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Association of Age at Diabetes Complication Diagnosis with Age at Natural Menopause in Women with Type 1 Diabetes: The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study

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Abstract

Objective: Vascular damage is thought to have a role in premature ovarian aging. We thus assessed the association between the presence, and age at onset of, vascular diabetes complications and age at natural menopause in women with type 1 diabetes.

Methods: Female participants of the Epidemiology of Diabetes Complications study with type 1 diabetes who experienced natural menopause and who never received hormone therapy during their menopausal transition were included in the analysis (n=105). Microalbuminuria (MA), overt nephropathy, proliferative retinopathy, confirmed distal symmetric polyneuropathy, and coronary artery disease, were assessed during biennial clinical exanimations for the first 10 years of follow-up and at year 18, 25 and 30. Menopausal status was determined via self-report and sex hormone data. For each complication, separate linear regression models were used to assess whether, compared with women without the complication of interest, an earlier age at complication development (i.e., <30 years of age) was associated with an earlier age at natural menopause.

Results: Although results from multivariable linear regression models suggested a similar age at menopause between women with normo-albuminuria and those diagnosed with MA after 30 years

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Trevor J Orchard: EDC study design and data acquisition, reviewed and edited the manuscript for intellectual content
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Declaration of competing interests

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of age, menopause occurred 2.06 years earlier (β±SE=−2.06±1.08) among women diagnosed with MA before age 30 (p=0.06). No significant association was observed for other complications.

Conclusion: Among women with type 1 diabetes, menopause appears to occur earlier in those diagnosed with MA before age 30 compared to those with normo-albuminuria, suggesting that vascular dysfunction associated with early microvascular disease may affect ovarian aging.

Keywords

type 1 diabetes; diabetes complications; age at natural menopause; microalbuminuria

Introduction

An earlier age at menopause has been associated with higher risks of cardiovascular disease and mortality from cardiovascular causes [1,2], atherosclerosis [3], and stroke [4]. The ovaries are highly vascular and have high rates of blood flow [5]; thus, it is logical to postulate that generalized vascular damage may have adverse impact on ovarian aging. Findings from two previous studies were supportive of this hypothesis [6,7]. Investigators from the Framingham Heart Study showed that each 1% increase in premenopausal Framingham risk score which represents the estimate of total coronary heart disease (CHD) risk (%) over the course of 10 years was related to 1.8 years earlier age at menopause [6]. A pooled analysis of over 170,000 women further found that women who experienced CHD or stroke before age 35 years had a two-fold risk of early menopause (<45 years), suggesting a harmful effect of a compromised vasculature following cardiovascular events on ovarian aging [7].

Individuals with type 1 diabetes are at high risk of vascular damage, which is manifested by macro- and microvascular complications. As discussed in a scientific statement from the American Heart Association and the American Diabetes Association [8], the age-adjusted risk of cardiovascular complications is approximately ten-fold higher in people with type 1 diabetes compared with the general population [9–11], and women are disproportionately affected, relative to their nondiabetic counterparts, than men [8,12]. In addition, cardiovascular events occur earlier in people with type 1 diabetes than in the general population [8]. For microvascular complications, investigators from the Pittsburgh Epidemiology of Diabetes Complications Study (EDC) showed that the cumulative incidence of proliferative retinopathy (PR), confirmed distal symmetric polyneuropathy (CDSP), and overt nephropathy (ON) were over 50%, 40%, and 30%, respectively, by 25 years of type 1 diabetes duration [13]. Indeed, compared to non-diabetic women, women with a diagnosis of type 1 diabetes were shown to experience an earlier natural menopause [14,15], although not all studies agree [16,17].

Conflicting findings have also been reported regarding the association between vascular complications and age at natural menopause among women with type 1 diabetes. A Finnish study found that proliferative retinopathy (n=17) and end-stage renal disease (n=9) were independently associated with earlier menopause[17]. However, data from the Diabetes Control and Complications Trial (DCCT) and its observational follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, suggested that microvascular complications were not associated with the onset of natural menopause after adjusting for

baseline age, although age of menopause per se was not evaluated as a main outcome in this study [18]. To date, no study has assessed the impact of timing of complication development on age at menopause. Therefore, the aim of the present study was to assess whether the age at the onset of vascular diabetes complications is predictive of the age at natural menopause in women with type 1 diabetes. We hypothesized that women with an earlier onset of vascular complications experience menopause earlier.

Methods

Study population

The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study is a prospective cohort study of childhood-onset (<17 years) type 1 diabetes. All participants were diagnosed, or seen within one year of diagnosis, at Children's Hospital of Pittsburgh between 1950 and 1980. The EDC study has been described in detail elsewhere [19]. Briefly, there were 658 participants (325 female and 333 male) who completed a baseline assessment in 1986–1988. The mean baseline age was 28 years (range 8–48 years) and the duration of type 1 diabetes was 19 years (range 8–37 years). All participants were subsequently surveyed biennially for up to 30 years and also reexamined at 2-, 4-, 6-, 8-, 10-, 18-, 25- and 30-years of follow-up. The EDC study protocols were approved by the University of Pittsburgh Institutional Review Board and all study participants provided written informed consent prior to performing any study procedures.

For the present analysis, from the 325 female EDC participants, we excluded women who did not have sex hormone data available due to missingness (n=53) or death (n=75), those who had a hysterectomy/oophorectomy before menopause (n=35), and those who received sex hormone therapy during the menopausal transition (n=20). In addition, we excluded women who had not yet reached natural menopause at their last available follow-up (n=37, age 18.3±4.0 years at baseline and 47.5±3.7 years at their last available follow-up). Therefore, a total of 105 female participants who experienced natural menopause during the 30-year study follow-up were included in the data analyses.

Risk factor assessment

At baseline assessment, survey questionnaires regarding demographic characteristics, medical history, and diabetes self-care (e.g. daily insulin dose per kilogram body weight) were completed by the participant. During the clinical visits, body mass index (BMI) was measured as weight in kilograms (kg) divided by height in meters squared (m^2). The waist to hip ratio (WHR) was measured as the circumference of the waist divided by that of the hips. Blood pressure was measured according to the hypertension detection and follow-up program (HDFP) protocol [20]. Hypertension was defined as blood pressure ≥140/90 mm Hg or the use of antihypertensive medications. The level of stable glycosylated hemoglobin (HbA1) was measured using ion exchange chromatography (Isolab, Akron, OH) during the first 18 months of the study, whereas automated high-performance liquid chromatography (Diamat, BioRad, Hercules, CA) was used for the remainder of the 10-year follow-up. These two assays were highly correlated (r=0.95). Original HbA1 measures were converted to DCCT standard HbA1c values using a regression equation derived from duplicate analyses

(DCCT HbA1c = [0.83 X EDC HbA1] + 0.14) [21]. Glucose disposal rate was estimated (eGDR) by using a regression equation derived from hyperinsulinemic-euglycemic clamp studies of 24 participants chosen to represent the full spectrum of insulin resistance (eGDR (mg/kg/min)=24.395-(12.971*WHR)-(3.388*Hypertension)-(0.601*HbA1c)) [22].

High-density lipoprotein cholesterol (HDL-C) was measured by means of a precipitation technique (heparin and manganese chloride) with a modification of the Lipid Research Clinics method [19,23]. Total cholesterol and triglycerides were measured enzymatically [19,23]. Non-HDL cholesterol (non-HDL-C) was computed by subtracting HDL-C from total cholesterol. White blood cell count was measured using a counter S-plus IV. Glomerular filtration rate(eGFR) was estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine formula [24]. Urinary albumin was measured by immunonephelometry [25].

Diabetes complication assessment

At baseline and biennial clinical examinations for the first 10 years of follow-up and at year 18, 25, and 30, participants underwent examinations for complication assessment, including microvascular complications such as microalbuminuria (MA), overt nephropathy (ON), proliferative retinopathy (PR), and confirmed distal symmetric polyneuropathy (CDSP), and macrovascular complications - coronary artery disease (CAD).

MA was defined as an albumin excretion rate (AER) of 20–200 μg/min (30–300mg/24 h), and ON was defined as an AER >200 μg/min (>300mg/24 h), in at least two out of three validated timed urine collections. Retinopathy was diagnosed by stereoscopic fundus photographs of fields 1, 2, and 4, which were filmed by a Zeiss camera and read by the Fundus Photography Reading Center at the University of Wisconsin–Madison [19,23]. PR was classified according to the modified Arlie House system [19,23]. CDSP was defined as experiencing at least two out of three of the following: symptoms consistent with distal symmetric polyneuropathy; sensory and/or motor signs; and absent/reduced tendon reflexes based on the Diabetes Control and Complications Trial clinical exam protocol [26], in addition to an abnormal age-specific vibratory threshold by the Vibratron II Tester (Physitemp Instruments, Clifton, NJ).

CAD is defined as CAD death, fatal or nonfatal myocardial infarction confirmed either by hospital records or Q-waves on electrocardiogram (Minnesota code 1.1, 1.2), angiographic stenosis ≥50% confirmed by hospital records, revascularization, EDC-diagnosed angina or ischaemic ECG changes (Minnesota code 1.3, 4.1–4.3, 5.1–5.3, 7.1) which include minor Q-waves, ST depression, T-wave inversion/flattening, or left bundle branch block.

Menopause status assessment

Natural menopause was defined as cessation of menstruation following one year of amenorrhea, not induced by surgical procedures or medications, including hysterectomy, oophorectomy, and hormone medications [27]. Women who had a hysterectomy and/or oophorectomy before menopause or those who received sex hormone therapy during the menopausal transition were thus excluded from analysis. Menopausal status was determined via self-report and sex hormone data as follows: women <45 years reporting regular

menstrual cycles were classified as pre-menopausal, whereas those >55 years with no menstrual periods for 12 months were classified as post-menopausal. Plasma follicle-stimulating hormone (FSH) and estradiol were measured in women falling outside this classification, in which case the Women's Ischemia Syndrome Evaluation (WISE) hormonal and historical algorithms [28] were used to assess menopausal status, but not making a distinction between peri- and pre-menopausal women. Age at menopause was defined as the chronological age at the time menopause was determined to have occurred.

Statistical analyses

Spearman correlation analysis was used to determine the correlation between age at complication diagnosis and age at natural menopause among women who had a complication diagnosed before menopause. Women were grouped into three categories based on presence and age at complication diagnosis prior to menopause onset: 1) complication diagnosed <30 years of age, 2) complication diagnosed >=30 years of age, and 3) no complication. Age 30 was selected as the cutoff because in this childhood-onset type 1 diabetes cohort, it would correspond to approximately 20 years of diabetes duration, and complication development by 20 years duration is considered "early". Linear regression models (PROC GLM) were used to assess the significance of the association between presence/age at complication onset (independent variable) with age at natural menopause (dependent variable). The presence/age at complication onset variable was entered as a class variable with the no complication group as the reference. Multivariable models were further constructed, adjusting for potential confounders, baseline BMI, smoking status, HDL, and HbA1c. Confounders for adjustment were selected based on previous reports of an association with age at menopause and were included in multivariable models regardless of statistical significance [29]. In the present study, age at baseline was statistically significantly correlated with age at complications diagnosis (r=0.35, p=0.03); thus, age at baseline was not included in the multivariable models as a covariate to avoid over adjustment. SAS version 9.4 (SAS Institute, Cary, NC) was used for all analyses.

Results

A summary of the baseline characteristics of the 105 female participants who reached natural menopause by the end of the 30-year follow-up is presented in Table 1. The mean baseline age was 29.5 years, with the mean age at diabetes onset of 9.3 years and duration of type 1 diabetes of 20.2 years. At baseline almost a third (32.3%) had prevalent MA, 16.5% had ON, 25.2% had PR, and 23.7% had CDSP, whereas only 3.8% had CAD. All 105 women were pre-menopausal at the baseline assessment but reached natural menopause within an average follow-up of 29.2±7.1 years. The mean age at natural menopause was 49.5 years.

For women who had a complication diagnosed before menopause, age at complication diagnosis, age at natural menopause, and their correlation coefficients are presented in Table 2. Age at MA diagnosis (r=0.28, p=0.03) and age at CDSP diagnosis (0.36, p=0.01) were positively correlated with age at natural menopause. Women with earlier onset of MA or CDSP had an earlier age at natural menopause. Although no statistically significant

correlations were observed for ON (r=0.32, p=0.12) and CAD (r=0.28, p=0.17), the magnitude of their correlations between age at diagnosis and age at menopause is similar to that seen for MA and CDSP. However, low correlation was observed for age at PR diagnosis and age at natural menopause (r=0.10, p=0.44).

Grouping women according to complication presence and diagnosis before or after age 30 (Table 3), differences in the age at natural menopause persisted for MA (p=0.02) and CDSP (p=0.02), with the youngest age at natural menopause among women who developed these complications before 30 years of age. Although not statistically significant, a similar pattern was observed for ON (P=0.27) and CAD (P=0.37), whereas age at menopause did not differ at all across categories of PR (P=0.95). Thus, women with ON or CAD diagnosed before 30 years had the youngest age at natural menopause while women with these complications diagnosed after 30 years and women without these complications had similar and older age at natural menopause.

Results from unadjusted and multivariable adjusted linear regression models for the association of presence and age at complications diagnosis with age at natural menopause were shown in Table 3. Generally, in unadjusted models, natural menopause occurred at a younger age among women with complications diagnosed before 30 years compared with those not developing the complication, although findings were statistically significant only for MA (β±Standard Error (SE)=−2.4±1.01, p=0.02)). After multivariable adjustment, this association was slightly attenuated (β±SE=−2.06±1.08, p=0.06).

In contrast, developing MA, ON, PR, or CAD after 30 years of age did not appear to be associated with an earlier age at menopause compared to those who never developed each respective complication. Interestingly, however, women developing CDSP after age 30 years reached natural menopause 2.19 years later (β±SE=2.19±0.86, p=0.01) compared with women without CDSP in the unadjusted model. This finding persisted (β±SE=2.95±0.91, p=0.002) after adjustment for baseline BMI, smoking status, HDL-C, and HbA1c.

Although parity, oral contraceptive use and educational status have been associated with an earlier age at menopause, they were not related to age at complication development in this cohort and thus, they could not constitute confounding factors. Nonetheless, when included in the final models, results remained similar.

Discussion

In the present study, we assessed the association of diabetes complications status before menopause and age at complication development with age at natural menopause in women with type 1 diabetes, using data from a prospective childhood-onset type 1 diabetes cohort. We observed that women with MA occurring before age 30 years experienced natural menopause earlier than women without MA before menopause, whereas no difference was observed between those diagnosed with MA after age 30 and women with normoalbuminuria. A similar pattern was observed for ON and CAD, although results were not statistically significant due to a smaller number with these complications. No difference

in age at menopause was observed by PR status, whereas women developing CDSP after age 30 reached menopause later compared with women free of CDSP.

Microalbuminuria, defined as an albumin excretion rate of 20–200 μg/min (30–300mg/24 h), is often the first clinical indicator of the presence of diabetic kidney disease [30], as well as a possible marker for kidney disease progression [31], although not all people with reduced glomerular filtration rate or diabetic kidney disease have or ever had MA [32]. Moreover, MA is a risk marker for cardiovascular events in diabetes [31,33] and also a strong predictor of all-cause mortality in patients with long-term type 1 diabetes [34]. Thus, MA is considered as a marker for generalized vascular dysfunction in patients with diabetes [33]. Despite the significance of MA in reflecting vascular injury, to the best of our knowledge, no study assessed the association of MA and ovarian aging in women with type 1 diabetes. In the present study, we found that women with MA occurring before 30 years had a younger age at natural menopause compared with women without MA before menopause, although this association became of marginal significance after multivariable adjustments (p=0.06). Among women with MA occurring after 30 years, age at natural menopause was similar to that of women with normoalbuminuria (p=0.55). These results suggest that long exposure to microvascular injury may be needed for age at natural menopause to be affected. Another explanation could be that early development of microalbuminuria represents vascular damage which also adversely affects age at natural menopause, i.e. vascular damage leads to both early presentation of complications and early menopause.

Currently, no other data are available on the role of age at MA presentation on age at natural menopause. However, our finding is supported by our previous observation in this population that for every 30% increase in albumin excretion rate over time, age at natural menopause decreased by 0.18 years (unpublished data, submission in progress). Moreover, as MA is known to increase cardiovascular risk [31,33] and data from the Framingham Heart Study showed that cardiovascular risk factors accelerate menopause [6], it is possible that MA affects the age of menopause.

Although not statistically significant, ON and CAD showed a similar pattern as MA in terms of their effects on age at menopause. The smaller number of cases in the present study for ON (n=26) and CAD (n=25) may not allow for adequate power to detect difference. Studies with a larger sample size of ON and CAD are needed to further confirm their roles in ovarian function in type 1 diabetes. Our results further showed that age at natural menopause was very similar regardless of absence, early or later onset of PR. The small number of cases diagnosed with PR before age 30 may also contribute to the lack of an association.

In contrast to findings for MA, we observed that women who developed CDSP after 30 years of age had an older age at natural menopause compared to women who never developed CDSP during follow-up, suggesting a protective effect of CDSP on ovarian function. While there is no direct evidence supporting this finding, animal studies in rats showed that activation of autonomic nerves (superior ovarian nerve in the suspensory ligament and the ovarian nerve plexus along the ovarian arterioles) to the ovary produces a decrease in ovarian blood flow and inhibition of estradiol and testosterone secretion [35,36]. However, if a protective effect of CDSP truly existed, an incremental increase in age at

menopause onset would have been expected from women without CDSP, to those with CDSP occurring after age 30 to women in whom CDSP occurred before 30 years of age. We did not detect a dose-response relationship which may suggest that the association of CDSP and age at natural menopause in the present study is a chance finding.

Strengths of this study include the well-characterized cohort of childhood-onset type 1 diabetes, including comprehensive ascertainment of vascular diabetes complications, and the long (mean of 29.2 years) follow-up. To the best of our knowledge, this is the first study assessing the impact of timing of complication onset on menopause by using age at complications diagnosis. Among the limitations, selection or survival bias may have been introduced by excluding from analyses women who died or dropped out prior to menopause onset. In addition, the generalizability of these findings may be limited due to lack of racial diversity in participants and a relatively small sample size.

In conclusion, women with type 1 diabetes in whom MA presented before age 30 experienced an earlier natural menopause compared to those with normoalbuminuria. A similar pattern was observed for ON and CAD, although results did not reach statistical significance. While it is necessary to validate these results in future studies with a larger sample size, our findings suggest that premature ovarian aging may be a further manifestation of vascular damage in women with type 1 diabetes. Our study findings also further emphasize the importance of preventing vascular impairment or delay the onset of vascular complications in type 1 diabetes by glycemic management and improvements in lifestyle.

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Highlights

- Conflicting findings have been reported regarding the association between vascular complications and age at natural menopause among women with type 1 diabetes.
- To date, no study has assessed the impact of timing of complication development on age at menopause
- Among women with childhood-onset type 1 diabetes, menopause occurred earlier in those diagnosed with microalbuminuria before age 30 compared to those with normo-albuminuria
- Although not statistically significant, overt nephropathy and coronary artery disease showed a similar pattern as microalbuminuria in terms of their effects on age at menopause

Table 1

Baseline characteristics of EDC female participants who experienced natural menopause during the study follow-up

Baseline Characteristics	n=105
Age at baseline (years)	29.5 ± 6.2
Age at diabetes onset (years)	9.3 ± 3.9
Duration of type 1 diabetes at baseline (years)	20.2 ± 7.0
Race (%, n)	
Non-Hispanic White	96.2 (101)
Black	3.8 (4)
Marital status (%, n)	
Single, never married	37.1 (39)
Currently married or living as if married	48.6 (51)
Divorced	7.6 (8)
Separated, Widowed, or others	6.7 (7)
Education (%, n=103)	
High school or less	35.0 (36)
Some college or received bachelor's degree	56.3 (58)
Graduate education beyond bachelor's degree	8.7 (9)
Smoking status (%, n)	
Never smoker	67.6 (71)
Past smoker	13.3 (14)
Current smoker	19.1 (20)
BMI (kg/m^2)	22.9 ± 2.9
Waist to hip ratio (n=104)	0.77 ± 0.05
Systolic blood pressure (mmHg)	107.9 ± 11.7
Diastolic blood pressure (mmHg)	68.5 ± 9.6
Hypertension (%, n)	8.6 (9)
Blood pressure medication use (%, n=103)	6.8 (7)
Total cholesterol (mg/dl)	181.0 (162.0, 197.0)
HDL-C (mg/dl)	61.0 (50.6, 73.0)
LDL-C (mg/dl) (n=100)	100.9 (87.0, 127.4)
Triglycerides (mg/dl) (n=102)	74.0 (51.0, 100.0)
ACE/ARB use (%, n=104)	1.9 (2)
Lipid medication use (%, n=104)	0 (0)
HbA1c (%, n=104)	8.4 ± 1.2
eGDR (mg*kg-1*min-1, n=103)	8.9±1.5
Insulin dose (units/day/kg, n=100)	0.71 ± 0.19
AER (μg/min)	10.4 (6.2, 25.7)
eGFR ($mL/min/1.73\ m^2$)	102.3 ± 27.9
WBC x $10^3/mm^2$	6.4 ± 1.9
Percent having ever used contraceptives (n=104)	63.5 (66)

Baseline Characteristics	n=105
Percent having ever been pregnant	72.4 (76)
Number of pregnancies (n=76)	2.4 ± 1.3
Number of live births (n=76)	1.4 ± 0.8
Microalbuminuria (%, n=99)	32.3 (32)
Overt nephropathy (%, n=97)	16.5 (16)
Proliferative retinopathy (%, n=103)	25.2 (26)
Confirmed distal symmetrical polyneuropathy (%, n=97)	23.7 (23)
Coronary artery disease (%, n=105)	3.8 (4)

Data are means (SD), median (IQR) or percent (n)

AER, albumin excretion rate; eGDR, estimated glucose disposai rate; eGFR, estimated glomerular filtration rate; WBC, white blood cell count

Table 2

Age at complication diagnosis and its association with age at natural menopause among women who had a complication diagnosed before menopause

Complications	Age at complication diagnosis	Age at natural menopause	Spearman Correlations	
	Mean (SD)	Mean (SD)	r	p-value
Microalbuminuria (n=59)	33.3±8.1	49.1±4.1	0.28	0.03
Overt nephropathy (n=26)	31.4±6.7	49.1±4.9	0.32	0.12
Proliferative retinopathy (n=61)	34.2±6.7	49.6±4.0	0.10	0.44
Confirmed distal symmetrical polyneuropathy (n=50)	35.5±7.0	50.1±3.2	0.36	0.01
Coronary artery disease (n=25)	40.9±8.7	49.8±2.9	0.28	0.17

Table 3

Linear regression models for the association of age at complication diagnosis with age at natural menopause

Age at complication diagnosis	Age at natural menopause		Unadjusted		Adjusted*	
	Mean (SD)	Overall P value	β coefficient (SE)	P value	β coefficient (SE)	P value
Microalbuminuria						
<30 yrs (n=25)	47.5±4.9	0.02	−2.40 (1.01)	0.02	−2.06 (1.08)	0.06
≥30 yrs (n=34)	50.2±3.1		0.31 (0.92)	0.74	0.60 (0.99)	0.55
No (n=40)	49.9±4.0		Ref		Ref	
Overt nephropathy						
<30 yrs (n=12)	47.7±5.8	0.27	−1.78 (1.28)	0.17	−1.42 (1.38)	0.31
≥30 yrs (n=14)	50.3±3.8		0.77 (1.20)	0.52	1.20 (1.28)	0.35
No (n=71)	49.5±3.8		Ref		Ref	
Proliferative retinopathy						
<30 yrs (n=17)	49.3±4.8	0.95	−0.03 (1.18)	0.98	0.24 (1.22)	0.85
≥30 yrs (n=44)	49.6±3.7		0.26 (0.88)	0.77	0.63 (0.94)	0.50
No (n=42)	49.4±4.1		Ref		Ref	
Confirmed distal symmetrical polyneuropathy						
<30 yrs (n=10)	48.0±3.4	0.02	−0.44 (1.39)	0.75	0.26 (1.50)	0.87
≥30 yrs (n=40)	50.6±3.0		2.19 (0.86)	0.01	2.95 (0.91)	0.002
No (n=47)	48.4±4.7		Ref		Ref	
Coronary artery disease						
<30 yrs (n=2)	46.0±4.2	0.37	−3.41 (2.90)	0.24	−3.46 (3.00)	0.25
≥30 yrs (n=23)	50.1±2.7		0.68 (0.96)	0.48	0.93 (0.99)	0.35
No (n=80)	49.4±4.4		Ref		Ref	

*Model allowed for baseline BMI, smoking status, HDL, and HbAlc