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Plasma basic fibroblast growth factor is correlated with plasminogen activator inhibitor–1 concentration in adults from the Veterans Affairs Diabetes Trial

Mark B. Zimering[a,b,*], Robert J. Anderson[c,d], Ping Luo[c], Thomas E. Moritz[c]
Investigators for the Veterans Affairs Diabetes Trial[c]

[a]*Medical Service, Department of Veterans Affairs New Jersey Health Care System, Lyons, NJ 07939, USA*
[b]*University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ, USA*
[c]*Hines Cooperative Studies Program Coordinating Center, Veterans Affairs Hospital, Hines, IL, USA*
[d]*Division of Epidemiology and Biostatistics, School of Public Health, University of Illinois at Chicago, Chicago, IL, USA*

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Abstract

Basic fibroblast growth factor (bFGF) is a potent mitogen in endothelial and vascular smooth muscle cells that increases in serum from adults with coronary artery disease and in microalbuminuric type 2 diabetes mellitus. There has been no prior study of plasma bFGF as a possible cardiovascular risk marker in type 2 diabetes mellitus. In this study, we tested for a correlation between log plasma bFGF immunoreactivity (bFGF-IR) and baseline cardiovascular risk factors in a baseline subset of subjects with advanced type 2 diabetes mellitus from the Veterans Affairs Diabetes Trial ([mean] age, 60 years; hemoglobin A_{1c}, 9.5%; diabetes' duration, 11 years). Plasma bFGF-IR was determined with a sensitive, specific, 2-site enzyme-linked immunoassay in 281 patients at the baseline visit. Results were compared with baseline risk factors or baseline medication use. Baseline plasma bFGF-IR ranged from 0 to 141 pg/mL. Log plasma bFGF correlated significantly with non-Hispanic white race ($P = .002$), waist-hip ratio ($P = .002$), and plasminogen activator inhibitor–1 concentration ($P < .0001$). Log plasma bFGF correlated inversely with African American race ($P = .0003$). In multiple regression analysis, plasminogen activator inhibitor–1 and race were significantly correlated with log plasma bFGF. These results suggest a significant correlation between log plasma bFGF-IR and plasminogen activator inhibitor–1, a marker of hemostatic risk.
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1. Introduction

Cardiovascular disease is the leading cause of mortality in adult type 2 diabetes mellitus. Basic fibroblast growth factor (bFGF) is a potent angiogenesis factor and broad-spectrum cell mitogen in endothelial, epithelial, and mesenchymal-derived cells [1]. Plasma bFGF is low or undetectable in healthy subjects [2], but increases in those with coronary artery disease [3,4]. Basic FGF may function as a local vascular growth factor to promote atherosclerosis [5,6].

Veterans Affairs Diabetes Trial (VADT) is a large ongoing clinical trial in adult patients with type 2 diabetes mellitus randomized to standard or intensive glycemic control [7]. The ongoing VADT substudy will test whether plasma bFGF is a novel marker of prospective (5 years) cardiovascular risk in adults with type 2 diabetes mellitus. The present baseline report analyzed the relationship between baseline plasma bFGF and baseline risk factors.

We now report that plasma bFGF is substantially increased in a subset of adult men with long-standing type 2 diabetes mellitus. Plasma bFGF levels varied widely from 0 to 141 pg/mL in 281 subjects. Because of the well-known log-linear dose-response relationship in bFGF-induced cellular proliferation over a similar range of bFGF concentrations (1-100 pg/mL) [1,8], a natural log transformation of bFGF values was performed to optimize the ability

* Corresponding author. Department of Veterans Affairs New Jersey Health Care System, Medical Service, Lyons, NJ 07939, USA. Tel.: +1 908 647 0180x4426; fax: +1 908 604 5249.
E-mail address: mark.zimering@med.va.gov (M.B. Zimering).

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to detect biologically significant correlations between bFGF and established cardiovascular risk factors.

Log plasma bFGF directly correlated with non-Hispanic white race, waist-hip ratio, and plasma plasminogen activator inhibitor–1 (PAI-1) level and inversely with African American race. These are the first in vivo data suggesting a correlation between log plasma bFGF and PAI-1; the latter is an important hemostatic risk marker.

2. Subjects and methods

2.1. Study subjects

Informed consent for the Investigational Review Board–approved substudy was obtained from 281 diabetic subjects at 5 outpatient sites who had consented to participate in the main VADT. Plasma was prepared from the EDTA-anticoagulated blood drawn in the morning from fasting subjects at each site. Plasma was aliquoted and shipped frozen (dry ice) to a central laboratory (Maveric, Boston Veterans Affairs Medical Center, Boston, MA), where it was inventoried and stored at −80°C for 1 to 2 years. Archived, coded, and frozen EDTA plasma from consecutively enrolled patients was shipped to Dr Zimering's laboratory (VA New Jersey Health Care System, Lyons, NJ), where bFGF immunoreactivity (bFGF-IR) assays were performed. All other assays were performed at the Central Laboratory of the VADT (Tufts University, Boston, MA).

2.2. Baseline characteristics

Baseline clinical characteristics are summarized in Table 1. Plasma bFGF-IR was determined at the baseline study visit. All subjects were older than 40 years. Ninety-seven percent of subjects were male; 16%, Hispanic; 20%, African American; and 63%, non-Hispanic white. Fourteen percent reported baseline occurrence of myocardial infarction (MI). Patients with chronic kidney disease were excluded from study participation.

Table 1
Baseline characteristics in study subjects

	Mean	SD
n	281	
bFGF (pg/mL)	11.5	16.7
log bFGF[a]	1.34	1.93
Age (y)	59.6	8.5
BMI (kg/m^2)	31.1	4.8
Waist circumference (cm)	108.9	12.9
Hip circumference (cm)	109.3	9.5
SBP (mm Hg)	130.9	18.1
DBP (mm Hg)	74.3	10.6
Diabetes' duration (y)	11.5	7.6
Urine albumin-creatinine ratio (mg/g)	138	422
HbA_{1c} (%)	9.5	1.4
Triglyceride (mg/dL)	193	190
Total cholesterol (mg/dL)	182	42
LDL cholesterol (mg/dL)	107	33
HDL cholesterol (mg/dL)	37	9

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[a] Results are natural log (bFGF + 0.05), such that bFGF values less than the assay detection limit, that is, 0, do not result in log bFGF that is undefined.

2.3. Medications

All patients were taking antidiabetic medications at baseline including oral agents and/or insulin. Baseline antihypertensive medication use included a thiazide diuretic (15%), calcium channel blocker (20%), angiotensin-converting enzyme (ACE) inhibitor (64%), and angiotensin II receptor blocker (ARB) (5.5%). Sixty-two percent of patients used a statin at baseline, 16% reported fibrate drug use, and 76% reported daily aspirin use. Twenty-one percent of patients used a cyclooxygenase inhibitor drug; nearly all such drugs belonged to the nonsteroidal anti-inflammatory class of medications.

2.4. Laboratory and clinical measures

Urinary microalbumin, plasma glycosylated hemoglobin (HbA_{1c}), and urine creatinine were determined by standard methods as previously described [7]. Urinary albumin-creatinine ratio was calculated as albumin concentration/creatinine concentration ×100. *Normo-*, *micro-*, and *macroalbuminuria* are defined as albumin-creatinine ratio of less than 30, 30.1 to 300, and at least 300.5 mg/g, respectively. Plasma total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol were determined by standardized direct enzymatic assay methods as previously reported [7]. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation on all samples with plasma triglyceride concentration less than 400 mg/dL. Blood pressure was recorded in the seated position after 5-minute rest. Three consecutive readings were obtained, and the median value of the 3 consecutive determinations was used for analysis.

2.5. Plasma samples

Archived, coded EDTA plasma samples were kept frozen (−40°C) for up to 2 years before assay for bFGF-IR. Plasma bFGF-IR and bFGF-like bioactivity were previously shown to be stable for 5 years or longer at −20°C, and for up to 3 freeze-thaw cycles [9].

2.6. Basic fibroblast growth factor assays

Basic FGF-IR in plasma was determined using a sensitive, specific, 2-site enzyme-linked immunoassay (R&D Systems, Minneapolis, MN).

The mean minimal detectable dose of FGF-2 was 0.5 pg/mL (n = 9 assays). The method was linear between 0.5 and 64 pg/mL. The average correlation coefficient (between bFGF dose and absorbance) for the runs was 0.99. The intraassay coefficients of variation for low- and high-dose calibration standards or human diabetic plasma samples

were less than or equal to 8%; the interassay coefficients of variation for patient samples or calibration standards ranged from 10% to 14%. Recovery of bFGF-IR in diluted (1:2) samples of normal human plasma ranged from 108% to 123%. The dilution curves of patient plasma samples were parallel to the standard curve. Fibroblast growth factor–1, FGF-4 (hst), FGF-5, and FGF-6 did not cross-react in the assay. In prior studies that used the same bFGF-IR assay method, mean serum bFGF-IR in 15 healthy subjects (men and women; age range, 39-74 years) was 0.9 pg/mL (range, 0-4 pg/mL) [10].

Plasma bFGF-IR in 43 healthy male blood donors, aged 21 to 63 years, ranged from 0 to 4 pg/mL; and there was no effect of age on plasma bFGF level [11].

2.7. Statistics

Basic FGF-IR was not normally distributed, at least partially because of a number of below-detection-limit values and partially because of extremely high values. The Wilcoxon rank sum test was used for group comparisons of bFGF-IR (Table 3), and the correlations reported are Spearman correlation coefficients.

Table 2
Relation of log bFGF to baseline categorical risk factors

Categorical variables	Mean of log (bFGF + 0.05)		*P* value[a]
	Yes	No	
Demographics			
Sex (**M**/F)	1.34	1.33	.9601
Hispanic (**Y**/N)	1.58	0.92	.8111
Non-Hispanic white (**Y**/N)	1.49	1.31	.0019
Black (**Y**/N)	0.47	1.55	.0003
Current smoker (**Y**/N)	1.22	1.36	.6053
Exercise regularly (**Y**/N)	1.52	1.21	.3366
Drug use at baseline			
Aspirin (**Y**/N)	1.38	1.19	.8051
ACE inhibitor (**Y**/N)	1.31	1.38	.9267
ARB (**Y**/N)	0.12	1.41	.0726
Thiazide diuretic (**Y**/N)	1.80	1.25	.0545
Statin (**Y**/N)	1.28	1.43	.8428
Fibrate (**Y**/N)	1.38	1.33	.8518
Calcium channel antagonist (**Y**/N)	0.85	1.46	.0561
Thiazolidinedione (**Y**/N)	1.53	1.28	.3653
Insulin (**Y**/N)	1.26	1.40	.7402
Sulfonylurea (**Y**/N)	1.41	1.20	.6624
Metformin (**Y**/N)	1.30	1.42	.4418
Gabapentin (**Y**/N)	1.98	1.30	.1764
Aldactone (**Y**/N)	2.20	1.33	.4430
α-Adrenoceptor blocker (**Y**/N)	1.37	1.33	.6717
COX inhibitor (**Y**/N)	1.19	1.38	.8267
Furosemide (**Y**/N)	1.49	1.32	.9314
History			
Hypertension (**Y**/N)	1.38	1.24	.1878
MI (**Y**/N)	1.74	1.27	.2339
Coronary revascularization (**Y**/N)	1.21	1.37	.1643
Stroke (**Y**/N)	1.24	1.34	.9795
Albuminuria[b]			
Macroalbuminuria	1.03		.4616
Microalbuminuria	1.29		
Normoalbuminuria	1.42		

Log indicates natural log; Y, presence (bolded) of indicated risk factor; COX, cyclooxygenase.
[a] *P* value based on χ^2 statistic.
[b] *P* value from Fisher exact test.

Table 3
Relation of log bFGF to baseline continuous risk factors

Continuous variables	Spearman correlation	
	Coefficients	*P* value[a]
Age	0.0574	.3378
BMI	0.0009	.9875
Waist circumference	0.0356	.5599
Hip circumference	−0.1097	.0714
Average SBP	−0.0135	.8236
Average DBP	0.0022	.9705
Total cholesterol	−0.0038	.9500
LDL cholesterol	−0.0219	.7242
HDL cholesterol	−0.0246	.6833
Triglycerides	−0.0025	.9667
Urine albumin-creatinine ratio	−0.0358	.5528
Plasma fibrinogen	0.0606	.3178
PAI-1	0.2820	<.0001
Waist-hip ratio	0.1857	.0021
Duration of diabetes	−0.0481	.4218
HbA_{1c}	−0.1272	.0331
Fasting plasma glucose	−0.0752	.2095
Serum creatinine	−0.1863	.3332

[a] *P* value for correlation with log (bFGF + 0.05), where "log" is the natural log.

3. Results

3.1. Relation of log bFGF to baseline characteristics

Baseline log plasma bFGF was directly correlated with non-Hispanic white race ($P = .002$) and inversely with African American race ($P = .0003$) (Table 2). Baseline log plasma bFGF was directly correlated with plasma PAI-1 ($P < .0001$) and waist-hip ratio ($P = .002$), and was inversely

Table 4
Multiple regression analyses of log bFGF and covariates including (A) non-Hispanic white or (B) African American race

Variable	Parameter estimate	SE	*P* value
A			
Intercept	1.005	1.975	.61
PAI-1	0.013	0.005	.01
Waist-hip ratio	1.623	1.843	.38
HbA_{1c}	−0.244	0.094	.01
NHW	0.525	0.259	.04
NHW indicates non-Hispanic white.			
B			
Intercept	1.852	1.973	.35
PAI-1	0.011	0.005	.03
Waist-hip ratio	1.413	1.832	.44
HbA_{1c}	−0.251	0.093	.008
African American	−0.845	0.307	.006
n = 236 subjects			

Table 5
Prevalence of baseline cardiovascular diseases by ethnicity

	Non-Hispanic white	Hispanic or African American	*P* value
Baseline MI	32 (19.1%)	7 (7.6%)	.014
Any macrovascular event	77 (45.8%)	25 (27.2%)	.003

Macrovascular event includes MI, stroke, angina, coronary artery bypass, percutaneous coronary intervention, and peripheral vascular disease.

correlated with HbA_{1c} (P = .03) (Table 3). No significant correlation was identified between log plasma bFGF-IR and patient age, diabetes' duration, or other continuous baseline risk factors (Table 3); and no significant difference in mean log plasma bFGF-IR was detected when comparing groups defined by baseline presence of MI, cigarette smoking, stroke, or hypertension (Table 2).

3.2. Relation of bFGF-IR to baseline medication use

Mean baseline log plasma bFGF-IR was higher with baseline thiazide diuretic use (P = .05) (Table 2) and lower at borderline significance with baseline ARB (P = .07) or calcium channel antagonist use (P = .06) (Table 2). There was no detected difference of mean plasma bFGF-IR with use of insulin, metformin, sulfonylurea, or a thiazolidinedione (Table 2).

3.3. Independent correlates of log plasma bFGF

In multiple regression analyses, PAI-1 (P = .01) and non-Hispanic white race (P = .04) were significantly correlated with log plasma bFGF-IR (Table 4A). African American race (P = .006) and baseline HbA_{1c} (P = .008) were inversely correlated with log plasma bFGF (Table 4B).

3.4. Prevalence of cardiovascular diseases by ethnicity

Baseline MI was reported in a significantly higher proportion of non-Hispanic white subjects (19.1%) compared with Hispanic or African American subjects (7.6%, P = .01 for the difference; Table 5). Any prior macrovascular event was reported in a significantly higher proportion of non-Hispanic white subjects (45.8%) compared with events in Hispanic or African American subjects (27.2%, P = .003 for the difference; Table 5).

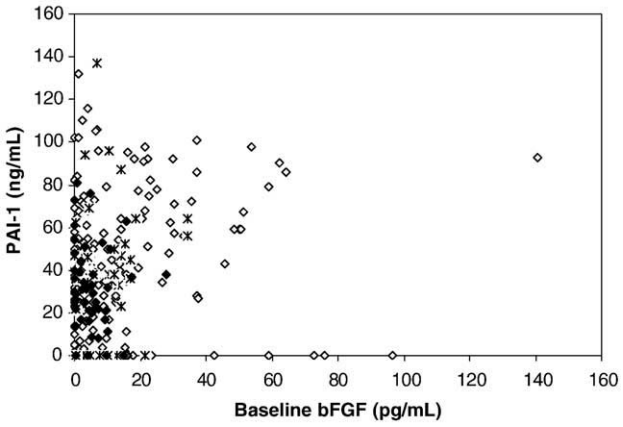

Fig. 1. Scatter plot of PAI-1 vs baseline plasma bFGF values (open diamonds represent non-Hispanic white subjects, stars represent Hispanic subjects, and filled diamonds represent African American subjects).

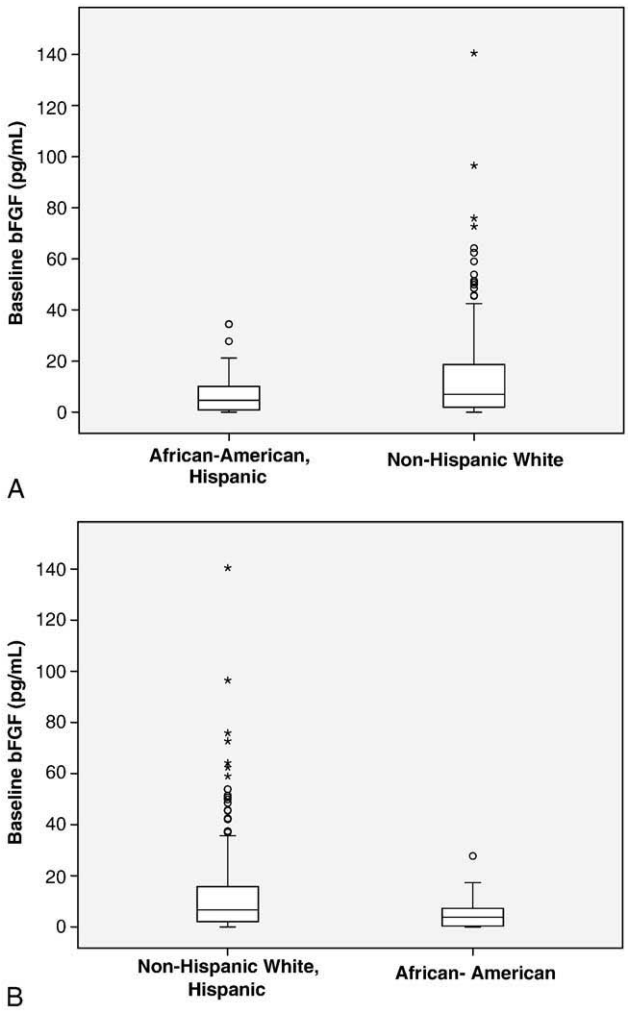

Fig. 2. Box/whisker plot of bFGF values in (A) non-Hispanic white or (B) African American diabetic subjects compared with subjects of other race/ethnicity. Lines inside boxes illustrate the median value; 25th and 75th percentile cutoff values: the lower and upper edges of the box. Whiskers illustrate the range of values occurring within a distance = 1.5 times the interquartile range (IQR) from the lower or upper edge of the box. Outliers are values between 1.5 and 3 times the IQR from the upper edge of the box and are represented by open circles; extreme values more than 3 times the IQR from the upper edge of the box are represented by asterisks.

3.5. Distribution of bFGF and PAI-1 values

Baseline plasma bFGF showed a wide range in values, from 0 to 141 pg/mL (Fig. 1). All but a few bFGF values greater than 20 pg/mL were observed in non-Hispanic white patients (Fig. 2A, B). Exponentially increased bFGF values (≥20 pg/mL) were generally associated with higher values of PAI-1 (Fig. 1). The mean PAI-1 level among

African American subjects (33.2 ± 17.6 ng/mL) was significantly lower compared with the mean PAI-1 levels in non-Hispanic white (50.5 ± 28.7 ng/mL) or in Hispanic subjects (50.1 ± 23.1 ng/mL, $P = .0004$ for the comparison) (data shown in Fig. 1).

4. Discussion

Circulating bFGF increases in a wide spectrum of cancers [12,13], consistent with its role as a tumor angiogenesis factor [14]. Yet there have been few if any reports of plasma bFGF levels from a large group of adults with long-standing type 2 diabetes mellitus. No prior study demonstrated both striking elevation [9] and wide variability in bFGF levels as were observed in the present study.

Basic FGF is one of the most potent known angiogenic factors. Half-maximal doses of bFGF needed for proliferative activity in many different cell types (10-50 pg/mL) [1] approximate the levels observed in a substantial proportion of our diabetic subjects (Fig. 1). Whether such high bFGF levels are transient or may persist in the circulation could not be determined in this study. The independent significant correlation between log plasma bFGF and PAI-1 may be consistent with bFGF-induced synthesis of PAI-1 reported in vitro [15,16]. It suggests that substantially elevated plasma bFGF is likely to be biologically active rather than an assay artifact. Basic FGF could directly contribute to PAI-1 levels in vivo or be tightly associated with one or more additional factors that induce both PAI-1 and bFGF synthesis.

Plasminogen activator inhibitor–1 inhibits fibrinolysis, resulting in a prothrombotic state. Plasminogen activator inhibitor–1 levels increase in diabetes [17]; and in prior studies, high PAI-1 level was associated with an increased risk for first or recurrent MI [18,19]. Plasminogen activator inhibitor–1 levels vary by race/ethnicity: African American subjects had the lowest levels in a multiethnic study of hemostatic markers [20], and there was evidence for decreased endothelial cell expression of PAI-1 among African American subjects [21]. Our findings of substantially lower log plasma bFGF and lower plasma PAI-1 among African American diabetic subjects may be consistent with common factors regulating the local endothelial production of both PAI-1 and bFGF. Additional factors, some perhaps more closely related to body mass index than was bFGF, for example, transforming growth factor–β [22], may have contributed to a subset of high plasma PAI-1 despite low plasma bFGF (Fig. 1). Markedly elevated plasma bFGF may not only promote angiogenesis, smooth muscle cell proliferation [23], and tumor cell proliferation [1]; but log bFGF may indicate (through its significant association with PAI-1) an increased risk for thrombosis in subsets of obese patients with type 2 diabetes mellitus.

The tissue sources for exponentially increased plasma bFGF are unknown. Human omental tissue is highly vascular: it contained much higher concentrations of a bioactive bFGF-like protein compared with normal or neoplastic renal or prostate tissues [24,25]. Omental preadipocytes from obese humans also expressed much higher levels of bFGF messenger RNA compared with those from lean control subjects [26]. Whether bFGF is released into the general circulation from omental storage sites is unknown. One possible mechanism for its release may involve macrophages abundant in visceral adipose tissue [27] that can release proteases capable of liberating bFGF from storage sites in extracellular matrix [28].

Angiotensin II increases vascular smooth muscle cell bFGF synthesis [29] and may promote increased plasma bFGF levels in subsets of diabetic patients. In a prior study in adults with microalbuminuric type 2 diabetes mellitus, treatment with ACE inhibitor drugs was associated with substantially lower levels of plasma bFGF bioactivity or immunoreactivity [9]. Because plasma renin activity varies considerably in humans [30], the present findings of substantially lower mean log plasma bFGF in African American subjects may be consistent (in part) with low renin hypertension common among African American patients [31]. Lower mean log bFGF for ARB use (Table 2) is consistent with a role for angiotensin II in the elaboration of increased plasma bFGF. Associations between log bFGF and other medications must be interpreted cautiously, however, because there may have been confounding by race (eg, increased use of calcium channel antagonists among African American hypertensive patients).

Other unknown factors may have contributed to substantially lower plasma bFGF among African American diabetic patients. It is also unclear whether inflammation, insulin resistance, or chance may have contributed to the apparent direct correlation between non-Hispanic white race and log plasma bFGF. For example, proinflammatory cytokines (tumor necrosis factor–α, interleukin-1, and interferon-γ) associated with visceral obesity [32] induced the synthesis and release of high levels of bFGF from normal endothelial cells in vitro [33]. Adipocytokine release (including tumor necrosis factor–α and PAI-1) was recently shown to be regulated in part by angiotensin II [34]. Thus, angiotensin II may trigger a cascade of cellular effects that results in amplified bFGF production and release from multiple storage sites.

The limitations of this study are that it is cross-sectional and the findings are applicable only to men. More study is needed in women with diabetes and in other racial and ethnic groups to determine whether differences in log plasma bFGF may mirror other population differences in PAI-1 concentration [20]. Still unexplained is whether unknown factors related to poor baseline glycemic control may have accounted for an unexpected inverse correlation between log bFGF and HbA_{1c} (Table 4), an association that could not be accounted for (in the multiple regression analysis) by race or waist-hip ratio.

In conclusion, plasma bFGF was unexpectedly elevated in a subgroup of non-Hispanic white patients with

advanced type 2 diabetes mellitus. These findings suggest the possibility that markedly increased plasma bFGF may reflect not only impaired fibrinolysis in type 2 diabetes mellitus but also, consistent with its role as a broad-spectrum cellular mitogen, the promotion of atherosclerosis, and/or plaque neovascularization [35]. Whether log plasma bFGF or PAI-1 may be a better predictor of newly occurring atherothrombotic cardiovascular events in adult men with advanced type 2 diabetes mellitus can be tested in the ongoing VADT.

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