oral hypoglycemic agents (OHGA) and/or insulin), BP and lipid-lowering medications. Laboratory values obtained included triglycerides, total, HDL and LDL cholesterol and serum creatinine. Triglycerides and total and HDL cholesterol were determined by standard analytical methods; LDL Cholesterol was calculated by the Friedwald formula. Dyslipidaemia was defined as high (≥2.6 mmol/L) LDL cholesterol and/or on lipid-lowering treatment. CKD was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/minute/1.73 m^2 based on standardized creatinine.[26] eGFR was measured using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Statistical Analyses

All statistical analyses were performed using SPSS version 21.0. Based on a previous study by Penno et al[18] reporting HbA1c to be normally distributed with a SD of 0.4, a sample size of at least 172 cases and 226 controls will have more than 99% power to detect a true difference in the mean iM as small as 0.17 between the two groups with a type 1 error probability of 0.05. For iSD, a sample size of at least 66 cases and 50 controls will have more than 80% power to detect a difference in the mean iSD as small as 0.05 between the two groups with a type 1 error probability of 0.05.

Data were expressed as mean ± SD for continuous variables and number of subjects and percentage for categorical variables. Continuous variables were compared by the Student t test or one-way ANOVA for normally distributed variables and by Mann-Whitney U test or Kruskal-Wallis test for variables with a skewed distribution. Pearson chi-square test was applied to categorical variables.

HbA1c and SBP variability: iM-HbA1c, iSD-HbA1c, iM-SBP and iSD-SBP were analysed as continuous variables (per unit increase). We examined the association of iM-HbA1and iSD-HbA1c with moderate DR in two separate logistic regression models: 1) age and sex-adjusted and 2) multivariable model additionally adjusted for ethnicity, duration of diabetes, presence of cardiovascular disease, albuminuria, anti-diabetic medications, iM-HbA1c, iSD-HbA1c, iM-SBP and iSD-SBP.

We tested for interactions between iMHbA1c and iM-SBP and iSD-SBP and between iM-SBP and iMHbA1c and iSD-HbA1c by including cross-product interaction terms in the multivariable logistic regression models. As the P-interaction for iSD-SBP was significant (0.048; other P-interactions were >0.05), we stratified the population by

HbA1c cut point of 7% (iM-HbA1c < 7% vs. iM-HbA1c and ≥7 %) and repeated the multivariable model in Table 2. Statistical analysis was performed using the statistical package IBM SPSS Statistics for Windows (Version 21.0. Armonk, NY: IBM Corp).

Results

Characteristics of participants

Baseline characteristics of the study population are summarized in **Table 1.** Compared to those without DR, those with moderate DR were younger, more likely to be female, have previous cardiovascular disease, not on anti-hyperglycemic, or hypoglycemic, or diabetic treatment and have higher levels of iM-HbA1c, iSD-HbA1c, iM-SBP, iSD-SBP, and iSD-DBP. There were no significant differences in the number of HbA1c or BP readings obtained between the two groups (4.71 vs 4.88, p = 0.31).

iM-HbA1c and iSD-HbA1C

In **Table 2** showing the age, gender-adjusted models, only iM-HbA1c was significantly associated with moderate DR. In the age-sex adjusted and multivariable models, the association of iM-HbA1c with moderate DR remained significant [OR 1.62 (95% CI 1.20-2.05)] and [OR 1.79 (95% CI 1.29-2.25)] respectively. The association of iSD-HbA1c with moderate DR remained insignificant.

iM-SBP and iSD-SBP

In **Table 2**, age- and gender-adjusted logistic regression analysis performed for moderate DR showed a significant association with iM-SBP [OR 1.03 (95% CI 1.01-1.04)] as well as iSD-SBP [OR 1.03 (1.01-1.05)] independently. However, in the age-sex adjusted and multivariable models, only iM-SBP remained independently associated with moderate DR [OR 1.03 (95% CI 1.01-1.04)] and [OR 1.03 (95% CI 1.01-1.05)] respectively. iSD-SBP however was not significantly associated [OR 1.02 (95% CI

0.98-1.07)] with moderate DR. In all logistic regression models, additional adjustment for diabetic mediation did not alter the results.

Finally, in subgroup analysis stratified by a HbA1c cut-point of 7% (**Table 3**), for participants with HbA1c < 7%, in the multivariate model adjusted for the same confounders as model 2, iSD-SBP alone was significantly associated with moderate DR [OR 1.11 (95% CI 1.01-1.21), P-interaction between iM-HbA1c and iSD-SBP was 0.048]. For those with HbA1c ≥ 7%, similar to the main analysis, iM-HbA1c [OR 1.49 (95% CI 1.09-2.03)] and iM-SBP [OR 1.03 (95% CI 1.00-1.05)] remained significantly associated with moderate DR.

Discussion

In a clinic-based sample of Asian patients with type 2 diabetes, both higher levels of mean HbA1c and mean SBP were associated with moderate DR independent of potential confounders. However, neither HbA1c variability nor SBP variability were associated with moderate DR. To our knowledge, this is the first study to examine the association of HbA1c and SBP variability with DR in Asian patients with type 2 diabetes.

Few studies have examined the association of HbA1c variability with DR in Western populations. Our study findings are similar to an earlier report by Penno et al. where higher mean HbA1c but not HbA1c variability, showed a significant association with all levels of DR in a multicentre Italian study.[16] This could be attributed to the limited ability of HbA1c to reflect short-term fluctuations in blood sugar. Also, it is unable to

separately reflect postprandial hyperglycemia and fasting hypoglycemia. In addition, HbA1c is a not a good predictor of hypoglycemic episodes as it only accounts for 8% of the probability of severe hypoglycemia.[27;28] Some studies have postulated that short-term glycemic fluctuation (instead of HbA1c) may contribute to the development or progression of DR in type 2 diabetes.[29] Future studies incorporating both long-term (HbA1c) and short-term markers of glycemic variability, such as 1,5-anhydroglucitol (1,5-AG), glycated albumin (GA) and fructosamine (FA),[27;31;32] as well as continuous glucose monitoring systems[33] could clarify the relationship between short and long-term glycemic variability and DR in type 2 diabetes.

This is in contrast to what has been shown in subjects with type 1 diabetes, where increasing HbA1c variability adds to the risk of DR beyond that predicted by the average HbA1c alone.[10-12] Kilpatrick hypothesised that periods of hyperglycemia are 'remembered' by the body, thus an increased HbA1c variability could underlie the 'metabolic memory' phenomenon including oxidative stress.[34] However the discrepancy of such an observation between patients with type 1 and 2 diabetes remained unclear. This is especially so in the context of type 1 diabetes, where a rapid improvement of their glycemic control can lead to a short-term worsening of DR followed by a net improvement in the long-term,[35] but the benefit could be lost if another HbA1c increase followed after.

In our study, we were not able to find significant association between SBP variability and moderate DR, and the null association persisted among those with poor glycemic control (HbA1c ≥7%). This is similar to the earlier study reported by Hata et al that

visit-to-visit SBP variability was not significantly associated with both DN and DR in those with type 2 diabetes,[18] although average SBP remained significantly associated with moderate DR.[19;36]

Interestingly, in patients with type 2 diabetes with HbA1c < 7%, the associations between moderate DR and SBP variability was significant. It appears that in patients with type 2 diabetes with good HbA1c control, long-term fluctuations in SBP possibly play a larger role towards the risk of DR compared to that in patients with poorly-controlled type 2 diabetes. This finding is in contrast to the findings of Takao et al, whereby visit-to-visit SBP variability was an independent predictor of the progression of DN but not DR.[37] A subsequent study by the same authors found that SBP control preceding 5 years seemed to be important to prevent DR.[38] The reason for the significant association observed between SBP variability and DR among those with good glycemic control is not clear. Poor glycemic control being a major risk factor for DR, it is possible that the effect of SBP variability was not evident in the presence of poor glycemic control. Alternatively, the observed effect could also represent a chance finding and future studies are warranted to confirm or refute our study findings.

Our study has some limitations. Due to patients' non-compliance to regular 3-monthly clinic visits, we were unable to collect the sequential HbA1c and SBP values at uniform intervals. In addition, while our sample size was adequate to examine the association of HbA1c and SBP variability with DR, it was not sufficient to perform subgroup analyses stratified by severity of DR. Future prospective studies with large sample size and

sequential HbA1c and SBP values collected at uniform intervals are warranted to confirm or refute our study findings.

In conclusion, in a sample of Asian patients with type 2 diabetes, while mean HbA1c and SBP were associated with moderate DR, HbA1c and SBP variability were not associated with moderate DR. Among those with good glycemic control, wider variability of SBP was associated with moderate DR.

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Disclosure

Conflicts of Interest: None declared.

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Table 1. Characteristics of the study population with diabetes (n = 398)

Characteristics	Retinopathy absent (n = 226)	Retinopathy present (n = 172)	p-value*
Age (years), mean, SD	62.0 (10.6)	59.7 (11.52)	**0.04**
Gender, female, %	12.3	37.8	**0.001**
Race, %			
Chinese	66.4	76.7	
Malay	19.5	12.2	
Indian	9.7	8.7	
Other	4.4	2.4	
Hypertension, %	84.4	87.2	0.47
Hyperlipidaemia, %	92.4	90.1	0.47
Cardiovascular disease, %	4.0	14.0	**0.001**
Chronic kidney disease, %	7.6	10.5	0.37
Albuminuria, %			**0.02**
Normoalbuminuria	80.6	73.3	
Microalbuminuria	17.6	19.8	
Macroalbuminuria	0.44	7.0	
iM-Systolic blood pressure, mm Hg	129.6 (13.6)	136.8 (16.2)	**0.001**
iSD-Systolic blood pressure	11.1 (5.22)	13.3 (7.21)	**0.002**
iM-Diastolic blood pressure, mm Hg	73.0 (10.2)	73.0 (9.4)	0.99
iSD-Diastolic blood pressure	6.26 (3.0)	7.07 (3.6)	**0.02**

iM-HbA1c, %	7.3 (1.2)	8.2 (1.8)	**0.001**
iSD-HbA1c	0.64 (0.7)	1.76 (20.14)	**0.007**
HbA1c < 7%	118 (52.2)	41 (23.8)	
HbA1c > 7%	108 (47.8)	131 (76.2)	
No. of readings	4.88 (1.65)	4.71 (1.73)	0.31
Fasting blood glucose, mmol/L, mean, SD	8.22 (5.5)	8.43 (3.1)	0.67
Duration of diabetes, y, mean, SD	7.3 (9.0)	10.9 (10.1)	0.53
Total cholesterol, mmol/L, mean, SD	4.35 (0.8)	4.38 (1.0)	0.67
HDL Cholesterol, mmol/L, mean, SD	1.31 (0.5)	1.27 (0.4)	0.43
LDL Cholesterol, mmol/L, mean, SD	2.40 (0.7)	2.42 (0.8)	0.70
Triglycerides, mmol/L, mean, SD	1.50 (0.7)	1.56 (0.9)	0.48
Antihypertensive treatment, %	60.4	29.8	0.06
Lipid-lowering treatment, %	83.3	83.0	0.99
Antidiabetic treatment, %	74.3	91.8	**0.00**
Diet control, %	17.6	5.3	**0.001**
OHA, %	74.3	88.3	**0.002**
OHA + Insulin, %	6.8	18.7	**0.002**

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; iM , intrapersonal mean, iSD, intrapersonal standard deviation; OHA, oral hypoglycemic agents.

*p-value represents the difference in characteristics by retinopathy status based on chi-square test or analysis of variance as appropriate for the variable.

Table 2. Association of HbA1c (iM-HbA1c, iSD-HbA1c) and SBP (iM-SBP and iSD-SBP) variables with moderate DR

Models	**Odds ratio (95% confidence interval)**			
	iM-HbA1c	**iSD-HbA1c**	**iM-SBP**	**iSD-SBP**
Age, sex-adjusted	**1.62 (1.29-2.05)**	1.15 (0.78-1.70)	**1.03 (1.01-1.04)**	**1.04 (1.00-1.09)**
Multivariable model*	**1.70 (1.29 – 2.25)**	1.03 (0.66 – 1.62)	1.03 (1.01-1.05)	1.02 (0.98-1.07)

*Adjusted for age, sex, ethnicity, duration of diabetes, presence of cardiovascular disease, albuminuria, anti-diabetic medications, iM-HbA1c, iSD-HbA1c, iM-SBP and iSD-SBP.

Table 3. Associations of HbA1c and SBP variables with moderate DR stratified by glycemic control

Variables	Multivariable odds ratio (95% confidence interval)*
HbA1c < 7% (n=159)	**Odds ratio for moderate DR**
iM-HbA1c	1.40 (0.28-7.02)
iSD-HbA1c	8.93 (0.92-86.79)
iM-SBP	1.03 (0.99-1.07)
iSD-SBP	**1.11 (1.01-1.21)**
HbA1c ≥ 7% (n=239)	
iM-HbA1c	**1.49 (1.09-2.03)**
iSD-HbA1c	0.92 (0.59-1.43)
iM-SBP	**1.03 (1.00-1.05)**
iSD-SBP	0.99 (0.94-1.05)

*Adjusted for age, sex, ethnicity, duration of diabetes, presence of cardiovascular disease, iM-HbA1c, iSD-HbA1c, iM-SBP and iSD-SBP.

Table 1. Characteristics of the study population with diabetes (n = 398)

Characteristics	Retinopathy absent (n = 226)	Retinopathy present (n = 172)	p-value*
Age (years), mean, SD	62.0 (10.6)	59.7 (11.52)	**0.04**
Gender, female, %	12.3	37.8	**0.001**
Race, %			
Chinese	66.4	76.7	
Malay	19.5	12.2	
Indian	9.7	8.7	
Other	4.4	2.4	
Hypertension, %	84.4	87.2	0.47
Hyperlipidaemia, %	92.4	90.1	0.47
Cardiovascular disease, %	4.0	14.0	**0.001**
Chronic kidney disease, %	7.6	10.5	0.37
Albuminuria, %			**0.02**
Normoalbuminuria	80.6	73.3	
Microalbuminuria	17.6	19.8	
Macroalbuminuria	0.44	7.0	
iM-Systolic blood pressure, mm Hg	129.6 (13.6)	136.8 (16.2)	**0.001**
iSD-Systolic blood pressure	11.1 (5.22)	13.3 (7.21)	**0.002**
iM-Diastolic blood pressure, mm Hg	73.0 (10.2)	73.0 (9.4)	0.99
iSD-Diastolic blood pressure	6.26 (3.0)	7.07 (3.6)	**0.02**
iM-HbA1c, %	7.3 (1.2)	8.2 (1.8)	**0.001**

iSD-HbA1c	0.64 (0.7)	1.76 (20.14)	**0.007**
HbA1c < 7%	118 (52.2)	41 (23.8)	
HbA1c > 7%	108 (47.8)	131 (76.2)	
No. of readings	4.88 (1.65)	4.71 (1.73)	0.31
Fasting blood glucose, mmol/L, mean, SD	8.22 (5.5)	8.43 (3.1)	0.67
Duration of diabetes, y, mean, SD	7.3 (9.0)	10.9 (10.1)	0.53
Total cholesterol, mmol/L, mean, SD	4.35 (0.8)	4.38 (1.0)	0.67
HDL Cholesterol, mmol/L, mean, SD	1.31 (0.5)	1.27 (0.4)	0.43
LDL Cholesterol, mmol/L, mean, SD	2.40 (0.7)	2.42 (0.8)	0.70
Triglycerides, mmol/L, mean, SD	1.50 (0.7)	1.56 (0.9)	0.48
Antihypertensive treatment, %	60.4	29.8	0.06
Lipid-lowering treatment, %	83.3	83.0	0.99
Antidiabetic treatment, %	74.3	91.8	**0.00**
Diet control, %	17.6	5.3	**0.001**
OHA, %	74.3	88.3	**0.002**
OHA + Insulin, %	6.8	18.7	**0.002**

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; iM , intrapersonal mean, iSD, intrapersonal standard deviation; OHA, oral hypoglycemic agents.

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