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Original Article

Insulin like growth factor 1 is linked to higher cardiovascular risk score in adults with type 2 diabetes mellitus and chronic kidney disease

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ABSTRACT

Introduction: Insulin-like growth factor-1 (IGF-1) is a peptide that shares sequence homology with insulin and has endocrine, paracrine and autocrine functions, acts on endothelial cells, and stimulates angiogenesis. IGF1 also affects renal hemodynamics both directly and indirectly by interacting with the renin-angiotensin system.

Objective: The study aimed at detecting a relation between age-adjusted IGF1 (AAIGF1) and cardiovascular risk score in adults with type 2 diabetes mellitus and chronic kidney disease.

Design: Patients were 90 females and 42 males with different stages of CKD ranging from 0 to 4. After taking a consent, serum IGF1 was recorded and adjusted for the age of the patient using the IGF1 score equation: *{[(log IGF-1 + 0.00625xage)-2.555]/0.104}*.

Both univariate and multivariate regression analyses of AAIGF1 to different metabolic parameters and microvascular complications of type 2 DM were done. A ROC curve for CV risk score was issued.

Results: AAIGF1 showed a significant bidirectional change with the stage of CKD. Univariate analysis was done including cardiovascular parameters in relations to AAIGF1. A significant positive correlation was found between AAIGF1 and CV risk score (B = 0.036, p = 0.003), SBP (B = 0.030, P = 0.004) and DBP (B = 0.071, P = 0.000), with a reciprocal relation to EF (B = -0.050, P = 0.016). Multivariate regression showed a significant correlation between AAIGF1 and age, HOMAIR, HOMAB, Uric acid. A ROC curve with AUC of 0.675, P = 0.003, showed that AAIGF1 of approximately −1.7 is a cut off for intermediate CV risk (10 year risk score >7.5%).

Conclusion: AAIGF1 shows a bidirectional relation to the grade of chronic kidney disease in adults with type 2 DM. A cut off point for AAIGF1 was set to indicate intermediate CV risk score, which can encourage using AAIGF1 as a prognostic marker for higher CV risk score. Medications that modulate IGF1 level can affect CV risk.

1. Introduction

Insulin-like growth factor-1 (IGF-1) is a peptide that shares sequence homology with insulin and has endocrine, paracrine and autocrine functions, acts on endothelial cells, and stimulates angiogenesis [1]. IGF1 also affects renal hemodynamics both directly and indirectly by interacting with the renin-angiotensin system [2].

2. Objectives

The study aimed at detecting a relation between age-adjusted IGF1 (AAIGF1) and cardiovascular risk score in adults with type 2 diabetes mellitus and chronic kidney disease. AAIGF 1 was studied in relation to IR, other metabolic parameters and microvascular complications of diabetes.

3. Materials and methods

Data were statistically described in terms of mean ± standard deviation (±SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of

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Abbreviations

SD	standard deviation
CC	creatinine clearance
FBG	fasting blood glucose
HDL	high density lipoproteins
LDL	low density lipoproteins
TG	triglycerides
ACR	albumin creatinine ratio
TSH	thyroid stimulating hormone
BMI	body mass index
SBP	systolic blood pressure
DBP	diastolic blood pressure
AAIGF1	age-adjusted IGF1
IGF1	insulin like growth factor 1
HOMAIR	homeostasis model assessment of insulin resistance
HOMAB	Homeostasis model assessment of B cell function
EF	ejection fraction
IVSd	interventricular septal thickness at diastole
PVD	peripheral vascular disease
IHD	ischemic heart disease
MI	myocardial infarction
CVA	cerebrovascular accident
CKD	chronic kidney disease
IR	insulin resistance
CV	cardiovascular
DM	diabetes mellitus

numerical variables between the study groups was done using Kruskal Wallis test. For comparing categorical data, Chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Univariate regression analysis models were used to test for the preferential effect of the independent variable(s) on IGF-1 score. *P* values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

Our patients were 90 females and 42 males with different stages of CKD ranging from Stage 0–4. Most of our patients were of Stage 1 CKD (60.7%). After taking a consent, serum IGF1 was recorded and adjusted for the age of the patients using the IGF1 score equation: *{[(log IGF-1 + 0.00625 × age)−2.555]/0.104}* (B.1). We did both univariate and multivariate regression analyses of AAIGF1 to different metabolic parameters, IR, and micro complications of type 2 DM. We checked AAIGF1 score of our patients: 108 (81.8%) of them were toward the low range, whereas only 24 (18.2%) to the high range for their age (we used normal range of IGF1 for each age group) which goes with the effect of DM on our population (see discussion). We got the mean, standard deviation (SD), and percentage of different parameters including age, AAIGF1, Creatinine (Cr.), fasting blood glucose (FBG), creatinine clearance (CC), CKD stage, A1C,insulin, homeostasis model assessment(HOMA IR), HOMAB, lipids, albumin to creatinine ratio (ACR), thyroid function test (TFT), uric acid (UA), CV risk score (using atherosclerosis CV disease risk score), and anthropometric measures.

4. Results

4.1. Studied population

Looking into our 132 patients, many of them had different examples of CV diseases including: ischemic heart disease (IHD): 28 patients, cerebrovascular accidents (CVA): 10 patients, peripheral vascular diseases (PVD): (2 patients) and myocardial infarction (MI): 10 patients.

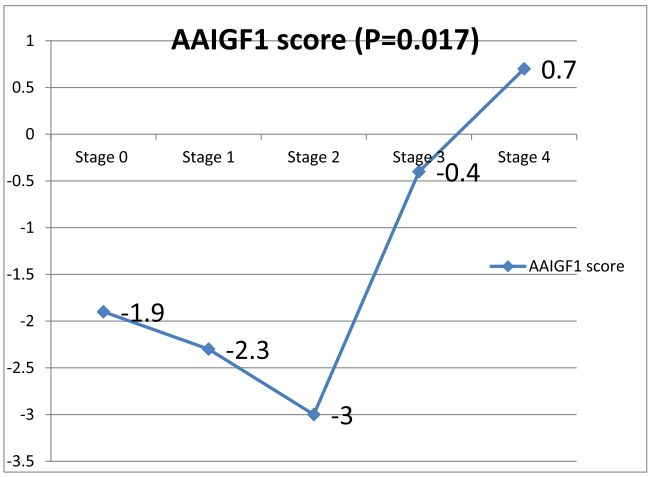
Regarding cardiovascular procedures: 2 patients had previous coronary angiography, 4 had coronary artery bypass graft, 2 had embolectomy and 4 had percutaneous coronary intervention (PCI) with stent application. 20 of the patients had at least 1 cardiovascular disease (CVD) or a cardiovascular (CV) procedure, 8 patients had 2 cardiovascular diseases or CV disease plus a procedure, 6 patients had a combination of 3 diseases and/or procedures, while 2 patients had a combination of 4 diseases and/or procedures. Table 1 shows means and SD of different study parameters.

AAIGF1 showed a significant change with the stage of CKD. This change was bidirectional where it tends to decrease to be in Stage 0 more than Stage 1 more than Stage 2 (means = −1.9, −2.3, −3.0, respectively) and then increases again with Stages 3 and 4 (means = −0.4 and 0.7 respectively) (P = 0.017) [Graph 1]. Since the number of patients was too small to be compared, the patients in the last three stages were grouped together to get a collective

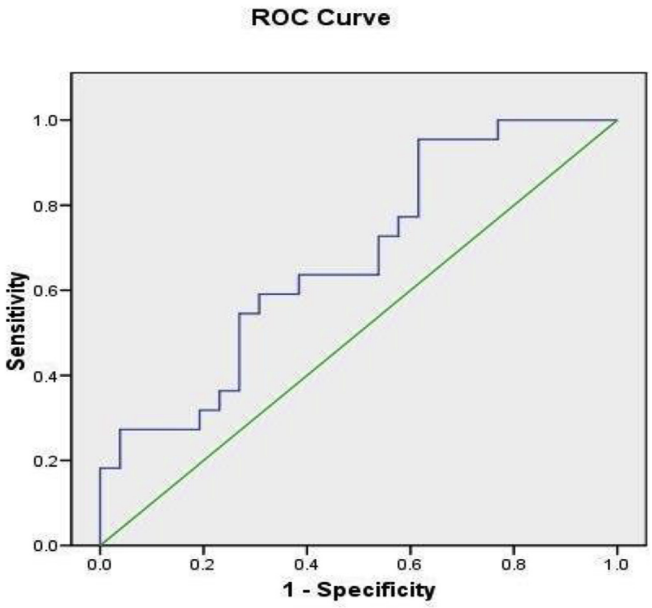
Table 1
Mean, SD of different study parameters.

Parameter	N	Mean	SD	Parameter	N	Mean	SD
Age(ys)	132	58.2	15.2	FT3(pmol/L)	132	4.1	0.7
Creatinine(mg/dL)	112	0.8	0.7	TSH(uIU/mL)	132	3	5.2
FBG(mmol/l)	132	8.9	4	Uric Acid (mg/dL)	132	5	1.4
CC(mL/min/1.73m2)	112	146.2	69.3	Age-adj.IGF1 score	132	−1.9	2
A1C (%)	132	7.9	1.8	CV risk score	96	14.2	16
Insulin(uIU/mL)	132	15.8	8.8	no of CV events and procedures	132	0.4	0.9
HOMA IR	132	6.3	4.8	IVSd(cm)	60	1.1	0.2
HOMA B	132	86.8	67.7	EF (%)	60	59	10.9
Cholesterol(mg/dL)	132	163.4	41.5	Insulin dose/kg(IU/kg)	46	0.6	0.3
TG(mg/dL)	132	126.7	87.8	SBP(mmHg)	124	135.6	17.8
HDL(mg/dL)	132	48.8	14.7	DBP(mmHg)	124	75.3	10.8
LDL(mg/dL)	132	101.2	41.4	BMI(kg/m2)	112	32.3	6.4
ACR(mg/gm)	108	232	472	no of microvascular complications	124	1	0.6
FT4(pmol/L)	132	14.9	2.8				

SD standard deviation, CC creatinine clearance, FBG fasting blood glucose, HDL high density lipoproteins, LDL low density lipoproteins, TG triglycerides, ACR albumin creatinine ratio, TSH thyroid stimulating hormone, BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, AAIGF1 age adjusted IGF1, IGF1 insulin like growth factor, HOMAIR homeostasis model assessment of insulin resistance, HOMAB Homeostasis model assessment of B cell function, EF ejection fraction, IVSd interventricular septal thickness at diastole.



Graph 1. Relation between AAIGF1 score and stage of CKD.



Graph 2. ROC curve for AAIGF1 cut-off point for CV risk.

group of "stage >1" (Stages: 0, 1, and more than 1). The same bidirectional relation was there but it was not significant (−1.9, −2.3, −1.2, respectively) (P = 0.298). We had a univariate regression analysis done between AAIGF1 and CV parameters. A significant positive correlation was found between AAIGF-1 and CV risk score (B = 0.036, P = 0.003), systolic blood pressure (SBP) (B = 0.03, P = 0.004) and diastolic blood pressure (DBP) (B = 0.07, P = 0.000) while a reciprocal significant relation was found to ejection fraction (EF) (B = −0.05, P = 0.016). A weak positive significant relation was there between CV events and procedures to AAIGF1 (B = 0.366, P = 0.063), while no significant relation at all was there between AAIGF1 and IVSd which is an indication for diastolic dysfunction. (B = −1.097, P = 0.305).

Table 2 shows multivariate regression analysis between AAIGF1 and different parameters. Doing multivariate regression showed only a significant correlation between AAIGF1 and age, HOMAIR, HOMAB, uric acid with weak significant relation to CV risk score, and thyroid-stimulating hormone. This study did not search for any causal relation between these parameters and AAIGF-1. Graph 2 is a receiver operating characteristic (ROC) curve with area under the curve of 0.675, P = 0.003, showed that AAIGF1 around −1.7 is a cutoff for intermediate CV risk score where 10 year risk ASCVD score is >7.5%, which is a cut-off point to start statins(A.2).

5. Discussion

5.1. IGF1 and CVD

IGF1, predominantly synthesized in the liver upon stimulation by growth hormone (GH), is usually bound to IGF-binding protein 3 (IGFBP-3) in circulation [3] IGF1 has an almost 50% amino acid sequence homology with insulin and elicits nearly the same hypoglycemic response [4]. It is found as one of the factors that favor atherosclerosis [5] and may also induce vascular smooth muscle cell proliferation and migration [6], promote macrophage activation, and thus may contribute to arterial obstructive lesions [7]. However IGF1 was found to have beneficial CV effects as well: in vivo and in vitro animal studies have shown that IGF1 induces vasodilatation by nitric oxide production, reduces endothelial dysfunction [8], promotes mRNA expression for specific contractile proteins, improves myocardial contractility, and limits ischemia-reperfusion injuries [9]. Low serum levels of IGF1 have been associated with carotid intima-media thickening [10], the presence of congestive heart failure [11], and angiographically documented coronary disease [12]. Low IGF1 levels have been also associated with an increased risk of ischemic heart disease (IHD) [13]. A study by Bourron et al., 2015 [14], showed that AAIGF1 levels were lower in patients with CV outcome events than in patients without CV outcome event. They interestingly found that patients with diabetes with low serum AAIGF1 levels were those with the poorest clinical outcomes. In a study by Conti et al., 2001 [15], patients with acute myocardial infarction (MI) had reduced serum levels of IGF1 compared with healthy controls, and among the acute MI patients, those with lower IGF1 levels had a higher frequency of 90-day events (recurrent ischemia, reinfarction, revascularization, sustained ventricular tachycardia after discharge, and death). Furthermore, lower serum levels of IGF1 were associated with 2-year mortality in 52 patients with acute MI [16].

Endothelial dysfunction has been observed in type 2 diabetes [17], and IGF1 is considered to be a potent regulator of endothelial function [18]. One hypothesis is that low IGF1 levels may exacerbate the preexisting endothelial dysfunction in patients with diabetes, proceeding to the poorer prognosis of patients with type 2 diabetes with low IGF1 concentrations. Another hypothesis is that type 2 diabetes, as observed in obesity, could be associated with endothelial IGF1 resistance [19]. In animal models, acute administration of IGF1 before and during early cardiac ischemia improves glucose uptake and tolerance to ischemia in hypertrophied hearts [20]. In our study, although the AAIGF1 was on the lower range as all patient had type 2 diabetes, there was a positive although weakly significant correlation between AAIGF1 to number of CV

Table 2
Multivariate regression analysis of different parameters to AAIGF1.

Parameter	B	P	Parameter	B	P
Age	−0.121	0.023	Cholesterol	0.010	0.769
CC	0.000	0.945	TG	−0.006	0.281
Micro.albumin. grade	−0.567	0.073	HDL	−0.056	0.083
A1C	0.177	0.327	LDL	−0.001	0.981
HOMAIR	−0.165	0.036	BMI	−0.053	0.156
HOMA B	−0.010	0.031	Uric acid	0.604	0.011
FT4	−0.108	0.385	CV risk	0.062	0.055
FT3	0.053	0.869	TSH	−0.209	0.055

events and procedures, and positive significant correlation to CV risk score, SBP, and DBP, whereas negative nonsignificant correlation to IVSd (indication of diastolic dysfunction) and negative significant correlation to EF. This may postulate that low AAIGF1 is associated more with heart failure outcome, whereas higher AAIGF1 is more related to vascular complications, e.g. IHD and atherosclerosis.

5.2. IGF1 and IR

Several studies have investigated the effect of IGF1 on insulin sensitivity and its relation to type 2 DM. Large longitudinal studies, including the National Health and Nutrition Examination Survey III, reported a higher risk of IR, metabolic syndrome (MetS), and type 2 diabetes in patients with low IGF1 serum concentrations or low IGF1-to-IGFBP-3 ratios [21]. An epidemiological study reported a negative correlation between IGF1 levels and insulin resistance (IR) measured by HOMA IR [22]. IGF1 leads to an increase in peripheral glucose uptake and a decreased production of hepatic glucose causing better insulin sensitivity [23]. On the other side, adult patients with GH replacement therapy revealed a higher prevalence of IR and MetS [24]. GH secretion is found to be blunted in type 2 diabetes [25], followed by IGF1 [26]. Our study confirmed the relation where HOMAIR and HOMAB showed a negative significant correlation to AAIGF1 by multivariate regression analysis [Table 2].

5.3. IGF11 and CV risk score

Our study may be the first to set a cutoff point for AAIGF1 to indicate higher CV risk score through a ROC curve [Graph 2], this cutoff point can encourage using AAIGF1 as a prognostic marker for CV risk in patients of type 2 DM with CKD.

5.4. IGF1 and kidney disease

IGF1 plays an important role in the early development of diabetic renal disease [27]. Most GH effects on glomerular hypertrophy appear to be mediated by IGF1, but some GH effects on glomerular sclerosis may be IGF1 independent [28]. Mesangial cells isolated from experimental models of diabetic nephropathy, exhibit altered IGF1 synthesis, IGF1 pathway activation, and higher IGF-1R (IGF1 receptors) expression, and activation than control mesangial cells [29]. As in rodent models, evidence has been obtained in humans that the GH/IGF1 axis is involved in the pathogenesis of diabetic nephropathy, with a specific effect on urinary albumin excretion. A correlation between urinary GH and IGF1 levels and microalbuminuria was observed in children and adolescents with type 1 diabetes, suggesting an important role of the GH-IGF1 system in the outcome of diabetic nephropathy during puberty, when both GH and IGF1 levels are physiologically elevated [30]. IGF1 may also contribute to the glomerular hyperfiltration observed in early diabetic nephropathy [31]. However, circulating levels of total IGF1 do not closely correlate to renal hypertrophy, and there is a lack of correlation between kidney size and the progressive decline in the glomerular filtration rate in patients with diabetes. Our study showed that primary decrease in serum AAIGF1 occurs followed by secondary increase in serum which appears as a biphasic graph. [Graph 1], whether this is related to initial increase of IGF1 in the renal parenchyma more than serum followed by its increase in the circulation, needs to be further studied. However, Brugts et al., in 2009 [32] postulated that heterophilic antibodies used in IGF1 immunoassays may give a false indication of decrease in IGF1. Our study proved a negative correlation between AAIGF1 and the microalbuminuria grade, although this correlation was weakly significant ($B = -0.567$, $P = 0.073$) [Table 2]. In our study, patients with micro and macroproteinuria had lower mean of AAIGF1 than patients with no proteinuria although this was insignificant ($P = 0.4$)

5.5. IGF1 and retinopathy

On the other hand, studies based on larger populations seem to indicate that with the factors of AlC, age, and course of disease controlled, IGF1 does not significantly correlate to the occurrence and progression of diabetic retinopathy in either teenage or adult patients with DM [33]. Our study matched this finding, while other studies, as the one done by Zhang et al., 2017,[34] showed that there is a positive significant correlation between the stage of retinopathy and the IGF1 level. They referred opposing results to different factors including difference in age, albuminuria, and BP and glucose control.

5.6. Limitations

However, one limitation in our study was that the number of patients with CKD stages 2–4 was too small compared to patients with CKD stage 1. Collecting the patients of the last 3 stages in one group showed the same biphasic relation although it was insignificant. More and preferably equal number of cases for each stage of CKD is needed in subsequent studies to detect a better correlation.

6. Conclusion

AAIGF1 shows a bidirectional relation to the grade of chronic kidney disease in patients with type 2 DM. A cut off point for AAIGF1 was set to indicate higher CV risk score, which can encourage using AAIGF1 as a prognostic marker for CV risk. Therapies that modulate IGF1 level to manage insulin resistance, proteinuria and decrease CV risk need further researches. Further studies that may include histological and molecular ones, with more and equal number of patients for each stage of CKD are needed to assess a more clear relation between IGF1 and CKD.

Declaration of interest

None.

Appendix A

A.1 Stages of Chronic kidney disease

GFR categories in CKD **in ml/min/1.73 m^2**
Grade 1 GFR ≥90 Normal or high.
Grade 2 GFR from 60 to 89 mildly decreased*
Grade 3a GFR from 45 to 59 mildly to moderately decreased.
Grade 3b GFR from 30 to 44 moderately to severely decreased.
Grade 4 GFR from 15 to 29 severely decreased.
Grade 5 GFR <15 Kidney failure.
According to National Kidney Foundation, USA. https://www.kidney.org/professionals/explore-your-knowledge/how-to-classify-ckd, last accessed 06/07/2019.

A.2 ASCVD risk score

It assesses the 10 year cardiovascular risk score of patients.
10-year risk for ASCVD is categorized as:
Low-risk (<5%)
Borderline risk (5%–7.4%)
Intermediate risk (7.5%–19.9%)

High risk (≥20%)

In our research ASCVD more than 7.5% was the cut point we used to indicate the transition to higher cardiovascular risk score that indicated statins, and it matches AAIGF1 of around −1.7.

According to D.C.Jr. Goff, D.M. Lloyd-Jones, G. Bennett et.al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* (2013) Nov 12, updated in (11/21/17)

A.3 Albuminuria categories in CKD

Regarding albuminuria grade patients were divided into.

Grade 0 (albumin/creatinine less than 20mg/gm)*

Grade 1 (albumin/creatinine from 20 to 299 mg/gm)*

Grade 2(albumin/creatinine more than 300mg/gm)*

*These numbers followed the laboratory technique and kits we used.

A.4 Stages of diabetic retinopathy

We divided our patients according to the degree of retinopathy as follows:

Grade 0- Patients with no maculopathy or any degree of diabetic retinopathy.

Grade 1- Patients with maculopathy or NPDR.

Grade 2- Patients with NPDR with maculopathy or patients with Preproliferative DR.

Grade 3- Patients with Preproliferative DR with maculopathy or patients with PDR.

Grade 4- Patients with PDR with maculopathy.

In our classification we used NHS diabetic retinopathy classification with some modulations. https://www.nhs.uk/conditions/diabetic-retinopathy/stages/last reviewed 30/10/2018 last accessed 07/06/19.

*A.5 Insulin resistance cut off value used in our study was 3**

*Due to lack of data from the Middle East that can assign a cut off value for HOMA IR to determine insulin resistance, an average value of 3 was used for HOMA IR depending on an article by Gayoso-Diz et al., 2013.

P. Gayoso-Diz, A. Otero-González, M.X. Rodriguez-Alvarez, F. Gude, F. García, A. De Francisco and A.G. Quintela. Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age: EPIRCE cross-sectional study, *BMC Endocrine Disorders* **13** (2013) 47, https://doi.org/10.1186/1472-6823-13-47.

Appendix B

Eq. (B.1) ([(log IGF-1 + 0.00625 × age)−2.555]/0.104)*

*S. Damanti, O. Bourron, M. Doulazmi, A.L. Mandengue Sosso, V.H. Nguyen-Michel, J. Mariani et al. Relationship between sleep parameters, insulin resistance and age-adjusted insulin like growth factor-1 score in non diabetic older patients, *PLoS One* **12** (2017) e0174876.

Appendix C. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.07.008.

References

[1] Nakao-Hayashi J, Hideki I, Kaneyasu T, Morita I, Murota S. Stimulatory effects of insulin and insulin-like growth factor I on migration and tube formation by vascular endothelial cells. Arteriosclerosis 1992;92:141–9.

[2] Bach LA, Hale LJ. Insulin-like growth factors and kidney disease. Am J Kidney Dis 2015;65:327–36.

[3] Jones JI, Clemmons DR. Insulin-like growth factors and their binding proteins: biological actions. Endocr Rev 1995;16:3–4.

[4] Boulware SD, Tamborlane WV, Rennert NJ, Gesundheit N, Sherwin RS. Comparison of the metabolic effects of recombinant human insulin-like growth factor-I and insulin. Dose-response relationships in healthy young and middle-aged adults. J Clin Investig 1994;93:1131–9.

[5] Okura Y, Brink M, Zahid AA, Anwar A, Delafontaine P. Decreased expression of insulin-like growth factor-1 and apoptosis of vascular smooth muscle cells in human atherosclerotic plaque. J Mol Cell Cardiol 2001;33:1777–89.

[6] Yano K, Bauchat JR, Liimatta MB, Clemmons DR, Duan C. Down-regulation of protein kinase C inhibits insulin-like growth factor I-induced vascular smooth muscle cell proliferation, migration, and gene expression. Endocrinology 1999;140:4622–32.

[7] Bayes-Genis A, Conover CA, Schwartz RS. The insulin-like growth factor axis: a review of atherosclerosis and restenosis. Circ Res 2000;86:125–30.

[8] Muniyappa R, Walsh MF, Rangi JS, Zayas RM, Standley PR, Ram JL, et al. Insulin like growth factor 1 increases vascular smooth muscle nitric oxide production. Life Sci 1997;61:925–31.

[9] Davani EY, Brumme Z, Singhera GK, Côté HC, Harrigan PR, Dorscheid DR, et al. Insulin-like growth factor-1 protects ischemic murine myocardium from ischemias/reperfusion associated injury. Crit Care 2003;7:176–83.

[10] van den Beld AW, Bots ML, Janssen JA, Pols HA, Lamberts SW, Grobbee DE, et al. Endogenous hormones and carotid atherosclerosis in elderly men. Am J Epidemiol 2003;157:25–31.

[11] Andreassen M, Raymond I, Kistorp C, Hildebrandt P, Faber J, Kristensen LØ, et al. IGF1 as predictor of all cause mortality and cardiovascular disease in an elderly population. Eur J Endocrinol 2009;160:25–31.

[12] Spallarossa P, Brunelli C, Minuto F, Caruso D, Battistini M, Caponnetto S, et al. Insulin-like growth factor-I and angiographically documented coronary artery disease. Am J Cardiol 1996;77:200–2.

[13] Laughlin GA, Barrett-Connor E, Criqui MH, Kritz-Silverstein D. The prospective association of serum insulin-like growth factor I (IGF-I) and IGF-binding protein-1 levels with all cause and cardiovascular disease mortality in older adults: the Rancho Bernardo Study. J Clin Endocrinol Metab 2004;89:114–20.

[14] Bourron O, Le Bouc Y, Berard L, Kotti S, Brunel N, Ritz B, et al. Impact of age-adjusted insulin-like growth factor 1 on major cardiovascular events after acute myocardial infarction: results from the fast-MI registry. J Clin Endocrinol Metab 2015;100:1879–86.

[15] Conti E, Andreotti F, Sciahbasi A, Riccardi P, Marra G, Menini E, et al. Markedly reduced insulin-like growth factor-1 in the acute phase of myocardial infarction. J Am Coll Cardiol 2001;38:26–32.

[16] Friberg L, Werner S, Eggertsen G, Ahnve S. Growth hormone and insulin-like growth factor-1 in acute myocardial infarction. Eur Heart J 2000;21:1547–54.

[17] Yavuz BB, Yavuz B, Sener DD, Cankurtaran M, Halil M, Ulger Z, et al. Advanced age is associated with endothelial dysfunction in healthy elderly subjects. Gerontology 2008;54:153–6.

[18] Graham MR, Evans P, Thomas NE, Davies B, Baker JS. Changes in endothelial dysfunction and associated cardiovascular disease morbidity markers in GH-IGF axis pathology. Am J Cardiovasc Drugs 2009;9:371–81.

[19] Imrie H, Abbas A, Viswambharan H, Rajwani A, Cubbon RM, Gage M, et al. Vascular insulin-like growth factor-I resistance and diet-induced obesity. Endocrinology 2009;150:4575–82.

[20] Friehs I, Stamm C, Cao-Danh H, McGowan FX, del Nido PJ. Insulin-like growth factor-1 improves postischemic recovery in hypertrophied hearts. Ann Thorac Surg 2001;72:1650–6.

[21] Sierra-Johnson J, Romero-Corral A, Somers VK, Lopez-Jimenez F, Mälarstig A, Brismar K, etal. IGF-I/IGFBP-3 ratio: a mechanistic insight into the metabolic syndrome. Clin Sci (Lond) 2009;116:507–12.

[22] Colao A, Di Somma C, Cascella T, Pivonello R, Vitale G, Grasso LF, et al. Relationships between serum IGF1 levels, blood pressure, and glucose tolerance: an observational, exploratory study in 404 subjects. Eur J Endocrinol 2008;159:389–97.

[23] Møller N, Jørgensen JO. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. Endocr Rev 2009;30:152–77.

[24] Attanasio AF, Mo D, Erfurth EM, Tan M, Ho KY, Kleinberg D, et al. Prevalence of metabolic syndrome in adult hypopituitary growth hormone (GH)-deficient patients before and after GH replacement. J Clin Endocrinol Metab 2010;95:74–81.

[25] Giustina A, Wehrenberg WB. Growth hormone neuroregulation in diabetes mellitus. Trends Endocrinol Metab 1994;5:73–8.

[26] Tattersall RB, Pyke DA. Growth in diabetic children. Studies in identical twins. Lancet 1973;2:1105–9.

[27] Flyvbjerg A. Putative pathophysiological role of growth factors and cytokines in experimental diabetic kidney disease. Diabetologia 2000;43:1205–23.

[28] Baud L, Fouqueray B, Bellocq A, Doublier S, Dumoulin A. Growth hormone and somatostatin in glomerular injury. J Nephrol 1999;12:18–23.

[29] Tack I, Elliot SJ, Potier M, Rivera A, Striker GE, Striker LJ, et al. Autocrine

activation of the IGF-I signaling pathway in mesangial cells isolated from diabetic NOD mice. Diabetes 2002;51:182–8.
[30] Verrotti A, Cieri F, Petitti MT, Morgese G, Chiarelli F. Growth hormone and IGF-I in diabetic children with and without microalbuminuria. Diabetes Nutr Metab 1999;12:271–6.
[31] Blakesley VA, LeRoith D. The role of growth factors in the pathogenesis of diabetic vascular complications. In: Le Roith D, Taylor SI, Olefsky JM, et al., editors. Diabetes mellitus. Philadelphia: Lippincott-Raven; 1996. p. 824–31.
[32] Brugts MP, Luermans JG, Lentjes EG, van Trooyen-van Vrouwerff NJ, van der Horst FA, Slee PH, et al. Heterophilic antibodies may be a cause of falsely low total IGF1 levels. Eur J Endocrinol 2009;161:561–5.
[33] Gokulakrishnan K, Velmurugan K, Ganesan S, Mohan V. Circulating levels of insulin-like growth factor binding protein-1 in relation to insulin resistance, type 2 diabetes mellitus, and metabolic syndrome (Chennai urban rural epidemiology study 118). Metabolism 2012;61:43–6.
[34] Zhang J, Zhang L, Quan L, Qi W, Jiang Y, Jiang S. Correlation of retinopathy with serum levels of growth hormones and insulin-like growth factor-1 in patients with diabetic retinopathy. Int J Clin Exp Med 2017;10:1325–9.