Original paper

Role of insulin-like growth factor 1 in stent thrombosis under effective dual antiplatelet therapy

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A b s t r a c t

Introduction: Accumulating evidence now indicates that insulin-like growth factors (IGF) and their regulatory proteins are growth promoters for arterial cells and mediators of cardiovascular diseases.

Aim: We hypothetised that IGF-1 levels could play a role in the development of stent thrombosis (ST), and aimed to investigate the associations between stent thrombosis under effective dual antiplatelet therapy and IGF-1 levels and other related factors such as disease severity and LV ejection fraction in patients undergoing coronary stent placement.

Material and methods: A total of 128 patients undergoing coronary stent implantation were included in the analysis. Seventy-seven patients experiencing ST in the first year after stent implantation were defined as the ST group. Fifty-one patients without ST at least 1 year after stent implantation were defined as the no-thrombosis (NT) group. The IGF-1 levels, Gensini scores, and other related factors were measured.

Results: The IGF-1 levels were significantly higher in the stent thrombosis group than in the no-thrombosis group (122.22 ±50.61 ng/ml vs. 99.52 ±46.81 ng/ml, respectively, $p < 0.039$). The left ventricle ejection fraction (LVEF) values were significantly lower (44.13 ±9.25% vs. 55.81 ±8.77%, $p < 0.0001$) and Gensini scores were significantly higher (63.74 ±26.54 vs. 48.87 ±23.7, $p < 0.004$) in the ST group than in the NT group, respectively. In the linear regression analysis, IGF-1, Gensini score, LVEF, total cholesterol, and triglycerides were found to be independent risk factors for ST.

Conclusions: This study revealed that the plasma IGF-1 levels, disease severity, were significantly higher and LVEF was lower in patients with ST. High IGF-1 levels may identify patients who are at increased risk for ST. Future trials are necessary to confirm these results.

Key words: insulin like growth factor 1, stent thrombosis, Gensini score, left ventricle ejection fraction.

Introduction

The most feared and serious complication of coronary stent placement is stent thrombosis (ST), occurring in 0.5% to 1% of patients within 1 year [1]. ST generally presents with death or a large non-fatal myocardial infarction, and it is estimated that up to 10% of cardiac deaths after stent placement are attributable to stent thrombosis [1]. It has been reported that insulin-like growth factor 1 (IGF-1) has anti-inflammatory and anti-atherogenic properties [2]. Circulating IGF-1 is mostly secreted by the liver under the control of growth hormone and carries out its physiological effects via its receptors [3]. However, epidemiological studies suggest that IGF-1 is involved in the development of atherosclerosis, type 2 diabetes, and common cancers [3–5]. Because of the wide range of its biological effects and therapeutic potential in a variety of clinical disorders, IGF-1 has become the focus of research by an increasing number of investigators. Accumulating evidence now indicates that IGFs and their regulatory proteins, secreted by cells of the cardiovascular system, are growth promoters for arterial cells and mediators of cardiovascular diseases [2–5]. Ac-

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cording to our knowledge, there is no study investigating the relations between IGF-1 and stent thrombosis.

Aim

In the present study, we hypothesised that IGF-1 levels may play a role in the development of stent thrombosis, and aimed to investigate the interactions between stent thrombosis under effective dual antiplatelet therapy (DAPT) and IGF-1 levels and other related factors such as disease severity and left ventricular (LV) ejection fraction in patients undergoing coronary stent placement.

Material and methods

Study population

This is an observational, case-controlled comparative study, which was conducted in a tertiary heart centre. One hundred and twenty-eight patients undergoing coronary stent implantation were included in the present study. Seventy-seven patients with ST diagnosed angiographically in the first year after stent implantation were defined as the ST group. Fifty-one patients who had never experienced a clinical event or angiographic thrombotic occlusion of the implanted stent at least 1 year after coronary stent placement were defined as the no-thrombosis (NT) group. The ST was classified as acute with intra-procedural or within 24 h of the procedure, subacute within 1 to 30 days, and late within 1 to 12 months. Clinical criteria considering ST consisted of a new episode of chest pain and/or ischaemic electrocardiographic changes and/or increased cardiac biomarkers. Angiographic criteria of ST consisted of partial or complete occlusion of the previously implanted stent with evidence of fresh thrombus. All study patients were questioned for complete medical history including the presence of hypertension, hyperlipidaemia, diabetes mellitus, alcohol use, drug use, smoking, family history of coronary artery disease (CAD), and medications used. The exclusion criteria of the study were previous coronary artery bypass grafting, low ejection fraction (< 30%), failed stenting procedures, remaining residual lesions, development of no-reflow phenomenon, complex procedures, cases of thrombosis as a procedural complication, patients not receiving dual antiplatelet therapy, renal or hepatic failure, haematological disorders, presence of chronic inflammatory or autoimmune disease, and known malignancy. All patients received dual antiplatelet therapy for 1 year after stenting. Transthoracic echocardiography was performed before discharge. The left ventricular ejection fraction (LVEF) was measured using the modified Simpson's rule [6]. Informed consent from all patients was obtained, and the study protocol was approved by the Ethics Committee of the institution in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Biochemical analysis

Blood samples for biochemical parameters were collected at admission. For IGF-1 levels, blood samples were taken after 1 month from procedure because there might have been changes in IGF-1 levels at the time of acute coronary syndrome. All samples were centrifuged at 3000 g for 10 min and the serum transferred to capped tubes and stored at –40°C until the analysis. All analyses were performed using Siemens Immulite IGF-I assay with solid-phase enzyme-labelled chemiluminescent immunometric assay [7]. Haemolysed, lipemic, and icteric serums were not used for analyses. Results of IGF-1 test are given as ng/ml. Venous blood samples were collected after the procedure. Troponin I levels were recorded during the hospitalisation. Glucose, creatinine level, and lipid profile were measured for all patients with a Cobas-C 501 biochemical analyser (Roche Diagnostics, Mannheim, Germany) using Roche kits. Haematological indices were evaluated from complete blood count analyses performed using a Mindray device BC-5800 (Mindray Bio-Medical Electronics Co. Ltd., Shenzhen, China) using the optical laser method. Haemoglobin, red cell distribution width, neutrophils, lymphocytes, platelets, and mean platelet volume were measured from ethylenediaminetetraacetic acid-(EDTA) based anticoagulated blood samples and assessed within 30 min of sampling. Clopidogrel and aspirin resistances were measured by impedance aggregometry method with a multiple electrode aggregometry device (Multiplate, Dynabyte Medical, Munich, Germany) [8].

Coronary angiography and disease scoring

All angiograms and stenting procedures were performed with 7 Fr guiding catheters at a speed of 15 frames per second by experienced operators. All observations were performed by two interventional cardiologists who were blinded to the study groups. Stent thrombosis was angiographically described as a filling defect seen in multiple projections or the presence of flow-limiting thrombus with Thrombolysis In Myocardial Infarction flow grade 0, 1, or 2 in the absence of calcification [9]. The severity and extent of CAD were evaluated via Gensini score [10]. According to the Gensini score, the degree of luminal narrowing and its geographic importance are evaluated. One point is given for 1–25% of stenosis, 2 points for 26–50%, 4 points for 51–75%, 8 points for 76–90%, 16 points for 91–99%, and 32 points for 100% stenosis, and each lesion's point is multiplied by the coefficient for each vascular segment because of the functional significance (left main coronary artery × 5; proximal segment of left anterior descending coronary artery (LAD) × 2.5; proximal segment of the circumflex artery × 2.5; mid-segment of the LAD × 1.5; right coronary artery, the distal segment of the LAD, posterolateral artery and the obtuse marginal artery × 1; and others × 0.5), and the sum of all gives the total score [10]. Scoring was per-

formed and averaged by two observers who were blinded to the study groups.

Statistical analysis

Number Cruncher Statistical System (NCSS) 2007 Statistical Software (Utah, USA) package program was used for statistical analysis. In statistical analysis, descriptive statistical methods such as mean, standard deviation, median, interquartile range, frequency distributions, and independent t test for comparison of groups of binary variables with normal distribution were used. The Mann-Whitney *U* test was used for comparison of two groups with a normal distribution of variables and χ^2 test was used for comparison of qualitative data. Logistic regression analysis was used to identify factors that may affect stent thrombosis. A p value < 0.05 was accepted to be statistically significant.

Results

The baseline clinical characteristics of patients are summarised in Table I. Both groups were similar in terms of sex, age, smoking habits, diabetes mellitus, body mass index (BMI), presence of hypertension, family history of CAD, and medications used. Of the ST patients, 27 were acute, 22 were subacute, and 28 were late ST. The left ventricle ejection fraction (LVEF) values were significantly lower (44.13 ±9.25% vs. 55.81 ±8.77%, respectively, $p < 0.0001$) and Gensini scores were significantly higher (63.74 ±26.54 vs. 48.87 ±23.7, respectively, $p < 0.004$) in the ST group than in the NT group. The IGF-1 levels were significantly higher in the ST group than in the NT group (122.22 ±50.61 ng/ml vs. 99.52 ±46.81 ng/ml, respectively, $p < 0.039$) (Table I). There were no differences in both groups with regard to ASA/clopidogrel resistances and haematological parameters (Table II). In biochemical analyses, total cholesterol, triglyceride and very low density lipoprotein cholesterol levels were significantly lower and glucose levels were significantly higher in ST group than NT group patients (Table II). Procedural methods in percutaneous coronary intervention (PCI) were not different both groups (Table III). When the ST group patients were analysed with regard to time to development of the ST, only LVEF was significantly different between subgroups ($p = 0.018$) (Table IV). In the linear regression analysis, IGF-1, LVEF, total cholesterol, and triglyceride levels were found to be independent risk factors for stent thrombosis (Table V).

Discussion

The present study revealed that the plasma IGF-1 levels and Gensini scores were significantly higher and the LVEF values were significantly lower in patients with ST than in patients without ST. In biochemical analyses, total cholesterol, triglycerides and VLDL cholesterol levels were significantly lower and glucose levels were significantly higher in patients with ST than in those without

Table I. Clinical characteristics of patients

Parameter	No-thrombosis (group 1) ($n = 51$)	Thrombosis (group 2) ($n = 77$)	Value of p
Age, mean ± SD [years]	56 ±9.43	55.38 ±11.97	0.755
Gender, *n* (%):			
Male	38 (74.51)	62 (80.52)	0.421
Female	13 (25.49)	15 (19.48)	
Diabetes mellitus, *n* (%)	16 (31.37)	24 (31.17)	0.981
Hypertension, *n* (%)	28 (54.90)	37 (48.05)	0.448
Hyperlipidaemia, *n* (%)	26 (50.98)	31 (40.26)	0.232
History of, *n* (%):			
Alcohol use	7 (13.73)	10 (12.99)	0.904
Smoking	21 (41.18)	42 (54.55)	0.139
Family history of CAD	26 (50.98)	39 (50.65)	0.971
Metabolic syndrome	27 (52.94)	31 (40.26)	0.158
BMI, mean ± SD [kg/m^2]	28.4 ±4.21	27.98 ±3.52	0.594
IGF-1, mean ± SD [ng/ml]	99.52 ±46.81	122.22 ±50.61	0.039
LVEF, mean ± SD (%)	55.81 ±8.77	44.13 ±9.25	0.0001
Gensini score, mean ± SD	48.87 ±23.7	63.74 ±26.54	0.004

CAD – coronary artery disease, BMI – body mass index, IGF-1 – insulin like growth factor-1, LVEF – left ventricular ejection fraction

Table II. Biochemical and haematological characteristics of patients

Parameter	No-thrombosis (group 1) (*n* = 51)	Thrombosis (group 2) (*n* = 77)	Value of *p*
Fasting glucose, mean ± SD [mg/dl]	117.77 ±24.56	142.94 ±57.56	0.015
Total cholesterol, mean ± SD [mg/dl]	199.94 ±46.82	175 ±44	0.009
Triglycerides, mean ± SD [mg/dl]	169.33 ±99.55	120.31 ±53.97	0.002
LDL-C, mean ± SD [mg/dl]	116.65 ±43.68	111.11 ±35.06	0.476
HDL-C, mean ± SD [mg/dl]	40.71 ±10.34	44.46 ±48.65	0.654
VLDL-C, mean ± SD [mg/dl]	35.1 ±20.71	26.33 ±14.17	0.016
TSH, mean ± SD [µ/l]	1.62 ±1.92	1.3 ±1.1	0.371
AST, mean ± SD [U/l]	50.81 ±101.5	101.4 ±169.52	0.152
Creatinine, mean ± SD [mg/dl]	0.91 ±0.22	1 ±0.34	0.147
HGB, mean ± SD [g/dl]	13.8 ±2.05	13.6 ±2.17	0.636
WBC, mean ± SD [× 10/µl]	9.28 ±2.99	10.22 ±3.14	0.141
RDW, mean ± SD (%)	14.24 ±3.47	13.76 ±1.7	0.356
Platelet count, mean ± SD [× 10/µl]	255.84 ±72.94	241.56 ±63.75	0.297
MPV, mean ± SD [fl]	8.16 ±0.85	8.16 ±0.98	0.993
Neutrophil count, mean ± SD [× 10/µl]	65.47 ±11.12	66.15 ±12.28	0.781
Lymphocyte count, mean ± SD [× 10/µl]	25.21 ±9.63	24.59 ±10.55	0.764
Neutrophil to lymphocyte ratio, mean ± SD	3.42 ±2.46	3.56 ±2.44	0.774
Clopidogrel resistance, mean ± SD [AU/min]	302.33 ±127.23	270.34 ±198.4	0.603
ASA resistance, mean ± SD [AU/min]	167.29 ±70.6	153.17 ±83.87	0.679

LDL-C – low density lipoprotein cholesterol, HDL-C – high density lipoprotein cholesterol, VLDL-C – very low density lipoprotein cholesterol, TSH – thyroid stimulating hormone, AST – aspartate amino transferase, HGB – haemoglobin, WBC – white blood cell, RDW – red blood cell distribution width, MPV – mean platelet volume, ASA – acetyl salicylic acid

ST. Contrary to common belief, in this study, IGF-1 levels were found to be lower in patients without any cardiovascular events 1 year after stent implantation.

The mechanisms underlying stent thrombosis are multifactorial and include patient-related factors such as clopidogrel/acetylsalicylic acid (ASA) resistance, pro-

Table III. Procedural characteristics of patients

Parameter	No-thrombosis (group 1) (*n* = 51)	Thrombosis (group 2) (*n* = 77)	Value of *p*
Stent diameter, mean ± SD [mm]	3.21 ±0.31	3.1 ±0.4	0.185
Stent length, mean ± SD [mm]	22.84 ±5.28	22.91 ±7.09	0.961
Type of stents, *n* (%):			
BMS	46 (90.20)	67 (87.00)	0.584
DES	5 (9.80)	10 (13.00)	
Indication of stent, *n* (%):			
Primary	23 (45.10)	38 (49.35)	0.637
Elective	28 (54.90)	39 (50.65)	
Location of stent with thrombus, *n* (%):			
LAD	18 (58.06)	43 (55.84)	0.750
Cx	4 (12.90)	7 (9.09)	
RCA	9 (29.03)	27 (35.06)	

BMS – bare metal stent, DES – drug eluting stent, LAD – left anterior descending artery, Cx – left circumflex artery, RCA – right coronary artery

Table IV. Clinical features according to time of stent thrombosis

Parameter	Acute (*n* = 27)	Subacute (*n* = 22)	Late (*n* = 28)	Value of *p*
Gender, *n* (%):				
Male	21 (77.78)	17 (77.27)	24 (85.71)	0.684
Female	6 (22.22)	5 (22.73)	4 (14.29)	
Mortality in hospital, *n* (%)				
Durviving	25 (92.59)	17 (77.27)	25 (89.29)	0.257
Exit	2 (7.41)	5 (22.73)	3 (10.71)	
Presence of diabetes mellitus, *n* (%)	12 (44.44)	6 (27.27)	6 (21.43)	0.164
Presence of hypertension, *n* (%)	13 (48.15)	12 (54.55)	12 (42.86)	0.714
Presence of hyperlipidaemia, *n* (%)	11 (40.74)	7 (31.82)	13 (46.43)	0.578
Use of alcohol, *n* (%)	3 (11.11)	4 (18.18)	3 (10.71)	0.692
Smoking, *n* (%)	14 (51.85)	13 (59.09)	15 (53.57)	0.872
Family history of CAD, *n* (%)	14 (51.85)	9 (40.91)	16 (57.14)	0.516
Metabolic syndrome, *n* (%)	9 (33.33)	9 (40.91)	13 (46.43)	0.611
Indication of first stent, *n* (%):				
Primary	17 (62.96)	8 (36.36)	13 (46.43)	0.167
Elective	10 (37.04)	14 (63.64)	15 (53.57)	
Admission, *n* (%):				
ST elevation MI	24 (88.89)	17 (77.27)	23 (82.14)	0.550
Non ST MI	3 (11.11)	5 (22.73)	5 (17.86)	
Location of stent with thrombus, *n* (%):				
LAD	11 (40.74)	13 (59.09)	19 (67.86)	0.302
Cx	4 (14.81)	2 (9.09)	1 (3.57)	
RCA	12 (44.44)	7 (31.82)	8 (28.57)	
Type of stent, *n* (%):				
BMS	24 (88.89)	17 (77.27)	26 (92.86)	0.249
DES	3 (11.11)	5 (22.73)	2 (7.14)	
LVEF, *n* (%):				
Normal (> 55%)	14 (51.85)	4 (18.18)	8 (28.57)	0.018
Borderline (40–55%)	2 (7.41)	10 (45.45)	11 (39.29)	
Low (< 40%)	11 (40.74)	8 (36.36)	9 (32.14)	

LAD – left anterior descending artery, Cx – left circumflex artery, RCA – right coronary artery, BMS – bare metal stent, DES – drug eluting stent

cedural factors including stent choice, and postprocedural factors including type and duration of antiplatelet therapy [11]. Stent thrombosis within the first year after implantation appears to occur with similar frequency in patients with bare metal stents (BMS) or drug-eluting stents (DES), as long as the patients are treated with DAPT for the recommended duration [12]. The period of risk requiring dual antiplatelet therapy is longer with DES due to delayed neointimal coverage [13]. The importance of the present study arises from the fact that the associations between IGF-1 levels and stent thrombosis were firstly investigated in this study excluding most important factors related to the development of stent thrombosis. In this study, all patients continued to be recommended antiplatelet therapy without interruption after stenting. There were no differences between

Table V. Logistic regression analyses for stent thrombosis

Parameter	*B*	S.E.	*P*	Exp(B)	95% CI OR	
					Lower	Upper
LVEF	–0.153	0.03	< 0.001	0.86	0.80	0.92
Total cholesterol	–0.012	0.005	0.013	0.99	0.98	1.00
Triglyceride	–0.009	0.003	0.004	0.99	0.99	1.00
IGF1	0.010	0.005	0.043	1.01	1.00	1.02
Gensini	0.025	0.009	0.006	1.03	1.01	1.04

the groups for procedural methods and clopidogrel/ASA resistance, so the effect of clopidogrel/ASA resistance and procedural and postprocedural factors for ST were similar for both groups. Also, we collected blood samples for IGF-1 levels after one month from admission because the level of IGF-1 can be affected by acute conditions such as inflammation [14]. Many studies in the past few decades have shown that acute MI results in a significant decrease in serum levels of total cholesterol, LDL cholesterol, and HDL cholesterol [15]. High blood glucose levels in patients admitted with AMI are common and are associated with an increased risk of death in both diabetic and non-diabetic subjects [16]. Similarly, in this study, fasting glucose was found to be higher and total cholesterol and triglycerides levels were found to be lower in patients with ST than in patients without, which is compatible with previous studies [16].

Coronary restenosis and ST remain major clinical problems after percutaneous revascularization procedures. For the last 20 years, the relationship between the IGF-1 system and cardiovascular disease has been a topic of interest. The relationships between IGF-1 levels and CAD have been pointed out in many studies. Low IGF-1 levels have been suggested as an important predictor of cardiovascular disease, even after correcting for BMI, smoking, blood cholesterol, alcohol intake, physical activity, gender, age, past history of diabetes, and family history of CAD [17]. Both traditional cardiovascular risk factors and low IGF-1 levels have been put forward as factors reducing endothelial function, as well as the progenitor cell reservoir; the latter, remaining as the main determinant of endothelial function, has also recently been shown to be directly associated with IGF-1 levels [18]. It has been asserted that another valuable protective activity of IGF-1 is the induction of prostacyclin (PGI2) synthesis in endothelial cells through the activation of phospholipase A2, PGI2 has important anti-platelet effects, and increases cAMP in vascular smooth muscle cells (VSMC), thereby inducing growth and vasodilation [18]. Moreover, IGF-1 has been put forward as increasing prothrombin time and partial thromboplastin time, without influencing circulating mediators of fibrinolysis [19, 20]. According to the data, by promoting vasodilation and inhibiting platelet aggregation, and by protecting endothelial cells and vascular smooth muscle cells from several mechanisms of injury and death, IGF-1 does not promote atherogenesis, prevents plaque formation, and counteracts plaque destabilisation and thrombosis and its clinical correlates [21, 22].

Despite its association with many cardiovascular protective effects, is IGF-1 always a protective agent for coronary artery disease? In the present study, it was found that free/dissociable IGF-1 levels were lower in patients without ST than patients with ST. Our findings may be partly explained by several studies indicating that IGF-I is involved in local cellular events leading to restenosis after coronary angioplasty [23, 24]. The IGF-1 is a potent stimulant of VSMC migration [25]. Different results of IGF-1 effects have been reported in the literature. Botker *et al.* and Lawlor *et al.* were unable to show any association between IGF-1 levels and coronary artery disease [26, 27]. In the early stages of restenosis, IGF-1 levels of VSMCs from human restenotic specimens are far higher than in normal coronary VSMCs [25]. Smooth muscle cell accumulation is the key to the neointimal proliferation after angioplasty, so IGF-1 can be effective on neointimal proliferation phase after angioplasty [23–25]. The predominant IGF-1 production and action in arterial media suggests that IGF-1 has a growth-promoting effect on VSMCs after balloon injury [24]. However, it was shown that there was no IGF-I mRNA expression in the restenotic tissue obtained several months after the intervention [28]. Some cross-sectional and prospective studies suggest a positive association between IGF-1, in some cases IGF binding protein (IGFBP)-3, and atherosclerosis [29, 30]. Others found that low IGF-1 is a predictor of risk of carotid and coronary artery disease and mortality [31–34]. However, several large prospective cohort studies failed to systematically confirm these findings [35, 36]. Harrela *et al.* reported that high fasting serum IGFBP-1 is related to increased 5-year total and cardiovascular mortality in elderly men [35]. Wallander *et al.* also reported that high levels of IGFBP-1 at admission are associated with increased risk for cardiovascular mortality and morbidity in type 2 diabetes patients with AMI [36]. On the other hand, it has been reported that IGF-1 plays a role in potentiating platelet aggregation [37–39]. Erem *et al.* also reported that IGF-1 may be associated with increased fibrinogen, plasminogen activator inhibi-

tor-1, and decreased protein S and tissue factor pathway inhibitor in acromegalic patients, which may represent a potential hypercoagulable and hypofibrinolytic state [40]. However, our results in a previous study did not show any significant association between IGF-1 levels and the development of no-reflow phenomenon in patients undergoing primary PCI for AMI [41], which may be related to the time for the measurement of IGF-1 because the level of IGF-1 may be affected by acute conditions such as inflammation [14]. Thus, IGF-1 measurement at the time of acute event may reveal uninterpretable and conflicting results.

The present study also has some limitations. It was a single-centred study and limited to the interventions of native vessels. The number of patients was small, representing a major limitation. We only measured free IGF-1 and were unable to measure IGFBPs, also representing an important limitation of the present study.

According to current reports and study results, high levels of IGF-1 may cause increased VSMC growth, migration, extracellular matrix synthesis, atherosclerotic plaque progression, neointimal proliferation [23–25], activation of platelets and coagulation system, ST, and increased mortality [35–40]. We cannot yet speculate whether IGF-1 itself would be a harmful mediator or would be helpful in determining early complications of coronary stent implantation. Measurement of IGF-1 may be useful in combination with other biomarkers. The present study suggests that high levels of IGF-1 may have a role in predicting stent restenosis and/or thrombosis at 12 months. Additional studies are also required to confirm our results and to determine whether genetically determined low IGF-1 levels or low bioactivity of IGF-1 is an important risk factor for atherosclerotic burden and ST.

Conclusions

The present study revealed that the plasma IGF-1 levels and disease severity were significantly higher and LVEF was lower in patients with ST. High IGF-1 levels may identify patients who are at increased risk for ST and would benefit from more aggressive medical therapies. Future investigations are necessary to confirm these results and to identify the precise underlying mechanisms of this relationship between IGF-1 and ST.

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