The correlation of serum IGF-1 levels with lower extremity atherosclerotic disease in type 2 diabetes patients

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Abstract

Objective: Clinical and basic studies have indicated the close association between Insulin-like growth factor-1 (IGF-1) and cardiovascular disease, however, the relationship between IGF-1 and lower extremity atherosclerotic disease (LEAD) has rarely been reported. Given that lower extremity arterial disease is the common macrocomplication of type 2 diabetes(T2DM), the purpose of this study was to explore the relationship between serum Insulin-like growth factor-1 levels and the presence of lower extremity atherosclerotic disease in patients with type 2 diabetes mellitus.

Methods: A total of 442 hospitalized T2DM patients(371 with LEAD and 71 without LEAD) were enrolled in the study. Serum IGF-1 levels were determined by an automatic chemiluminescence assay. The LEAD was evaluated through color doppler ultrasonography.

Results: Compared with patients without LEAD, patients with LEAD exhibited much lower serum IGF-1 levels [115.4 ng/mL (interquartile range = 89.6-145.2 n g/ml) versus 124 ng/mL (interquartile range = 101.3-161.5 ng/mL), repectively, $P = 0.03$]. Multivariate line regression analysis identified that serum IGF-1 levels were independently and negatively related to age (standardiazed $\beta = -0.208$, $P < 0.001$) and gender (standardiazed $\beta = -0.126$, $P = 0.019$). However, multivariate logistic regression analysis revealed that serum IGF-1 level has no significantly relationship with the presense LEAD with OR value of 0.993 in the total population.

Conclusion: In T2DM patients, though low serum IGF-1 levels were found in LEAD patients, the IGF-1 may not contribute to the presence of LEAD.

Introduction

Diabetes mellitus (DM) is one of the most important problems for public health worldwide, leading to significant morbidity and premature mortality(1, 2). It was estimated that 462 million individuals have been affected by type 2 diabetes mellitus in 2017 (6.28% of the world's population)(3). This number was expected to increase to 578 million (10.2%) in 2030 and 700 million (10.9%) in 2045. In China, with the fast urbanization, its overall prevalence has increased to 12.7% in 2017, comparing 9.7% in 2007(4, 5). As we know, diabetes increases the risk of microvascular and macrovascular complications in the general population and results in a huge economic burden for society.

Lower extremity arterial disease (LEAD), often called peripheral artery disease(PAD), is one of the common macrovascular complications of diabetes, which is manifested by the increase in the thickness of the lower extremity artery intima-media, arterial plaque formation, or even lower extremity vascular stenosis and occlusion(6). As surveyed, as many as 64% of the LEAD patients were accompanied by diabetes, which means blood sugar may be an important factor for the development of LEAD(7). However, the genetic and molecular bases of LEAD are largely unknown.

IGF-1 is a peptide growth factor containing 70 amino acids, which was renamed “insulin-like growth factor 1” due to its structural resemblance to pro-insulin (8). In the human body, it is synthesized in virtually every tissue(9), yet mainly produced by the liver cells under the regulation of growth hormone(10). Recently the effects of IGF-1 on aging and chronic diseases attract much attention. IGF-1 controls cell growth through anti-apoptotic effects and has some physiological role in the metabolic pathway(11). Some clinical and basic studies have provided evidence showing that circulating IGF-1 level is related to the development of atherosclerosis through its effect on endothelial dysfunction, inflammation and lipid distribution(12, 13). On the contrary, other prospective and cross-sectional studies show that higher levels of IGF-1 are related to increased artery intima-media thickness and promote cardiovascular mortality(14, 15). These varying results likely reflect the complexity of IGF-1 effects on the vasculature. LEAD, as a common diabetes macrovascular complications, has the common pathology base with cardiovascular disease, while the correlation between IGF-1 levels and LEAD in diabetes patients has been less explored. Hence, the purpose of this study is to investigate the relationship between serum IGF-1 levels and LEAD and explore factors that affecting IGF-1 levels in type 2 diabetes.

Methods

Study population and samples

With the approval of the institutional review board and human ethics committee, a total of 442 T2DM patients (254 men, 188 women, age range: 20–85 years) between December 2018 and November 2020 were obtained from the Department of Endocrinology Luoyang Central Hospital Affiliated to Zhengzhou University. Written informed consents were obtained from all included individuals. The diagnosis of T2DM was performed according to the 2010 American Diabetes Association (ADA) classification and diagnostic criteria of diabetes(16). The exclusion criteria were as follows: (1) patients with type 1 diabetes mellitus, gestational diabetes, or specific types of diabetes mellitus; (2) patients with hepatic dysfunction (acute vital hepatitis; alanine aminotransferase,or aspartate aminotransferase > 1.5-fold the upper limit of normal) ; (3) patients with renal dysfunction (serum creatinine ≥ 115 μmol/L) ; (4) patients with hyper- or hypothyroidism, acute infection, malignant tumor; (5) patients with psychiatric disease; (6) patients with malignant tumors. were excluded. All participants were asked to report their clinical information regarding diabetes duration, alcohol consumption, smoking status, and medications.

Anthropometric assessments

Anthropometric measurement of each subject was performed by trained nurses in the morning after fasting for at least 8 h. Body height was recorded to the nearest 0.5 cm and body weight to the nearest 0.1 kg. The body mass index (BMI) was calculated as a person’s weight in kilograms divided by the square of the height in meters(kg/m^2). Waist circumference (W) was measured midway between the lowest rib and the iliac crest with the subject in the standing position, hip circumference (H) was measured around the widest portion of the buttocks, and both measurements were correct to the nearest 0.1 cm. The waist-to-hip ratio (WHR) measures the ratio of the waist circumference to the hip

circumference. Blood pressure was measured with a mercury sphygmomanometer after the subject had rested for at least 10 min.

Biochemical measurements

Peripheral blood was taken with a vacutainer after fasting for at least 8 h in the morning. Plasma glucose (FPG), 2-h postprandial plasma glucose (2hPG), Total cholesterol(TC), triglycerides (TG), HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), D-dimer, C-reactive protein (CRP), and Blood creatinine (Scr) were measured with an automatic analyzer (BC-6800; Mairui Biology Medical Systems Co, Ltd. Shengzhen, China). HbA1c was measured by an automatic analyzer (MQ6000; Huizhong Medical Technology Co, Ltd. Shanghai, China). Urine samples are collected for Urine albumin creatinine ratio (ACR) measurement with automatic analyzers (EH-2080; Mairui Biology Medical Systems Co, Ltd. Shengzhen, China). Serum IGF-1 levels were measured with an automatic chemiluminescence analyzer (Maglumi 4000, New Industries Biomedical Engineering Co, Ltd. Shenzhen, China), and the intra- and inter-assay coefficients of variation were 2.6 and 4.9%, respectively. The estimated glomerular filtration rate (eGFR) is calculated using the CG-GFR formula(17).

Ultrasonography measurements and diagnosis of LEAD

Lower limb arteries of all participants underwent color Doppler ultrasound examinations equipped with a 4–12 MHz xMatrix transducer (Philips EPIQ7, USA). Ultrasound examination included measurement of atherosclerotic plaque and femoral IMT (F-IMT). Seven arteries in each lower limb, including the femoral artery, deep femoral artery, superficial femoral artery, popliteal artery, anterior tibial artery, posterior tibial artery, and peroneal artery, were checked for atherosclerotic plaque. IMT was defined as the distance between the leading edge of the lumen-intima echo and the leading edge of the media-adventitia echo. F-IMT was defined as the mean value of IMTs of the bilateral femoral arteries(18). According to the Mannheim consensus(18), atherosclerotic plaques were defined as focal structures encroaching into the arterial lumen at least 0.5 mm, or greater than 50% of the surrounding IMT value, or IMT of > 1.5 mm. LEAD was defined as the presence of lower extremity arterial atherosclerotic plaque in any of the bilateral seven lower extremity artery segments mentioned above(19).

Statistical analysis

Statistical analysis was carried out using SPSS version 24.0 for the study. A normality test was performed on all data variables. Variables conforming to the normal distribution are expressed as the mean ± standard deviation (SD), while skewed data and categorical variables are presented as the median (interquartile range: 25–75%) and percentages (%), respectively. The unpaired Student's t test and Mann–Whitney U test were used to perform inter-group comparisons of normally distributed data and skewed data, respectively. Multiple linear regression analysis was used to explore multiple factors independently correlated with IGF-1 levels. Logistic regression analysis was conducted to analyze the risk factors associated with LEAD. A statistically significant difference was set at a two-tailed $p < 0.05$.

Results

The IGF-1 levels in diabetes patients

Chemiluminescence assay was performed to analyze the levels of IGF-1 in T2DM patients with 371 LEAD and 71 without LEAD. As shown in **Figure 1**, Compared with patients without LEAD, patients with LEAD exhibited much lower serum IGF-1 levels 115.4 ng/mL (interquartile range = 89.6-145.2 ng/mL) versus 124 ng/mL (interquartile range = 101.3-161.5 ng/mL), respectively, (P=0.03).

We next evaluated whether IGF-1 levels differed by the selected clinical characteristics. The clinical characteristics were summarized in **Table 1**[end of document]. We categorized the 442 diabetes patients into two groups based on gender, age (≤60 *vs.* >60 years), waist circumstance (≤90 *vs.* >90 cm^2), BMI (≤28 *vs.* >28 kg/m^2), TC (median level, ≤4.9 *vs.* >4.9 mmol/L), TG (median level, ≤1.7 *vs.* >1.7 mmol/L), HbA1c (median level, ≤9.6 *vs.* >9.6 %), ACR (≤300 *vs.* >300 mg/mmol), CRP (median level, ≤1.5 *vs.* >1.5 mg/L), eGFR (≤60 *vs.* >60 $ml/min/1.73m^2$), D-dimer value (median level, ≤180 *vs.* >180 ug/L), Diabetes duration (75% level, ≤13 *vs.* >13 years), SBP (≤140 *vs.* >140 mmHg), DBP (≤80 *vs.* >80 mmHg). As shown in **Figure 2**, serum IGF-1 levels were significantly negatively correlated with age (P < 0.001), diabetes duration (P = 0.001) and ACR (P <0.001). The analysis shows that levels of IGF-1 are lower in people who have the older age, the longer course of diabetes, or the higher ACR. Notably, although no significant difference between females and males in serum IGF-1 levels, male subjects appeared to have a lower IGF-1 level (*P = 0.07).* However, we did not find the significant correlation of IGF-1 levels with Waist, BMI, TC, TG, HbA1c, CRP, eGFR, D-dimer (**Figure 2**). Collectively, our analysis revealed that low serum IGF-1 levels may be significantly associated with an increased risk of LEAD.

Association between serum IGF-1 levels and clinicopathological parameters in T2DM patients

Given frequently altered IGF-1 levels in T2DM patients, the associations between the IGF-1 level and the clinicopathological characteristics were investigated in the collected 442 diabetes patients. Serum IGF-1 levels were defined as the dependent variable. The independent variables were age, gender, W, BMI, ACR, TC, TG, HbA1c, D-dimer, CRP, eGFR and diabete duration. As shown in **Table 2**[end of document], univariate analysis showed age, gender, Waist, ACR, diabete duration were negatively correlated with serum IGF-1 levels (P < 0.05). Further multivariate line regression analysis identified that serum IGF-1 levels were independently and negatively related to age(standardiazed β = -0.208, P < 0.001) and gender (standardiazed β = -0.126, P = 0.019).

Logistic regression analysis for the relationship of IGF-1 Levels with LEAD

To determine the relationship between serum IGF-1 levels and LEAD, univariate and multivariate logistic regression analysis were conducted. LEAD was defined as the dependent variable, and IGF-1, gender, W, BMI, ACR, TC, TG, HbA1c, D-dimer, CRP, eGFR and diabete duration were defined as the independent variables. Considering that SBP, DBP also were risk factors of LEAD, we also put SBP, DBP into the independent variables. As shown in **Table 3**[end of document], in univariate analysis, the result showed that IGF-1, SBP, DBP, diabetes duration, ACR, and D-dimer are significantly associated with LEAD (P <0.05). Though we found that decrease of serum IGF-1 levels were associated with an increased risk of

LEAD (P = 0.019), the reslult indicated that IGF-1 almost has no effect on the LEAD with OR value of 0.994 (95 % CI = 0.988-0.999). In multivariate analysis, the same resultss were observed with OR value of 0.993 (95 % CI =0.987-1.000, P = 0.042) after adiustment for SBP, DBP, D-dimer and ACR. (**Table 3**) end of document.

Discussion

Lower extremity atherosclerosis disease is one of the major complications of T2DM, and its clinical presentation varies from no symptoms to intermittent claudication, atypical leg pain, rest pain, ischemic ulcers, or gangrene, adversely affecting the quality of life. To date, the definite mechanisms that instigate and propagate atherosclerosis remain unclear. Most studies focused on diabetes with cardiovascular and cerebrovascular risks, but investigations about lower extremity atherosclerosis disease were extremely scarce. Therefore, we carried out this cross-sectional study to explore risk factors of lower extremity atherosclerosis disease in Chinese hospitalized type 2 diabetes.

In the present study, we investigated serum IGF-1 level in a cohort of T2DM with LEAD and without LEAD patients (control subjects). Our data showed that patients with LEAD have lower serum IGF-1 level as compared with the control subjects, which implies decreased IGF-1 levels may be involved in the progression of LEAD. It is well known that IGF-1, along with growth hormone, helps promote normal bone and tissue growth and development(20). IGF-1 also was found to affect vascular function and atherosclerosis in many ways, including anti-inflammatory, anti-apoptotic actions(21, 22) and stimulation of angiogenesis(23–25). IGF-1 improved cardiac contractility by increasing nitric oxide production in endothelial and vascular smooth muscle cells through activation of nitric oxide synthetase via Akt-catalyzed phosphorylation(26). Moreover, higher levels of IGF-I seem to prevent adult endothelial dysfunction and early coronary artery disease(27). Meanwhile, it was reported that infusion of IGF-1 for 12 weeks in ApoE-deficient mice on a western diet reduced the progression of atherosclerotic plaques and improve vascular inflammation(28, 29). Arterial intima-media thickness (IMT) has been recognized as a good predictor of cardiovascular disease risk(30). All these proved that the IGF-1 is strongly related to the occurrence of atherosclerosis. As such, elevation of IGF-1 levels during the pathological process of atherosclerosis may be a promising approach to treat atherosclerosis related diseases including LEAD.

Notably, we found that IGF-1 levels were higher in male, young patients, lower uric ACR and shorter diabetes duration patients. In the univariate and multivariste analysis, the IGF-1 level exhibited a significantly independently negative association with female and age. Many studies has elucidated the age-related decline in GH and IGF-1 secretion(27, 31). The interrelationships of IGF-1 and gender are complex and incompletely understood. Lv. et la. Also showed IGF-1 levels were lower in women than those in men(32), while Pehlivan et al. reported that the IGF-1 concentrations were significantly higher in female White goat kids. More studies need to clarify the relationship of IGF-1 and gender.

In recent basic science studies, IGF-1 has been shown to reduce atherosclerosis burden through anti-apoptotic(21) and anti-inflammatory properties(33), and enhance insulin sensitivity(34). Low circulating

IGF-1 levels have been associated with increased carotid intima-media thickness(35) in an elderly population. In the present study, our data verified that age, SBP, diabetes duration, uric ACR were the independent risk factors for LEAD, which was consistent with previous study(36). However, we observed that IGF-1 level was a negative independent risk factor with LEAD, the OR value is of 0.993 (95% CI = 0.987-1.000, P = 0.042), which means IGF-1 level has almost no relationship with LEAD. While, in the prospective Framingham Study, after a mean follow-up of 10.2 years, IGF-1 levels were inversely associated with ischemic stroke with subjects in the lowest quintile of IGF-1 levels having a 2.3-fold higher risk of incident ischemic stroke(37). Given that our study is a retrospective study and have fewer samples, which make it difficult to clarify the causal relationship between decreased serum IGF-1 levels and presence of LEAD. Hence, further studies need to expand the sample size and confirm the validity of the results of this study.

Conclusion

In summary, we investigated the serum IGF-1 levels in a large cohort of T2DM patients and demonstrated that the IGF-1 level was higher in patients without LEAD. The IGF-1levels were strongly associated with age and gender. However, though decreased IGF-1 level is an independent risk factor in LEAD, the OR value is of 0.993 (95 % CI =0.987-1.000, P = 0.042). More studies are required to further clarify the relationship between IGF-1 and LEAD in type 2 diabetes patients.

Abbreviations

IGF-1: Insulin-like growth factor-1; LEAD: Lower extremity atherosclerotic disease; T2DM: Type 2 diabetes mellitus; PAD: Peripheral artery disease; ADA: American Diabetes Association; ORs: Odds ratios; CI: Confdence interval; W: Waist circumstance; BMI: Body mass index; TC: Total cholesterol; TG: Triglyceride; HbA1c: Hemoglobin A1c; ACR: Albumin/Urine Creatinine Ratio; CRP: C-reactive protein; eGFR: Glomerular fltration rate; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Declarations

Authors' contributions

YZ and FL initiated the study. All authors contributed substantially to the study design and planning. JS and HW assessed the participants' eligibility for the intervention. FL managed the data collection, conducted the data analysis and wrote the frst draft of the manuscript. YZ, DL, WZ and YG contributed with a statistical plan and advice. YZ, PM and XL substantively revised the manuscript. YW Guided the study. All authors are collectively responsible for the interpretation of the results and critical reviews of the subsequent drafts of the manuscript and have approved the submitted version.

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Availability of data and materials

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

Ethics approval and consent to participate

All protocols of this study were approved by the institutional Ethics Research Committee of Henan Provincial Luoyang Central Hospital Affiliated to Zhengzhou University. The study was performed according to the declaration of Helsinki. Written informed consent for this study was also approved by the Henan Provincial Luoyang Central Hospital Affiliated to Zhengzhou University Ethics Committee.

Consent for publication

Consent for publication is not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Clinicopathological characteristics of all subjects. Numbers, percentages

Characteristics	No. of patients(%)
Gender	
Female	188 (42.5)
Male	254 (57.5)
Age, years	
≤ 60	262 (59.3)
> 60	180 (40.7)
W, cm	
≤ 90	195 (46.7)
> 90	223 (53.3)
BMI, kg/m^2	
≤28	357 (81.5)
>28	81 (18.5)
TC, mmol/L	
≤ 4.9	202 (51)
> 4.9	194 (49)
TG, mmol/L	
≤ 1.7	203 (50.2)
> 1.7	201 (49.8)
HbA1c, %	
≤ 9.6	215 (51.4)
> 9.6	203 (48.6)
ACR, mg/mmol	
≤ 300	321 (89.2)
> 300	39 (10.8)
CRP, mg/L	
≤ 1.5	191 (50.1)
> 1.5	190 (49.9)
eGFR, ml/min/1.73m^2	

≤ 60	42 (10.4)
> 60	362 (89.6)
D-dimer, μg /L	
≤ 180	233 (53.8)
> 180	200 (46.2)
Diabetes duration, years	
≤ 13	339 (76.7)
> 13	103 (23.3)
SBP, mmHg	
≤ 140	280 (63.8)
> 140	159 (36.2)
DBP, mmHg	
≤ 80	169 (38.5)
> 80	270 (61.5)

W Waist circumstance, *BMI* Body mass index, *TC* total cholesterol, *TG* triglyceride, *HbA1c* glycated hemoglobin A1c, *ACR* Albumin/Urine Creatinine Ratio, *CRP* C-reactive protein, *eGFR* glomerular fltration rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

Table 2 Univariate and multivariate linear regression analyses of factors associated with serum IGF-1 levels

Variables	Univariate analysis		Multivariate analysis	
	standardiazed *β*	P	standardiazed *β*	P
Gender	-0.095	0.045	-0.126	0.019
Age	-0.209	<0.001	-0.208	<0.001
W	-0.102	0.037	-0.034	0.527
ACR	-0.105	0.047	-0.094	0.081
Diabete duration	-0.13	0.006	-0.005	0.931

Table 3 Factors for LEAD identified by Univariate and multivariate logistic regression analysis

characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
IGF1	0.994 (0.988,0.999)	0.019	0.993 (0.987,1.000)	0.042
SBP	1.014 (1.000,1.027)	0.046	1.022 (0.998,1.047)	0.069
DBP	0.973 (0.954,0.992)	0.006	0.976 (0.934,1.001)	0.057
Diabete duration	1.218 (1.144,1.297)	<0.001	1.146 (1.068,1.231)	<0.001
ACR	1.005 (1.000,1.010)	0.039	1.002 (0.998,1.007)	0.274
D-dimer	1.004 (1.002,1.007)	0.001	1.003 (1.000,1.006)	0.065

OR odds ratio, *CI* confidence interval

Figures

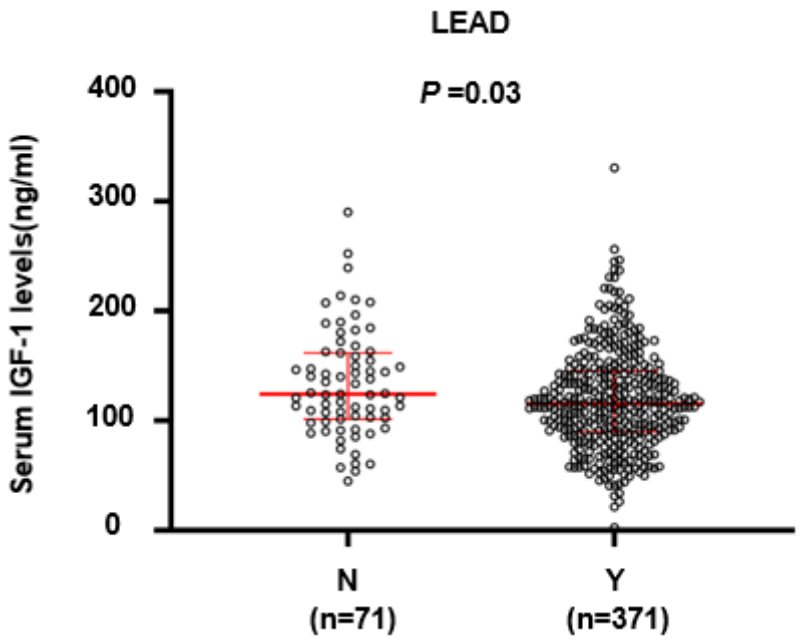

Figure 1

Comparion of serum IGF-1 levels between diabetes patients with and LEAD without LEAD. The automatic chemiluminescence analyzer was used to analyse IGF-1 levels in serum of T2DM subjects. The horizontal lines represent median ± interquartile range. N, without LEAD; Y, with LEAD.

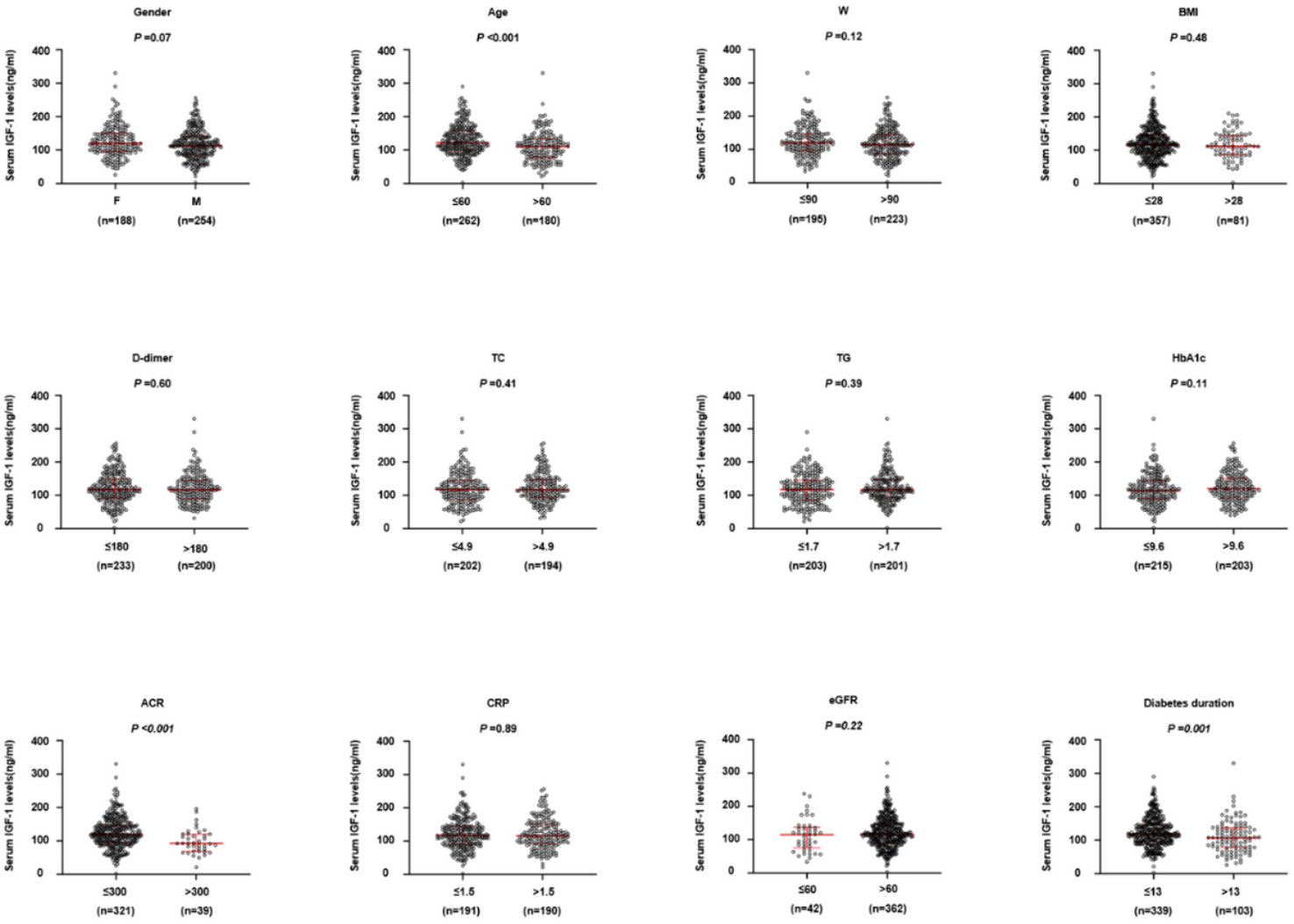

Figure 2

Association of IGF-1 levels with clinicopathological characteristics in T2DM patients. The automatic chemiluminescence analyzer was used to analyse serum IGF-1 levels of all subjects. The circle represents IGF-1 level of each diabetes patient. The horizontal lines represent median ± interquartile range. The sample medians were compared using the Mann-Whitney U test. F, female; M, male; N, No; Y, Yes.