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Original Article

Serum GLP-1 and IGF-1 levels are candidate diagnostic biomarkers for type 2 diabetes mellitus complicated by coronary heart disease

Jingpu Wang[1*], Xue Chen[2*], Yipeng Zhao[3]

[1]Department of Endocrinology, Baoding Second Hospital, Baoding 071000, Hebei, China; [2]Department of Cardiology, Baoding Second Hospital, Baoding 071000, Hebei, China; [3]Department of Medicine, Affiliated Hospital of Hebei University, Baoding 071000, Hebei, China. [*]Equal contributors and co-first authors.

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Abstract: Background: Objective: The aim of this study was to analyze the role of blood Glucagon like peptide-1 (GLP-1), insulin-like growth element-1 (IGF-1), and type 2 diabetes mellitus (T2DM) in coronary heart disease (CHD). Method: In this study, the clinical data of T2DM patients (n=203) admitted to Baoding Second Hospital from June 2020 to June 2021 were retrospectively analyzed. The patients included 65 T2DM patients without CHD who were assigned to the T2DM group and 138 T2DM patients with a CHD and T2DM comorbidity assigned to the CHD group. The baseline demographic characteristics and laboratory indexes of the two groups were explored, and the relationship between expression profiles of GLP-1 and IGF-1 levels and T2DM complicated by CHD was evaluated. The patients in the CHD group were sub-classified by the SYNTAX score system according to the results of coronary angiography. The three groups included a low-risk group with 52 cases, medium-risk group with 45 cases, and high-risk group with 41 cases. The relationship between GLP-1 and IGF-1 levels and the risk level of T2DM complicated by CHD was evaluated. Results: Significant differences in age, smoking history, total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), fasting blood glucose, GLP-1, and IGF-1 were observed between the two groups. Multivariate analysis revealed that smoking history, LDL-C, GLP-1, and IGF-1 were risk factors for CHD. Spearman correlation analysis showed a positive correlation between GLP-1 level and the occurrence of T2DM complicated by CHD, whereas IGF1 level was negatively correlated with the occurrence of T2DM complicated by CHD. GLP-1 and IGF-1 levels showed significant differences between risk groups. The GLP-1 level in the high-risk group was higher than that in the low- and medium-risk groups whereas IGF-1 level was lower in the high-risk group relative to the other two groups. Conclusion: Blood GLP-1 and IGF1 levels were associated with occurrence of T2DM complicated by CHD. Elevated level of blood GLP-1 was positively correlated with high risk of T2DM complicated by CHD whereas a lower blood IGF1 level was positively correlated with risk of T2DM complicated by CHD.

Keywords: Glucagon-like peptide-1, insulin-like growth element-1, type 2 diabetes mellitus, coronary heart disease, inflammation

Introduction

Diabetes mellitus (DM) is a major risk for cardiovascular and cerebrovascular diseases. The disease causes systemic inflammation and oxidative stress which play a significant role in promoting occurrence of cardiovascular disease [1, 2]. Glucagon-like peptide-1 (GLP-1) is implicated in improving vascular endothelial function and modulating atherosclerosis [3, 4]. Insulin-like growth factor-1 (IGF-1) is a low molecular protein homologous to insulin. IGF-1 promotes cardiomyocyte differentiation and hypertrophy *in vitro*, promotes vascular endothelial cell hyperplasia and fibrous tissue hyperplasia, and plays a protective role in ischemic cardiomyocytes [5, 6].

GLP-1 and IGF-1 are implicated in inflammation and oxidative stress, thus modulating occurrence of coronary heart disease (CHD). GLP-1 alleviates inflammatory damage caused by stroke by inhibiting astrocyte inflammation through interaction with IGF-1 receptor [7]. In addition, a study on experimental rats with amyotrophic lateral sclerosis induced by methyl-

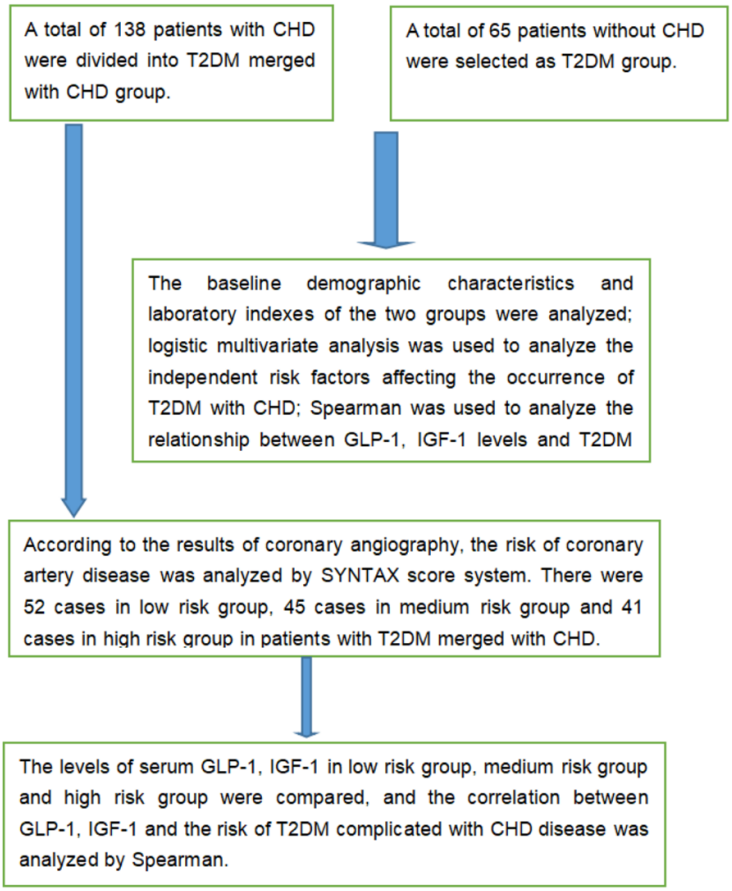

Figure 1. Graphic summary of the study. Type 2 diabetes mellitus (T2DM), coronary heart disease (CHD), Glucagon like peptide-1 (GLP-1), insulin-like growth element-1 (IGF-1).

mercury showed that IGF-1/GLP-1 signaling mediates oxidative stress injury in motoneurons [8]. However, the association between GLP-1 and IGF-1, and type 2 diabetes mellitus (T2DM) complicated by CHD has not been fully elucidated.

Therefore, the aim of this study was to retrospectively evaluate the clinical data of T2DM patients with or without CHD who had attended our hospital. The association between GLP-1 and IGF-1, and the occurrence of T2DM complicated by CHD was explored.

Methods

Study design and procedures

The study design is presented in **Figure 1**. This study was a case-controlled trial with repeated measurements from June 2020 to June 2021. In this retrospective study, baseline demographic characteristics and laboratory indexes of subjects in the T2DM-CHD group and T2DM group were compared. The relationship between GLP-1 and IGF-1 expression levels and T2DM complicated by CHD was assessed. In this study, 65 T2DM patients without CHD were assigned to the T2DM group, whereas 138 T2DM patients with CHD were assigned to the T2DM-CHD group.

Selection of study participants

The inclusion criteria of study subjects were: i) Meeting the diagnostic criteria for T2DM [9]; ii) Patients who had undergone coronary angiography and were diagnosed with CHD; iii) Subjects more than 18 years old. The exclusion criteria for the study were: i) Trauma, infection and bleeding before examination; ii) Diseases such as blood system and immune system; iii) Liver and kidney dysfunction; iv) Incomplete clinical data. No participant dropped out during the study period. This study was approved by the Ethics Review Committee of the Baoding Second Hospital. All subjects signed an informed consent before participating.

Collection of clinical data

Baseline demographic characteristics: Demographic characteristics of the subjects including sex, age, disease history and other data were recorded. Laboratory indicators: Venous blood samples were obtained from all subjects in the morning after a fasting overnight to evaluate biochemical indexes such as Hemoglobin A1c (HbA1C), fasting blood glucose, low density lipoprotein cholesterol (LDL-C), total cholesterol (TC), GLP-1, and IGF-1 levels. HbA1C was analysis was conducted using a fully automated HbA1C analyzer (Xisen Meikang Medical Electronics Co., Ltd.). Fasting blood glucose, TC and LDL-C were evaluated using AU-5800 series automatic biochemical analyzer (Beckman

Table 1. Demographic data and clinical indexes of the subjects

Clinical characteristic	T2DM complicated by CHD group (n=138)	T2DM group (n=65)	*T* or χ^2	*P*
Gender (male/female)	83 (60.14)	32 (49.23)	2.143	0.143
Age ($\bar{x}$ ± s, years)	62.83 ± 7.59	60.32 ± 8.18	2.144	0.033
Smoking history [n (%)]	63 (45.65)	19 (29.23)	4.949	0.026
Drinking history [n (%)]	27 (19.57)	15 (23.08)	0.332	0.564
Hypertension history [n (%)]	91 (65.94)	38 (58.46)	1.067	0.302
Family history of CHD [n (%)]	14 (10.14)	11 (16.92)	1.880	0.170
TC ($\bar{x}$ ± s, mmol/L)	4.39 ± 1.12	4.02 ± 0.98	2.283	0.024
LDL-C ($\bar{x}$ ± s, mmol/L)	2.25 ± 0.67	2.01 ± 0.52	2.548	0.012
HbA1C($\bar{x}$ ± s, %)	8.14 ± 1.87	7.67 ± 1.35	1.815	0.071
Fasting blood glucose ($\bar{x}$ ± s, mmol/L)	11.23 ± 3.11	8.82 ± 2.11	5.660	
GLP-1 ($\bar{x}$ ± s, pmol/L)	24.28 ± 5.44	20.12 ± 3.87	5.537	< 0.001
IGF-1 ($\bar{x}$ ± s, ug/L)	98.17 ± 28.19	124.39 ± 30.28	6.037	< 0.001

Type 2 diabetes mellitus (T2DM), coronary heart disease (CHD), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), Hemoglobin A1c (HbA1C), Glucagon like peptide-1 (GLP-1), insulin-like growth element-1 (IGF-1).

Kurt Co., Ltd.). Enzyme linked immunosorbent assay (ELISA) was conducted to evaluate GLP-1 and IGF-1 expression.

The degree of lesions in T2DM complicated by CHD

The degree of lesions in T2DM complicated by CHD was assessed by the SYNTAX score system [10]. A SYNTAX score between 1~22 indicated low severity, 23~32 represented medium severity, and ≥ 33 indicated high severity. The scoring results showed 52 cases of low severity, 45 cases of medium severity and 41 cases of high severity for the subjects with co-occurrence of T2DM and CHD. The analysis and evaluations were performed by two experienced CHD intervention experts.

Statistical analysis

SPSS 20.0 software was used for data analysis. Age and laboratory indicators were expressed as mean ± standard deviation ($\bar{x}$ ± s). In this study, *t*-test was conducted to compare the differences between the two groups. Gender and medical history data were expressed as percentages and chi square test was conducted to evaluate the differences between the two groups. Logistic multiple regression analysis was performed to explore the potential risk factors in T2DM-CHD comorbidity. Spearman correlation analysis was conducted to evaluate the relationships among blood GLP-1, IGF-1 levels and the occurrence and lesion degree of T2DM-CHD comorbidity. $P < 0.05$ was considered a significant difference.

Results

Demographic data and laboratory indexes

The results showed significant differences in age, smoking history, TC, LDL-C, fasting blood glucose, GLP-1 and IGF-1 between the two groups ($P < 0.05$). However, sex, drinking history, hypertension history, CHD family history, and HbA1C were not significantly different between the two groups ($P > 0.05$) (**Table 1**).

Independent risk factors for T2DM co-occurring with CHD

A logistic regression analysis was conducted with the occurrence of CHD as the dependent variable, to explore possible risk factors for co-occurrence of T2DM and CHD. The results revealed that smoking history, LDL-C, GLP-1, and IGF-1 were risk factors for CHD ($P < 0.05$) (**Table 2**). Smoking history, LDL-C, GLP-1 and IGF-1 were used as test variables whereas CHD was used as the state variable for ROC curve analysis. The results showed that the AUC and 95% confidence intervals of smoking history, LDL-C, GLP-1, IGF-1 and all the variables in predicting the occurrence of CHD were 0.733 (0.602-0.864), 0.816 (0.700-0.932), 0.783 (0.650-0.917), 0.753 (0.627-0.878) and 0.852 (0.753-0.952), respectively (**Figure 2**). Spearman correlation analysis was conducted

Table 2. Independent risk factors for T2DM complicated by CHD

Risk factor	*β*	*SE*	*Wald* χ^2	*OR*	95% *CI* online	95% *CI* offline	*P*
Age (years)	1.018	0.631	2.603	2.768	0.804	9.533	0.107
Smoking history (n)	1.025	0.398	6.633	2.787	1.278	6.080	0.010
TC ≥ 4.14 (mmol/L)	1.187	0.871	1.857	3.277	0.594	18.068	0.174
Fasting blood glucose ≥ 9.87 (%)	1.176	0.693	2.880	3.241	0.833	12.607	0.090
GLP-1 ≥ 22.15 (pmol/L)	1.071	0.514	4.342	2.918	1.066	7.922	0.038
IGF-1 ≥ 115.71 (ug/L)	-0.983	0.415	5.611	2.672	1.185	6.028	0.018
LDL-C ≥ 2.13 (mmol/L)	1.131	0.512	4.880	3.099	1.136	8.453	0.028

Type 2 diabetes mellitus (T2DM), coronary heart disease (CHD), total cholesterol (TC), Glucagon like peptide-1 (GLP-1), insulin-like growth element-1 (IGF-1).

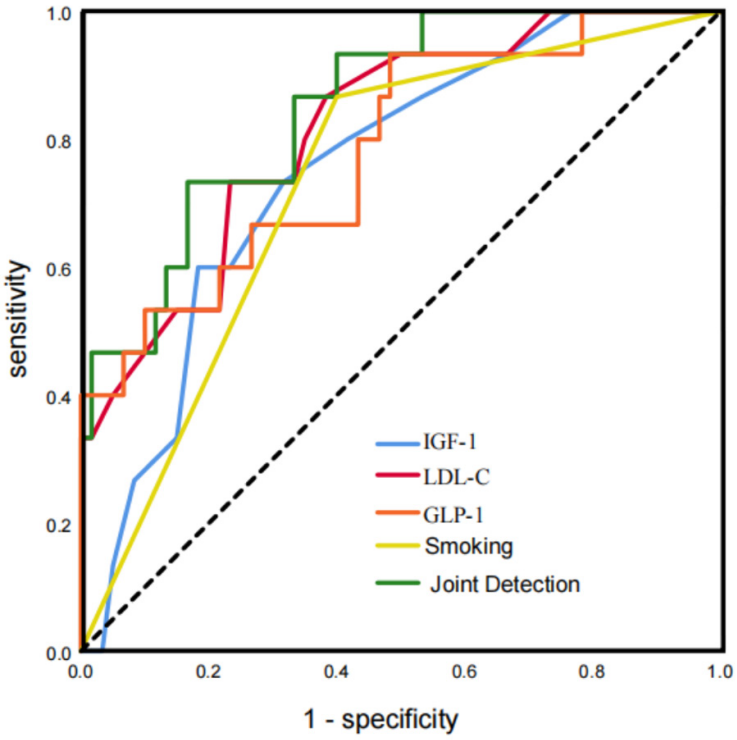

Figure 2. A ROC curve for the diagnostic value of the risk factors for T2DM complicated by CHD. Type 2 diabetes mellitus (T2DM), coronary heart disease (CHD).

to explore the relationship between GLP-1 and IGF1 serum levels and occurrence of T2DM-. The results showed a positive correlation between GLP-1 level and the occurrence of T2DM-CHD and a negative correlation was observed between IGF1 level and occurrence of T2DM-CHD ($P < 0.05$) (**Table 3**).

Blood GLP-1 and IGF-1 levels in patients with different severity levels

The expression levels of GLP-1 and IGF-1 were significantly different among the three groups ($P < 0.05$). The expression level of GLP-1 was higher in the high-severity group than that in the low-severity group and medium-severity group ($P < 0.05$). The expression level of IGF-1 in the high-severity group was lower than that in the low-severity group and medium-severity group ($P < 0.05$) (**Table 4**). Correlation analysis between the level of serum GLP-1 and IGF1 and the degree of lesion in T2DM-CHD showed a positive correlation between GLP-1 level and the lesion severity in the T2DM-CHD group ($P < 0.05$). On the contrary, IGF1 was negatively correlated with lesion severity in the T2DM-CHD group ($P < 0.05$) (**Table 5**).

Discussion

The incidence of T2DM accompanied by CHD has gradually increased in recent years with more incidences reported in young people. Dysregulated lipid metabolism and activation of inflammatory responses are the common pathologic features of these two chronic diseases. The NCEP-ATPIII guidelines established in the United States indicate that T2DM and CHD have similar features [11]. Chinese guidelines classify patients with atherosclerotic cardiovascular disease including CHD in the extremely high-risk group whereas T2DM patients are grouped in the high-risk group [12]. Dysregulation of lipid metabolism is a major risk factor for occurrence and progression of CHD. Moreover, lipid metabolism promotes the occurrence and pro-

Table 3. Correlation analysis between blood GLP-1 and IGF1 levels, and the occurrence of T2DM complicated by CHD

	Occurrence of T2DM complicated by CHD	
	r	*P*
GLP-1	0.351	< 0.001
IGF-1	-0.374	< 0.001

Type 2 diabetes mellitus (T2DM), coronary heart disease (CHD), Glucagon like peptide-1 (GLP-1), insulin-like growth element-1 (IGF-1).

Table 4. Blood GLP-1 and IGF-1 levels in patients with different risk levels

Group	n	GLP-1 (pmol/L)	IGF-1 (ug/L)
Low-danger group	52	20.93 ± 3.20	113.39 ± 21.38
Medium-danger group	45	24.11 ± 4.15*	102.10 ± 22.19*
High-danger group	41	27.92 ± 4.87*,#	81.43 ± 24.40*,#
F		33.933	23.210
P		< 0.001	< 0.001

Note: Compared to the moderate risk group, *$P < 0.05$; Compared to the low-risk group, #$P < 0.05$. Glucagon like peptide-1 (GLP-1), insulin-like growth element-1 (IGF-1).

Table 5. Correlation analysis between blood GLP-1 and IGF1 levels, and the lesion degree of T2DM complicated by CHD

	Lesion degree of T2DM complicated by CHD	
	r	*P*
GLP-1	0.301	0.002
IGF-1	-0.307	0.001

Type 2 diabetes mellitus (T2DM), coronary heart disease (CHD), Glucagon like peptide-1 (GLP-1), insulin-like growth element-1 (IGF-1).

in transport of cholesterol from the liver to various organs and tissues of the body. An increase in LDL-C level can result in accumulation of cholesterol in the blood vessels of various organs and tissues. These cholesterol deposits induce an inflammatory response to the vascular intima causing endothelial damage. LDL-C then enters the vascular endothelium and undergoes oxidation and phagocytosis by macrophages. Macrophages with high amounts of cholesterol are transformed into foam cells and deposited in the vascular endothelium causing atherosclerosis. The number of subjects with smoking history was significantly higher in the T2DM-CHD groups relative to the T2DM group. The results showed that smoking history was an independent risk factor for T2DM complicated by CHD. Jiang et al. [17] reported that smoking was independently associated with occurrence of non-calcified, chocking and broader coronary artery plaques by comparing the plaque features of diabetes patients with different smoking status. A longer smoking time was correlated with a higher risk of mixed, chocking and broader plaques. These findings were observed because smoking causes inflammation of the vascular endothelium leading to vascular wall damage, which provides favorable conditions for lipid deposition, and ultimately causes arteriosclerosis.

gression of diabetes [13, 14]. A previous study revealed that more than 40% of T2DM patients in China presented with dysregulated lipid metabolism [15]. Liu et al. [16] observed higher TC and LDL-C levels in T2DM complicated by CHD compared to the levels in T2DM alone. This finding is consistent with the results of the present study, indicating that TC and LDL-C levels are associated with the occurrence of CHD. However, the independent risk factors for CHD have not been fully elucidated [16]. The present findings showed that TC and LDL-C levels were independent risk factors for the occurrence of T2DM complicated with CHD. Levels of TC ≥ 4.14 mmol/L and LDL-C ≥ 2.13 mmol/L are associated with markedly high risk of co-occurrence of T2DM with CHD, indicating that TC and LDL-C can be used as biomarkers for diagnosis of T2DM complicated by CHD. LDL-C is involved

GLP-1 is a peptide hormone that modulates cardiovascular function and glucose metabolism. GLP-1 is encoded by a glucagon precursor gene in intestinal endocrine cell subsets and released under the stimulation of nutrients. GLP-1 amide is the bioactive form of GLP-1 during circulation. A decrease in GLP-1 plasma level is observed in T2DM subjects, which may be caused by dysregulation in metabolism. GLP-1 is rapidly broken down by 4-dipeptidyl peptidase to a GLP-1 metabolite. Only about 10-15% of the total concentration of GLP-1 reaches the cycle. The fasting concentration of bioactive GLP-1 is very low with a concentration ranging from 0~15 pmol/l reported in previous studies [18-21]. Krizhanovskii et al. [22] conducted a case-control study and observed that diabetes is associated with significant upregulation of blood GLP-1 level during fasting. Aortic

dilatation in diabetic patients is correlated with significant increase in blood GLP-1 level during fasting. IGF-1 is a key modulator of somatic growth after birth (pre-puberty and adolescence). The IGF-1 protein mediates the role of growth hormone. IGF-1 levels are highest in the middle of adolescence, and then decrease with age. IGF-1 molecules can bind to IGF binding proteins in circulation and prevent IGF-1 from binding to insulin receptors, or regulate the binding of IGF-1 with IGF-1 receptors. IGF-1 receptors are expressed in several cell types and previous findings indicate that IGF-1 is implicated in pathogenesis of cardiovascular disease [23-25]. Ruidavets et al. [26] reported that the baseline level of IGF-1 decreases significantly under acute coronary syndrome, and subjects with the highest IGF-1 concentration have a 55% lower relative risk of myocardial infarction. Moreover, De Leronzo et al. [27] observed significant decrease in the level of IGF-1 in early-onset CHD. In the present study, GLP-1 level was significantly higher in T2DM complicated by CHD relative to the level in T2DM alone. On the contrary, IGF-1 level was significantly lower in T2DM complicated by CHD compared to the level in T2DM, but the two factors were independent risk factors for T2DM complicated by CHD. GLP-1 level ≥ 22.15 pmol/L is associated with increased risk of complicated CHD whereas IGF-1 level ≥ 115.71 ug/L is associated with a decreased risk of complicated CHD. The level of GLP-1 was also positively correlated to the lesion degree of T2DM complicated with CHD, whereas IGF-1 was negatively correlated with the lesion degree. The high serum GLP-1 and low serum IGF-1 levels may be implicated in regulation of basic metabolism of cellular fat and glucose, inhibition of insulin-mediated glucose uptake and cholesterol transport, and induction of inflammation and oxidative stress, which ultimately promotes occurrence and progression of CHD.

The present study had some limitations. The study was a single-center, observational, case-controlled study. Therefore, studies with data from multiple centers should be conducted to verify the findings. In addition, the sample size used in the study was relatively small. Large samples from multiple centers should be used to verify these findings.

Conclusions and study limitations

In summary, GLP-1 level was higher whereas IGF-1 level was lower in T2DM subjects with CHD versus T2DM alone. The levels of GLP-1 and IGF-1 were positively correlated with the lesion degree of T2DM complicated by CHD. Therefore, these two proteins can be used for diagnosis of T2DM patients with CHD and high-risk patients.

Disclosure of conflict of interest

None.

Address correspondence to: Yipeng Zhao, Department of Pharmacy, Hebei University Affiliated Hospital, No. 212 Yuhua East Road, Baoding 071000, Hebei, China. E-mail: fywjp@hbu.edu.cn

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