Intensity of Glycemic Exposure in Early Adulthood and Target Organ Damage in Middle Age: The CARDIA Study

Yifen Lin
First affiliated hospital of Sun Yat-sen University https://orcid.org/0000-0002-8803-3389
Xiangbin Zhong
Sun Yat-sen University First Affiliated Hospital
Zhenyu Xiong
Sun Yat-sen University First Affiliated Hospital
Shaozhao Zhang
Sun Yat-sen University First Affiliated Hospital
Menghui Liu
Sun Yat-sen University First Affiliated Hospital
Yongqiang Fan
Sun Yat-sen University First Affiliated Hospital
Yiquan Huang
Sun Yat-sen University First Affiliated Hospital
Xiuting Sun
Sun Yat-sen University First Affiliated Hospital
Huimin Zhou
Sun Yat-sen University First Affiliated Hospital
Xingfeng Xu
Sun Yat-sen University First Affiliated Hospital
Yue Guo
Sun Yat-sen University First Affiliated Hospital
Yuqi Li
Sun Yat-sen University First Affiliated Hospital
Daya Yang
Sun Yat-sen University First Affiliated Hospital
Xiaomin Ye
Sun Yat-sen University First Affiliated Hospital
Xiaodong Zhuang
Sun Yat-sen University First Affiliated Hospital
Xinxue Liao (liaoxinx@mail.sysu.edu.cn)

first affiliated hospital of Sun Yat-Sen University https://orcid.org/0000-0001-7631-1866

Original investigation

Keywords: Hyperglycemia, Left Ventricular Hypertrophy, Cardiac Dysfunction, Coronary Artery Calcium, Albuminuria

DOI: https://doi.org/10.21203/rs.3.rs-72341/v1

Abstract

Background

To determine whether long-term intensity of glycemic exposure (IGE) during young adulthood is associated with multiple target organs function at midlife independent of single fasting glucose (FG) measurement.

Methods

We included 2,859 participants, aged 18–30 years at Y0, in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. IGE was calculated as the sum of (average FG of two consecutive examinations × years between the examinations) over 25 years. Target organs function was indicated by cardiac structure, left ventricular (LV) systolic function, LV diastolic function, coronary artery calcium (CAC) and urine albumin-to-creatinine ratio (UACR) at Y25. We evaluated the associations between IGE with target organs function using linear regression models and estimated the associations between IGE with numbers of organs involved (0, 1, or ≥ 2 organs) using multinomial logistic regression models.

Results

A 1-SD increment of IGE was significantly associated with worse target organs function after multivariable adjustment: left ventricular mass (β [SE], 5.468 [1.175]); global longitudinal strain (β [SE], 0.161 [0.071]); E/e' ratio (β[SE], 0.192 [0.071]); CAC score (β [SE], 27.948 [6.116]) and log UACR (β [SE], 0.076 [0.010]). Besides, IGE was independently associated with having ≥ 2 organs involved in both overall population (OR [95% CI], 1.48 [1.23, 1.41], $p < 0.001$) and subgroups stratified by diabetes at Y25.

Conclusions

Higher intensity of glycemic exposure during young adulthood was independently associated with subclinical alterations of target organs function at midlife. Our findings highlight the importance of early screening and management of IGE in youth.

Introduction

Individuals with long-term exposure to hyperglycemia underwent chronic injuries to multiple organ systems. Previous studies have confirmed strong correlations between elevated blood glucose with coronary artery disease (CAD), diabetic cardiomyopathy and diabetic nephropathy in late life [1–3]. Since chronic exposure to glycemia shows detrimental impacts on target organs, a life-course evaluation of glycemic exposure taking into account both the magnitude and duration of exposure to hyperglycemia should be established for comprehensive assessment of its toxicity. However, the association between

increased intensity of glycemic exposure (IGE) in young adulthood with target organ damages in midlife is unknown.

Subclinical target organ damages of hyperglycemia, indicated by coronary artery calcium (CAC), early cardiac deformation and dysfunction as well as albuminuria in our study, are efficient markers and well precursors of adverse clinical outcomes [4–6]. The Coronary Artery Risk Development in Young Adults (CARDIA) Study, which only enrolled young adults aged 18–30 years at baseline and underwent 6 blood glucose monitoring over 25 years, offers the opportunity to assess the impact of IGE on subclinical indicators of organ dysfunction in life-course pattern since young adulthood.

In this study, we aimed to determine how the intensity of glycemic exposure from young adulthood to middle adulthood affects target organ function in 2,859 CARDIA study participants. We firstly assessed the associations between IGE with clinical measures of coronary artery calcification, cardiac deformation and dysfunction as well as albuminuria. We also evaluated the association between IGE with number of target organs involved.

Material And Methods

Study Population

The datasets of the CARDIA study were obtained at the CARDIA Coordinating Center (cardia.dopm.uab.edu/contact-cardia) according to the application procedure required.

The CARDIA study was a prospective and observational investigation of 5,115 healthy black and white adults from 4 U.S. metropolitan communities (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA). Briefly, men and women aged 18–30 years were recruited at 1985–1986 (Y0) and reexamined after 2 (Y2), 5 (Y5), 7 (Y7), 10 (Y10), 15 (Y15), 20 (Y20), 25 (Y25) years. Further details of the CARDIA study have been published previously[7]. Institutional Review Boards approved the CARDIA study protocols, and all participants provided written informed consent at each examination.

For this analysis, we evaluated 3,498 participants who attended reexamination at Y25 and excluded those who had race other than white or black (n = 11), those with missing data on blood glucose at Y0 and Y25 (n = 75) and those with missing data on covariates (n = 553). Finally, 2,859 participants were included in our analysis. Baseline characteristics at examination in Y0 of individuals who were included and excluded were summarized in Supplemental table 1.

Intensity of glycemic exposure assessment and incident diabetes

Participants were asked to fast > 8 hours for measurements of fasting glucose at Y0, Y7, Y10, Y15, Y20, Y25. Fasting glucose was measured using the hexokinase ultraviolet method by American Bio-Science Laboratories at baseline and hexokinase coupled to glucose-6-phosphate dehydrogenase at the following

reexamination. Intensity of glucose exposure from young to middle adulthood was evaluated by the sum of (average blood glucose of two consecutive examinations × years between the examinations) (Supplemental Fig. 1). Similar approach was also used to assess the deleterious effects of elevated cumulative exposure to blood pressure in early adulthood [8, 9]. We determined diabetes based on any one of the following: self-report of hypoglycemic medications (measured at Y0, Y7, Y10, Y15, Y20 and Y25); fasting glucose levels ≥ 7.0 mmol/L or ≥ 126 mg/dL (measured at Y0, Y7, Y10, Y15, Y20 and Y25); 2-hour postload blood glucose ≥ 11.1 mmol/L or ≥ 200 mg/dL in 75 g oral glucose tolerance test (measured at Y10, Y20, Y25); or glycated hemoglobin ≥ 6.5% (measured at Y20 and Y25).

Outcome measurements

Cardiac structure and function were assessed by echocardiographic measurements in standardized methods following American Society of Echocardiography guidelines across all field centers at Y25, as described previously [10, 11]. Echocardiographic images were collected using a commercially available cardiac ultrasound machine (Artida; Toshiba Medical Systems) by trained sonographers and were interpreted using a standard offline image analysis system (Digisonics, TX). For cardiac structure assessment, left ventricular mass (LVM) was estimated from the Devereux formula and relative wall thickness (RWT) was calculated as (diastolic interventricular septal + diastolic left ventricular (LV) posterior wall thickness)/diastolic internal LV diameter. For LV systolic function assessment, left ventricular ejection fraction (LVEF) was evaluated based on LV end-systolic and end-diastolic volumes. Global longitudinal strain (GLS), a more sensitive and prognostic index of LV systolic function, was measured using speckle-tracking echocardiography and calculated as the systolic change of segmental length divided by the segmental length at end-diastole (in percentile) [12]. Peak velocities in mitral inflow at early (E), late diastole (A) and early peak diastolic mitral annular velocity (e') were measured for assessment of E/A ratio and E/e' ratio to reflect LV diastolic function.

Coronary artery calcium (CAC) was measured by multidetector computed tomography (CT) scanner in all center using standardized approach at Y25 [13]. The analysts in CARDIA Reading Center who were blinded to participants information analyzed the images and calculated a CAC score using on modified Agatston method [14]. Briefly, the total CAC score in Agatston units (AU) was determined based on numbers, areas and maximal computed tomographic numbers of the lesions. Besides, albuminuria was assessed by measurement of urine albumin to creatinine ratio (UACR). Urine albumin and urine creatinine levels were measured using nephelometry-based assay at Y25 examination according to the standardized exam protocol available at cardia.dopm.uab.edu.

For categorical analyses of significant target organ dysfunction, we defined left ventricular hypertrophy (LVH) as increased LVM > 224 g for men and > 162 g for women [15]. Concentric remodeling was defined as increased RWT > 0.42 [11]. LV systolic dysfunction was defined by decreased LVEF (< 50%) or abnormal GLS (> 90th percentile) [16]. LV diastolic dysfunction was defined as abnormal filling patterns (E/A ratio ≤ 0.8 or ≥ 2) or increased filling pressure (E/e´ ratio > 15) [9, 17]. We also defined CAC as an Agatston score > 0 and albuminuria as UACR > 30 mg/g.

Covariates measurements

Demographic characteristics, clinical history, medication use, anthropometric and laboratory data was collected based on standardized approaches as reported in study protocol [7]. Age, gender, race, educational attainment, smoking and drinking status were self-reported. Smoking status and drinking status was recorded as ever/never smoking and ever/never drinking, respectively. Educational attainment was evaluated by years in school. Height and weight were measured in light clothing and body mass index (BMI) was calculated as the ratio of weight (kg) to the square of height (m^2). After 5 minutes quiet rest, seated blood pressure (BP) in right arm was measured 3 times with 1-minute intervals using validated Omron HEM907XL oscillometric BP monitor at Y25 and the mean of the second and third readings was used for analysis. Total cholesterol, high-density lipoprotein cholesterol (HDL-c) were enzymatically determined and low-density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald equation.

Statistical Analysis

Participants eligible in our analysis were subdivided into 3 categories based on tertiles of IGE. Baseline characteristics of participants at Y25 were compared using one-way ANOVA (continuous variables), χ^2 tests (categorical variables) and the Kruskal-Wallis test as appropriate. Urine albumin to creatinine ratio was log-transformed due to skewed distribution. We also compared the baseline characteristics of participants in CARDIA study who were included in final analysis with those excluded. Data were presented as means ± SD or median (interquartile range) for continuous variables and frequencies (percentages) for categorical variables.

Multivariable linear regression models were performed to evaluate the longitudinal associations between IGE over 25 years with target organs function at Y25, including cardiac structure and function, CAC and albuminuria. Multivariable models were adjusted for covariates at Y25: model 1 included age, gender, race; model 2 was additionally adjusted for smoking, drinking, BMI and educational attainment; model 3 was further adjusted for systolic BP, LDL-c, HDL-c and Y25 blood glucose; and model 4 was additionally adjusted for aspirin, medication for lower cholest, HTN and DM. The effects were assessed by calculating the estimates (βs) and standard errors (SEs) for per 1-SD increment on IGE. To investigate the robust of the associations, we additional adjusted for average FG across follow-up examination instead of FG in Y25 in model 5 and number of measurements of FG in model 6 in sensitive analysis. In an explorative analysis, we further performed categorical analyses to explore the effects on significantly clinical organ dysfunction. Multivariable logistic regression models were used to evaluate the association between per 1-SD increment on IGE with target organs dysfunction, including CAC, LVH, concentric remodeling, impaired LVEF, abnormal GLS, abnormal filling patterns, increased filling pressures and albuminuria. In logistic models, we accounted for same covariates as in linear models and presented the effects using odds ratios (ORs) and 95% confidential intervals (95%CIs).

For further analysis in the prevalence of TOD derived from LGE, we defined numbers of TODs as the sum of presence of cardiac deformation (LVH or concentric remodeling), cardiac systolic dysfunction (impaired LVEF or abnormal GLS), cardiac diastolic dysfunction (abnormal filling patterns or increased filling pressures), CAC and albuminuria, ranging from 0 to 5. Multinomial logistic regression models were performed to explore the relationship between IGE and numbers of TODs (0, 1, or ≥ 2). We adjusted for traditional cardiovascular risk factors at Y25, including age, gender, race, smoking, drinking, BMI, educational attainment, SBP, LDL-c, HDL-c, Y25 blood glucose, aspirin, medication for lower cholest, HTN and DM. We also compared the effects of IGE on numbers of TOD stratified by presence of DM.

All statistical analyses were performed using SPSS version 18.0. A 2-tailed $P < 0.05$ was considered as statistically significant.

Result

Baseline characteristics of 2,859 eligible participants in CARDIA study were summarized in Table 1. Overall, the mean age at Y25 was 50.0 ± 3.6 years; 43.4% of the participants were male (n = 1,240) and 44.6% were black (n = 44.6). The average intensity of glycemic exposure was 2237.5 ± 324.7 mg/dl$\times$Yrs over 25 years in total eligible population (ranged 1717.0 to 5713.0 mg/dl$\times$Yrs). Participants with higher IGE were more frequently male, had higher BMI, SBP, DBP, fasting glucose at Y0 and Y25 (all $P < 0.001$). Among them, only very few participants (n = 10, 0.3%) had diabetes at Y0 and 373 participants (13.0%) developed diabetes up to Y25. Supplemental table 2 described the baseline characteristics of participants who had diabetes and remained free from diabetes at Y25. Participants who developed diabetes were more likely black, had higher IGE, BMI, SBP and DBP.

Table 1
Baseline Characteristics for 2,859 CARDIA participants

Characteristic	Total	Intensity of Glycemic exposure			
		Group 1	Group 2	Group 3	P value
IGE (mg/dl $\times$ Yrs)	2237.5 ± 324.7	2016.4 ± 72.2	2183.2 ± 42.1	2514.0 ± 426.5	< 0.001
Age, years	50.0 ± 3.6	49.4 ± 3.7	50.0 ± 3.6	50.6 ± 3.4	< 0.001
Male	1240 (43.4)	213 (22.4)	442 (46.2)	585 (61.6)	< 0.001
Black	1275 (44.6)	436 (45.8)	382 (40.0)	457 (48.1)	0.001
BMI, kg/m2	29.9 ± 6.8	27.7 ± 6.2	29.8 ± 6.5	32.2 ± 6.8	< 0.001
SBP, mmHg	118.2 ± 15.3	115.3 ± 15.3	118.1 ± 14.7	121.3 ± 15.2	< 0.001
DBP, mmHg	73.6 ± 10.8	71.6 ± 11.1	73.7 ± 10.5	75.4 ± 10.4	< 0.001
FG at Y0, mg/dl	81.9 ± 10.4	76.6 ± 6.0	81.8 ± 7.4	87.2 ± 13.2	< 0.001
FG at Y25, mg/dl	98.6 ± 27.0	86.5 ± 6.6	94.0 ± 7.6	115.3 ± 40.5	< 0.001
DM at Y0	10 (0.3%)	0	3 (0.3)	7 (0.7)	0.011
DM at Y25	373 (13.0%)	20 (2.1)	57 (6.0)	296 (31.2)	< 0.001
Smoking	1541 (53.9)	491 (51.5)	512 (53.6)	538 (56.6)	0.079
Drinking	2253 (78.8)	750 (78.7)	772 (80.8)	731 (76.9)	0.126
Educational attainment	14.8 ± 1.8	14.9 ± 1.8	14.9 ± 1.8	14.5 ± 1.9	< 0.001
LDL-c, mg/dl	111.8 ± 32.6	109.4 ± 30.5	113.9 ± 31.8	112.0 ± 35.3	0.011

Data are presented as mean ± SD, number (percentage) or median (interquartile range), as appropriate.

Sample characteristics were drawn from examination 8 at Y25 unless otherwise indicated.

IGE, intensity of glycemic exposure; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FG, fasting glucose; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CAC, coronary artery calcium; LVM, left ventricular mass; RWT, relative wall thickness; LVEF, left ventricular ejection fraction; GLS, global longitudinal peak strain; UACR, urine albumin to creatinine ratio.

Characteristic	Total	Intensity of Glycemic exposure			
		Group 1	Group 2	Group 3	P value
HDL-c, mg/dl	58.5 ± 18.0	65.2 ± 18.4	57.8 ± 17.4	52.6 ± 15.7	< 0.001
DM medication	201 (7.0)	7 (0.7)	16 (1.7)	178 (18.7)	< 0.001
HTN medication	761 (26.6)	164 (17.2)	236 (24.7)	361 (38.0)	< 0.001
Lipid medication	437(15.3)	79 (8.3)	117 (12.2)	241 (25.4)	< 0.001
Aspirin use	480 (16.8)	97 (10.2)	146 (15.3)	237 (24.9)	< 0.001
Echocardiographic parameters					
LVM (n = 2553)	167.3 ± 51.9	148.5 ± 44.4	168.8 ± 48.5	186.8 ± 55.5	< 0.001
RWT (n = 2549)	0.4 ± 0.1	0.3 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.005
LVEF (n = 2553)	69.8 ± 8.0	69.9 ± 7.4	69.9 ± 7.8	69.6 ± 8.8	0.773
GLS (n = 2497)	-15.1 ± 2.4	-15.2 ± 2.3	-15.2 ± 2.3	-14.5 ± 2.5	< 0.001
E/A (n = 2810)	1.3 ± 0.4	1.4 ± 0.4	1.3 ± 0.3	1.2 ± 0.4	< 0.001
E/e' (n = 2785)	9.0 ± 2.7	8.8 ± 2.6	8.8 ± 2.7	9.3 ± 2.9	< 0.001
CAC score, AU (n = 2616)	0.0 (0.0, 3.9)	0.0 (0.0, 0.0)	0.0 (0.0, 1.9)	0.0 (0.0, 29.0)	< 0.001
UACR, mg/g (n = 2794)	4.7 (3.3, 8.1)	4.7 (3.3, 7.5)	4.4 (3.1, 7.1)	5.1 (3.4, 10.2)	< 0.001

Data are presented as mean ± SD, number (percentage) or median (interquartile range), as appropriate.

Sample characteristics were drawn from examination 8 at Y25 unless otherwise indicated.

IGE, intensity of glycemic exposure; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FG, fasting glucose; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CAC, coronary artery calcium; LVM, left ventricular mass; RWT, relative wall thickness; LVEF, left ventricular ejection fraction; GLS, global longitudinal peak strain; UACR, urine albumin to creatinine ratio.

IGE and Target Organ Function

As shown in Fig. 1, higher deciles of IGE produced higher LVM, GLS, E/e' ratio, CAC score, UACR and lower E/A ratio. Table 2 represented the associations between IGE over 25 years with target organs function parameters in linear regression models. In model 1, a 1-SD-increment higher IGE was significantly associated with higher LVM, E/e' ratio, CAC score, log UACR and lower E/A (all $P < 0.001$). Further adjustments for smoking, drinking, BMI and educational attainment in model 2 did not alter the results. The association between E/A ratio with IGE dissipated after further adjustments in model 3 while other associations remained significant. A 1-SD increment of IGE were still positively associated with LVM (β [SE], 5.468 [1.175]), GLS (β [SE], 0.161 [0.071]), E/e' ratio (β[SE], 0.192 [0.071]), CAC score (β [SE], 27.948 [6.116]) and log UACR (β [SE], 0.076 [0.010]) after full adjustment in model 4. Sensitive analysis with additional adjustment for average blood glucose in model 5 and number of measurements of FG in model 6 demonstrated consistent results (Supplemental table3).

Table 2
Linear Regression Models to Examine the Associations between Intensity of Glycemic Exposure During Young Adulthood with Target Organ Function in Midlife

Variables	Per 1 SD increment of IGE (standardized value)			
	Model 1	Model 2	Model 3	Model 4
	β (SE)	β (SE)	β (SE)	β (SE)
Cardiac Structure and Function				
Structure				
LVM (n = 2553)	8.359 (0.890) ***	4.139 (0.829) ***	5.293 (1.085) ***	5.468 (1.175) ***
RWT (n = 2549)	0.002 (0.001)	0.000 (0.001)	-0.001 (0.002)	-0.002 (0.002)
Systolic Function				
LVEF (n = 2553)	-0.071 (0.157)	-0.075 (0.161)	-0.100 (0.215)	-0.024 (0.233)
GLS (n = 2497)	0.398 (0.049) ***	0.318 (0.050) ***	0.214 (0.067) **	0.161 (0.071) *
Diastolic Function				
E/A (n = 2810)	-0.048 (0.007) ***	-0.030 (0.007) ***	-0.017 (0.009)	-0.007(0.010)
E/e' (n = 2785)	0.367 (0.051) ***	0.260 (0.051) ***	0.207 (0.066) **	0.192 (0.071) **
Subclinical Atherosclerosis				
CAC score (n = 2616)	35.315 (4.303) ***	34.917 (4.393) ***	30.161 (5.707) ***	27.948 (6.116) ***
Renal Function				
Log UACR (n = 2794)	0.115 (0.007) ***	0.111 (0.007) ***	0.085 (0.010) ***	0.076 (0.010) ***
IGE, intensity of glycemic exposure.				
All models were adjusted for covariates measured at Y25.				
Model 1 was adjusted for age, gender, race; Model 2 was additionally adjusted for smoking, drinking, BMI, educational attainment; Model 3 was additionally adjusted for SBP, LDL-c, HDL-c, Y25 blood glucose; Model 4 was additionally adjusted for aspirin, medication for lower cholest, HTN and DM.				
***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$.				

Supplemental table 4 presented multivariable logistic regression models to further investigate the impacts of IGE on subclinical target organs dysfunction. For cardiac structural and functional outcomes, per 1-SD increment of IGE was significantly associated with higher prevalence of LVH (OR [95% CI], 1.25 [1.09, 1.43]) and abnormal GLS (OR [95% CI], 1.22 [1.02, 1.45]) in fully adjusted model. In the contrast, IGE

was not related to clinical diastolic dysfunction, including abnormal filling patterns and increased filling pressure after full adjustments. Besides, per 1-SD increment of IGE showed correlations with higher prevalence of subclinical atherosclerosis (OR [95% CI], 1.24 [1.08, 1.43]) and albuminuria (OR [95% CI], 1.40 [1.20, 1.63]).

IGE and Number of TOD

Prevalence of TOD (0, 1, or ≥ 2 organ damaged) in overall population and subgroups stratified by incident diabetes were shown in Fig. 2. Compared with non-diabetes population, those with DM at Y25 had higher prevalence of 2 or more damaged organs, indicating a greater vulnerability to target organ damages in diabetes population. Figure 2 presented the odds ratio of having 1 or ≥ 2 organ damaged by long-term IGE in multivariable multinomial logistic regression models. A 1-SD increment of IGE was independently associated with having ≥ 2 organs involved in overall population (OR [95% CI], 1.48 [1.23, 1.41]; $P < 0.001$; Fig. 2), suggesting the higher the levels of IGE, the more advanced the target organs involvement. It should be noted that the association with were statistically significant in both DM and non-DM subgroups.

Discussion

In this prospective cohort of young adults followed up over 25 years, we demonstrated greater IGE during young adulthood was associated with unfavorable impairment of multiple target organs, including subclinical cardiac structural and functional impairment, subclinical atherosclerosis and albuminuria independent of fasting glucose at Y25. The long-term IGE was associated with prevalence of TOD and the higher IGE tended to involve more target organs, which remained consistent even among those free from diabetes at Y25.

Previous researches have established that diabetes is responsible for multiple target organs injury [18]. Diabetic cardiomyopathy is characterized by myocardial hypertrophy and myocardial remodeling, manifested as diastolic dysfunction in the earlier and systolic dysfunction during disease progression [19]. Besides, individuals with diabetes are also at increased risk of atherosclerosis and diabetic nephropathy in later life [3, 20]. Overall, these prior studies suggested that diabetes is a strong predictor of adverse clinical events in later life. However, previous studies always investigated the detrimental impacts of hyperglycemia based on measurement of blood glucose at a single time point and whether lifespan exposure to hyperglycemia derived subclinical adverse effects earlier is still unknown. To the best of our knowledge, our study was the first to comprehensively focus on the chronic impacts of long-term intensity of glycemic exposure during young adulthood on multiple target organs in midlife, accounting for the magnitude and duration of glycemic exposure simultaneously. Our findings extended the prior studies by showing that higher IGE over 2nd, 3rd and 4th decade of life was associated with earlier target organs dysfunction at 5th decade. Besides, our results also suggested that the numbers of target organs involvement depended on the cumulative effects of IGE, even in a non-diabetic subset of participants who were younger with less clinical comorbidities.

The underlying pathophysiologic pathways that links higher long-term IGE with target organs impairment may share common pathogenic mechanisms. Study have shown that hyperglycemia induces and accelerates the deposition and accumulation of glycosylation products within myocardium and arterial wall, leading to cardiac and vascular injury [19, 21, 22]. Besides, endothelial dysfunction is also a main pathogenic factor contributing to diabetic vascular impairment, e.g., initiating the pathogenesis of atherosclerosis [23]. Furthermore, hyperglycemia and insulin resistance also promote myocardial collagen deposition and myocyte hypertrophy, causing myocardial remodeling [16]. Some other mechanisms may also involve in the pathogenesis, including oxidative stress, altered substrate metabolism, mitochondrial dysfunction, inflammation activation and so on [19, 24, 25].

For cardiac functional measurements, it has been demonstrated that global longitudinal strain is a sensitive marker of systolic dysfunction than ejection fraction and provide additional prognostic value on adverse outcomes [12, 26]. Meanwhile, previous studies indicated that E/e' ratio was more predictive for primary cardiac events than E/A ratio [27]. In our study, we noted associations between long-term IGE with worse global longitudinal strain but not ejection fraction. We also found that IGE over young adulthood was associated with worse E/e' ratio rather than E/A. Therefore, GLS and E/e' ratio seemed to be powerful in showing the adverse effects of IGE that classical echocardiographic indicators failed to identify, which may be explained by a young age of CARDIA population with lower prevalence of clinical organ dysfunction at advanced stage. Similar, IGE was also associated with CAC and albuminuria, the well-known and powerful precursors of adverse outcomes [5, 28]. In fact, identification of the predisposing factors for subclinical organ dysfunction provide the insight towards long-term risk of organ dysfunction. From a disease-prevention perspective, given the independent prognostic significance of TOD, it would make sense to establish screening strategies on IGE and implement intensive blood glucose management during young adulthood, avoiding irreversible organs damage [4–6].

An unexpected finding was that long-term IGE showed subclinical adverse effects on target organs in both diabetes and non-diabetes subgroups, which highlights the need to investigate the cumulative effects of glycemic exposure in participants below the diagnostic criteria of diabetes. Indeed, even in examination at Y25, only a minority of participants (13.0%) were diagnosed as diabetes and the FG level in non-diabetes population was on average below the current threshold of prediabetes (92.8 ± 9.1 mg/dl, Supplemental table 2), suggesting exposure to subclinical hyperglycemia over young adulthood could precipitate organ dysfunction. Prospective study may be warrant to determine the optimal cut-off points for evaluation of the subclinical impacts of cumulative glycemic exposure. On the other hand, given the subclinical hyperglycemia is a modifiable factor, the optimal glycemic control target remains controversial despite several randomized controlled trials (RCTs) published [29–32]. UKPDS trial demonstrated a great microvascular benefit from intensive glucose control therapy, which was confirmed in subsequent ADVANCE and ACCORD trial. However, whether intensive glucose control therapy reduce risk of macrovascular events is still disputed. Indeed, the participants in these RCTs were characterized by old age, long duration of diabetes and poor glycemic control. Irreversible subclinical organ impairment in these participants may weaken the effects of intensive glucose control therapy and lead to unclear macrovascular benefit. Thus, further research is need to clarify whether intensive glucose control in

young patients with subclinical hyperglycemia can prevent or delay the early organ dysfunction, ultimately improving prognosis. Nevertheless, the accompanying risk of adverse reaction, especially hypoglycemic episodes, should be carefully assessed.

Our study results are strengthened by a population-based cohort with large sample size; regular screening fasting glucose using standardized protocols over 25 years, facilitating assessment of cumulative intensity of glycemic exposure; a cohort of young adults with less comorbidities, almost non-diabetic population, was optimal for exploring the subclinical effects of IGE on target organs and providing evidences on prevention of diabetes-induced end-organ damage. However, several limitations in our study needs to be considered. First, cardiac function and CAC were measured in detail until examination in Y25, hindering further assessment of the long-term changes of target organs function from young adulthood to midlife. Hence, we can only assume that the measurements in Y25 could reflect the declines of organs function. Second, only approximately a half of participants in CARDIA performed echocardiographic measurements and CAC assessment in Y25, thus our analysis may be subjected to selection bias. To address this issue, we further compared the baseline characteristics between the analyzed sample with the excluded sample (Supplemental table 1). The participants who were excluded in our study were more frequently male, black, smoker, have lower educational attainment, higher FG and SBP levels. In fact, the participants included in our analysis may have a lower risk of target organs impairment than those excluded, which likely bias towards the null and may underestimate the deleterious effects of IGE. Third, owing to the calculation method of IGE, each individual had unequal number of measurements of FG and those who were less measured may have inaccurate evaluation of glycemic exposure. Indeed, more than 80% of individuals completed all 6 measurements of FG and we observed consistent associations when additionally adjusted for number of measurements (Supplemental table 3). Fourth, given the nature of observational study, our findings may be susceptible to reverse causation and residual confounding. Last but not least, CARDIA is a biracial cohort including white and black individuals so that our findings required external validation in other ethnic population, e.g., Asian.

Conclusions

In conclusion, our study finds associations between long-term intensity of glycemic exposure during young adulthood with subclinical impairment of cardiac structure and function, CAC and albuminuria at midlife. Higher IGE is also associated with increased numbers of target organs involvement, even in non-diabetic populations. Our findings emphasize the importance of screening and management of subclinical hyperglycemia in youth, thus preventing or delaying the early organs dysfunction and ultimately improving the prognosis.

Abbreviations

IGE, intensity of glycemic exposure

BMI, body mass index

SBP, systolic blood pressure

DBP, diastolic blood pressure

FG, fasting glucose

DM, diabetes mellitus

HDL-C, high-density lipoprotein cholesterol

LDL-C, low-density lipoprotein cholesterol

CAC, coronary artery calcium

LVM, left ventricular mass;

RWT, relative wall thickness

LVEF, left ventricular ejection fraction

GLS, global longitudinal peak strain

UACR, urine albumin to creatinine ratio

LVH, left ventricular hypertrophy

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Boards, and all participants provided written informed consent at each examination.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Funding

The CARDIA study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (HHSN268201300025C and HHSN268201300026C), Northwestern University (HHSN268201300027C), University of Minnesota (HHSN268201300028C), Kaiser Foundation Research Institute (HHSN268201300029C), and Johns Hopkins University School of Medicine (HHSN268200900041C). CARDIA is also partially supported by the Intramural Research Program of the National Institute on Aging (NIA) and an intra-agency agreement between NIA and NHLBI (AG0005).

This work was supported by the National Natural Science Foundation of China [81600206 to ZXD; 81870195 to LXX], and Natural Science Foundation of Guangdong Province [2016A030310140 to ZXD; 2016A020220007 and 2019A1515011582 to LXX]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' contributions

LXX, ZXD conceived and designed the study; obtained funding; acquired the data; LYF, ZXB conceived and designed the study, performed all analysis and interpretation of data, drafted the manuscript; XZY, ZSZ, LMH advised on statistical analysis methods and critically revised the manuscript for important content; YQF, YQH, SXT interpreted the data and critically revised the manuscript for important content; ZHM, XXF, GY, LYQ, YDY, YXM critically revised the manuscript for important content and contributed to the discussion. LXX is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgements

The authors thank the staff and participants of the CARDIA Study for their important contributions.

References

1. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255–323.
2. Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, Welty TK, Fabsitz RR, Robbins D, Rhoades ER, Howard BV. Impact of diabetes on cardiac structure and function: the strong heart study. Circulation. 2000;101(19):2271–6.
3. Rossing K, Christensen PK, Hovind P, Tarnow L, Rossing P, Parving HH. Progression of nephropathy in type 2 diabetic patients. Kidney Int. 2004;66(4):1596–605.
4. Yeboah J, Young R, McClelland RL, Delaney JC, Polonsky TS, Dawood FZ, Blaha MJ, Miedema MD, Sibley CT, Carr JJ, et al. Utility of Nontraditional Risk Markers in Atherosclerotic Cardiovascular Disease Risk Assessment. J Am Coll Cardiol. 2016;67(2):139–47.

5. **Low eGFR and high albuminuria predict end stage kidney disease and death at all ages**. *Bmj* 2012, 345:e7478.
6. Medvedofsky D, Maffessanti F, Weinert L, Tehrani DM, Narang A, Addetia K, Mediratta A, Besser SA, Maor E, Patel AR, et al. 2D and 3D Echocardiography-Derived Indices of Left Ventricular Function and Shape: Relationship With Mortality. JACC Cardiovasc Imaging. 2018;11(11):1569–79.
7. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR Jr, Liu K, Savage PJ. CARDIA: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol. 1988;41(11):1105–16.
8. Mahinrad S, Kurian S, Garner CR, Sedaghat S, Nemeth AJ, Moscufo N, Higgins JP, Jacobs DR Jr, Hausdorff JM, Lloyd-Jones DM, et al. Cumulative Blood Pressure Exposure During Young Adulthood and Mobility and Cognitive Function in Midlife. Circulation. 2020;141(9):712–24.
9. Kishi S, Teixido-Tura G, Ning H, Venkatesh BA, Wu C, Almeida A, Choi EY, Gjesdal O, Jacobs DR Jr, Schreiner PJ, et al. Cumulative Blood Pressure in Early Adulthood and Cardiac Dysfunction in Middle Age: The CARDIA Study. J Am Coll Cardiol. 2015;65(25):2679–87.
10. Armstrong AC, Ricketts EP, Cox C, Adler P, Arynchyn A, Liu K, Stengel E, Sidney S, Lewis CE, Schreiner PJ, et al. Quality Control and Reproducibility in M-Mode, Two-Dimensional, and Speckle Tracking Echocardiography Acquisition and Analysis: The CARDIA Study, Year 25 Examination Experience. Echocardiography. 2015;32(8):1233–40.
11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1–39.e14.
12. Potter E, Marwick TH. Assessment of Left Ventricular Function by Echocardiography: The Case for Routinely Adding Global Longitudinal Strain to Ejection Fraction. JACC Cardiovasc Imaging. 2018;11(2 Pt 1):260–74.
13. Carr JJ, Nelson JC, Wong ND, McNitt-Gray M, Arad Y, Jacobs DR Jr, Sidney S, Bild DE, Williams OD, Detrano RC. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. Radiology. 2005;234(1):35–43.
14. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990;15(4):827–32.
15. Kirkpatrick JN, Vannan MA, Narula J, Lang RM. Echocardiography in heart failure: applications, utility, and new horizons. J Am Coll Cardiol. 2007;50(5):381–96.
16. Kishi S, Gidding SS, Reis JP, Colangelo LA, Venkatesh BA, Armstrong AC, Isogawa A, Lewis CE, Wu C, Jacobs DR, Jr. et al: **Association of Insulin Resistance and Glycemic Metabolic Abnormalities With LV Structure and Function in Middle Age**: **The CARDIA Study**. *JACC Cardiovasc Imaging* 2017, **10**(2):105–114.

17. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):277–314.
18. de Simone G, Wang W, Best LG, Yeh F, Izzo R, Mancusi C, Roman MJ, Lee ET, Howard BV, Devereux RB. Target organ damage and incident type 2 diabetes mellitus: the Strong Heart Study. Cardiovasc Diabetol. 2017;16(1):64.
19. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. Circulation. 2007;115(25):3213–23.
20. Raffield LM, Cox AJ, Criqui MH, Hsu FC, Terry JG, Xu J, Freedman BI, Carr JJ, Bowden DW. Associations of coronary artery calcified plaque density with mortality in type 2 diabetes: the Diabetes Heart Study. Cardiovasc Diabetol. 2018;17(1):67.
21. Naka Y, Bucciarelli LG, Wendt T, Lee LK, Rong LL, Ramasamy R, Yan SF, Schmidt AM. RAGE axis: Animal models and novel insights into the vascular complications of diabetes. Arterioscler Thromb Vasc Biol. 2004;24(8):1342–9.
22. West NA, Hamman RF, Mayer-Davis EJ, D'Agostino RB Jr, Marcovina SM, Liese AD, Zeitler PS, Daniels SR, Dabelea D. Cardiovascular risk factors among youth with and without type 2 diabetes: differences and possible mechanisms. Diabetes Care. 2009;32(1):175–80.
23. Calles-Escandon J, Cipolla M. Diabetes and endothelial dysfunction: a clinical perspective. Endocr Rev. 2001;22(1):36–52.
24. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol. 2011;11(2):98–107.
25. Ceriello A, Testa R. Antioxidant anti-inflammatory treatment in type 2 diabetes. Diabetes Care. 2009;32(Suppl 2):232–6.
26. Russo C, Jin Z, Elkind MS, Rundek T, Homma S, Sacco RL, Di Tullio MR. Prevalence and prognostic value of subclinical left ventricular systolic dysfunction by global longitudinal strain in a community-based cohort. Eur J Heart Fail. 2014;16(12):1301–9.
27. Sharp AS, Tapp RJ, Thom SA, Francis DP, Hughes AD, Stanton AV, Zambanini A, O'Brien E, Chaturvedi N, Lyons S, et al. Tissue Doppler E/E' ratio is a powerful predictor of primary cardiac events in a hypertensive population: an ASCOT substudy. Eur Heart J. 2010;31(6):747–52.
28. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. New Engl J Med. 2008;358(13):1336–45.
29. **Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group**. *Lancet* 1998, 352(9131):837–853.
30. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, et al. Intensive blood glucose control and vascular outcomes in patients with type 2

diabetes. New Engl J Med. 2008;358(24):2560–72.

31. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, et al. Effects of intensive glucose lowering in type 2 diabetes. New Engl J Med. 2008;358(24):2545–59.
32. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. New Engl J Med. 2008;359(15):1577–89.

Figures

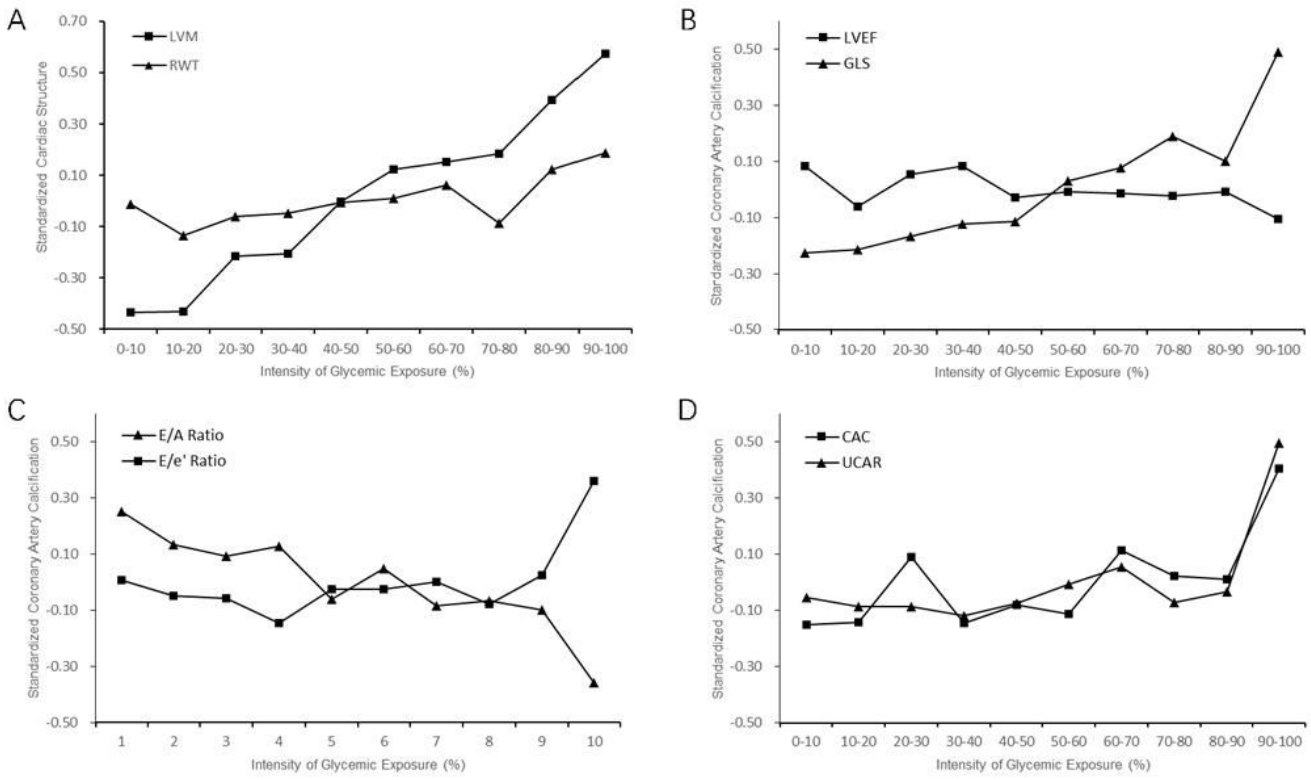

Figure 1

Early Adulthood Intensity of Glycemic Exposure and Middle-Age Target Organ Function The trajectory slopes showed indices of target organs function with increasing decile of intensity of glycemic exposure (IGE). (A) Cardiac structure; (B) Left ventricular (LV) systolic function; (C) LV diastolic function; (D) Coronary artery calcium (CAC) and albuminuria. Higher deciles of IGE produced higher level of left ventricular mass (LVM) (A), global longitudinal strain (GLS), CAC and urine albumin to creatinine ratio (UACR)

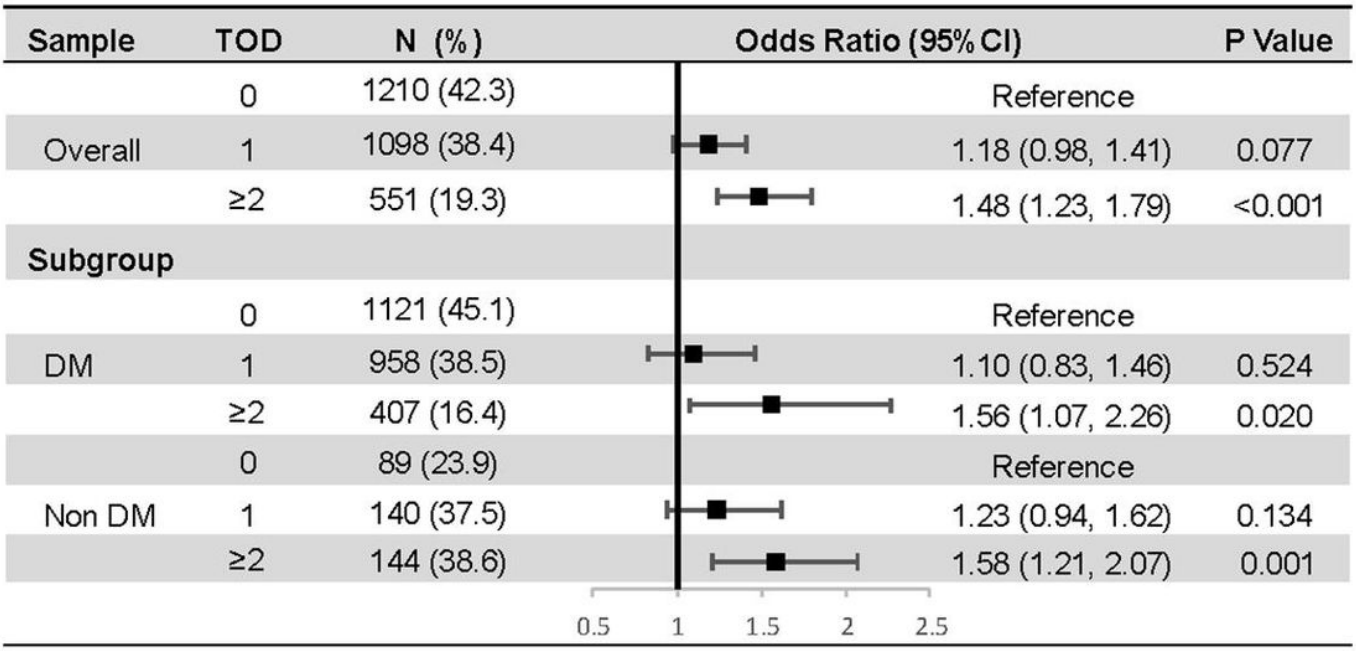

Figure 2

Multinomial Logistic Regression Models to Examine the Odds Ratio of Having 0, 1or ≥2 Target Organ Damages by Intensity of Glycemic Exposure

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.docx
- SupplementalFigure1.pdf