VEGF and PDGF in liver cirrhosis and their relation to echocardiographic parameters and Carotid Intima-Media Thickness

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Abstract: Background: Liver fibrosis is an important pathological event in chronic hepatitis patients that eventually progresses to liver cirrhosis. Vascular endothelial growth factor (VEGF) stimulates angiogenesis and perpetuates hepatic inflammation and fibrosis. VEGF has been shown to be important in atherosclerotic plaque development. Platelet-derived growth factor (PDGF) is a major mitogen for fibroblasts, smooth muscle cells, and other cells. It is well established that platelet-derived growth factors (PDGFs) are involved in several pathological settings, including liver fibrosis and atherosclerosis. **Aim**: We aimed to evaluate the serum level of VEGF and PDGF in liver cirrhosis and the possible association with portal vein diameter, echocardiographic parameters and Carotid Intima Media Thickness (CIMT). **Methods:** sixty patients with post liver cirrhosis (group 1) and 20 age and sex matched normal volunteers (group 2) underwent echo-Doppler study for evaluation of left ventricular (LV) hypertrophy and mass, left atrium, aortic and left ventricular dimensions and EF%. Serum levels of VEGF and PDGF were measured by ELISA in serum of all subjects. Ultrasonographic measurement of CIMT, abdominal ultrasound and laboratory evaluation were also done to all subjects. **Results:** There were statistically significant increase in plasma levels of VEGF (483.6±242.3 vs 252±180.7) and PDGF (73.4±25.7 vs 49.27±0.9) in patients group compared to the controls. The levels of VEGF were positively correlated with portal vein diameter, aortic diameter and CIMT (r=0.306, r=0.236, r=0.252 respectively).While the PDGF levels were positively correlated with interventricular septum thickness (IVST), posterior wall thickness (PWT), left ventricular mass (LVM) and carotid intima-media thickness (CIMT) (r=0.242, r=0.289, r=0.331, r=0.256 respectively**). Conclusion:** Liver cirrhosis may be associated with increase in VEGF level and as it was correlated with portal vein diameter, VEGF might be involved in cirrhosis associated with portal hypertension. VEGF levels were positively correlated with aortic diameter as it is an endothelium-specific secreted protein that induces vasodilation and increases endothelial release of nitric oxide. As VEGF was also positively correlated with the sonographically measured CIMT (which is an indicator of atherosclerosis and cardiovascular risk) it may have some role in the progression of coronary atherosclerosis in humans. Patients with liver cirrhosis also have increased PDGF levels that were positively correlated with IVS, PWT, LVM and CIMT. So, our data raise the possibility that PDGF may be involved not only in liver fibrosis but also in cardiac fibrosis and atherosclerosis.

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1.Introduction:

Liver fibrosis is an important pathological event in chronic hepatitis patients that eventually progresses to liver cirrhosis. Host factors can affect the progression of liver fibrogenesis in chronic hepatitis patients. Pathological angiogenesis is linked to necroinflammation and fibrosis in these patients. Vascular endothelial growth factor (VEGF) is a soluble 46 kDa, angiogenic glycoprotein that stimulates angiogenesis and perpetuates hepatic inflammation and fibrosis (1).

It is well-recognized that angiogenesis plays a critical role during progression of chronic inflammatory conditions. Angiogenesis is regulated by a myriad of angiogenic factors and the major factor among them is VEGF (2). VEGF is a highly specific mitogen for endothelial cells. It stimulates their growth and inhibits apoptosis, increases vascular permeability in many tissues, promotes vasculogenesis and angiogenesis. It can be produced by a wide variety of human cells including vascular smooth muscle cells, tumor cells, keratinocytes, fibroblasts, and epithelial and mesengial cells (3). In response to liver injury, VEGF may enhance the regenerative potential of residual hepatocytes and that of non-parenchymal cells. A significant change in the vascular architecture along with neovascularization is generally detected in cirrhotic livers (4).

VEGF has been shown to be important in atherosclerotic plaque development. There is some

disagreement as to whether VEGF acts as a pro-atherosclerotic or anti-atherosclerotic factor (5).

Lazarous et al., reported that VEGF administration exacerbated neointimal thickening after vascular injury in dogs (6). Also, *Inoue et al.,* demonstrated distinct expression of VEGF and its receptors (flt-1 and Flk-1) in atherosclerotic lesions in human coronary arteries and suggest that VEGF may have some role in the progression of human coronary atherosclerosis, as well as in recanalization processes in obstructive coronary diseases (7).

Platelet-derived growth factor (PDGF) is a major mitogen for fibroblasts, smooth muscle cells, and other cells (8). It is a dimeric molecule consisting of disulfide-bonded, structurally similar A- and B-polypeptide chains, which combine to homo- and heterodimers (9). It is the most prominent mitogen contributing to fibrosis of the liver (10). Hepatic fibrogenesis involves activation and proliferation of hepatic stellate cells that acquire a myofibroblastic phenotype and ultimately are responsible for the excessive production of extracellular matrix proteins (11).

Whereas PDGF is expressed at low levels in arteries from healthy adults, its expression is increased in conjunction with the inflammatory-fibroproliferative response that characterizes atherosclerosis (12). Thus studies of balloon catheter-injured arterial tissue (13), naturally occurring atherosclerosis (14,15), coronary arteries after percutanous transluminal coronary angioplasty (16), and experimentally induced atherosclerosis (17) revealed increased expression of PDGF and PDGF receptors in these lesions. These observations suggest that PDGF, produced by activated macrophages, smooth muscle cells, or endothelial cells, or released from platelets in thrombi, is important for the formation of the lesion (9). The reason for the increased production of PDGF and PDGF receptors in atherosclerotic lesions may be in response to external stimuli but may also be due to rheological changes; low blood flow leads to an increased production of PDGF by endothelial cells (18).

Cardiac fibrosis, which is a common feature in heart disease, involves a disproportionate accumulation of extracellular matrix between muscle fibers and around blood vessels (19).The mechanisms directing cardiac fibrosis are not completely understood, but it has been suggested that growth factors, cytokines, extracellular matrix-modulating enzymes, and components of the fibrinolytic system may contribute (20)

It is well established that platelet-derived growth factors (PDGFs) are involved in several pathological settings, including tissue fibrosis, atherosclerosis, and tumor growth (10).

In the present study we aimed to evaluate the serum level of VEGF and PDGF in liver cirrhosis and the possible association with portal vein diameter, echocardiographic parameters and Carotid Intima Media Thickness (CIMT).

2.Subjects and Methods:

The present study was conducted on 80 subjects from inpatients and outpatients services of Theodor Bilharz Research Institute Hospital, selected to represent two groups:

Group (1) included 60 patients with liver cirrhosis (all of them post hepatitis C virus infection).

Group (2) included 20 apparently healthy volunteers as control group matched for age and sex and with normal liver ultrasonography, normal liver function tests and negative hepatitis markers.

Subjects with heart disease, diabetes mellitus, hypertension (blood pressure >130/85 mmHg), hyperlipidemia, acute or chronic kidney disease, any malignancy, alcohol consumption, pregnancy, liver masses, anemia with hemoglobin less 10 gm% or taking any medication with adverse effects on liver or cardiovascular system were excluded.

All patients were provided by informed consent, and the ethical committee of hospital approved this study.

All patients and normal volunteers were subjected to:

Thorough history taking and physical examination.

Blood sampling for blood picture including hemoglobin percent, liver function tests, renal function tests, serum electrolytes, cholesterol, triglyceride, HBs antigen and HCV antibody. Serum levels of VEGF and PDGF were measured by ELISA in serum of all subjects.

Twelve lead surface resting ECG.

Abdominal ultrasound scanning was performed to all participants by one trained radiologist who was blinded to all clinical and laboratory data, using a Toshiba Nemo 30 scanner equipped with a 3.5 mHz linear transducer.

Liver cirrhosis (Post hepatitis C virus cirrhosis) was diagnosed based on the results of laboratory tests (hepatitis C virus antibody, low serum concentrations of albumin, high INR and low platelet count) and abdominal ultrasonographic findings (irregularity of the liver surface).

Echo-Doppler study:

All echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography (21) by a member of the study team in a blinded manner.

M-mode, Two dimensional echocardiography and Doppler ultrasound studies (pulsed, continuous wave and color flow imaging) were made using a high resolution (ALT 5000 HDI) Toshiba Nemo 30 scanner equipped with a 2.5 mHz transducer.

Left ventricular mass was calculated according to Devereux and associates convention: LVM gm = 1.04 x {(LVED + IVST+ PWT) 3 – LVED3 } × 0.8 + 0.6 (34) where LVED was the left ventricular end diastolic diameter, IVST is the interventricular septum thickness, and PWT was the left ventricular posterior wall thickness.

High resolution B mode ultrasonography of both the common and internal carotid arteries were performed using an ultrasound machine (Toshiba Nemo 30 scanner) equipped with a 7.5 mHz high resolution transducer.

Statistical Analysis:

Statistical analysis was performed using SPSS version 17. Data were expressed as the mean ± standard deviation (SD) for numerical variables. $P \leq 0.05$ was considered to be statistically significant.

3.Results:

The demographic data of the patients group and the control group revealed mean ages 43.4±10.4 years and 43.5±8.6 years, respectively. In group 1 (patients group) 45 were males (75%) and 15 were females (25%), in group 2 (control group) 14 were males (70%) and 6 were females (30%) (Table1).

The echocardiographic data showed a statistically significant increase in left atrium diameter, interventricular septum thickness (IVST), posterior wall thickness (PWT), end-systolic diameter (ESD) and left ventricular mass (LVM) in patients group compared to the controls (P <0.01) and a statistically significant increase in aortic diameter in patients group compared to the controls (P <0.05). Also, there was significant increase in CIMT in patients group compared to the controls (P <0.01) (Table 2).

Plasma levels of Na was significantly decreased and that of K was significantly increased in patients group compared to the controls (P <0.01), together with a statistically significant increase in ALT, AST, total bilirubin and direct bilirubin in patients group compared to the controls. However, there were a statistically significant decrease in albumin in patients group compared to the controls (P <0.01) (Table 3).

Plasma levels of VEGF and PDGF were significantly increased in patients group compared to the controls (P <0.01) (Table 4).

The liver span was decreased in patients group compared to the controls and the portal vein diameter was increased in patients group compared the control group (P <0.01) (Table 5).

The level of VEGF was positively correlated with portal vein diameter, aortic diameter, CIMT and K level. While the PDGF level was positively correlated with IVST, PWT, LVM, CIMT and direct bilirubin (Table 6).

The IVS, PWT, LVM and CIMT were negatively correlated with NA level and all of them were positively correlated with K level and PV diameter, while the LA and CIMT were negatively correlated with liver span (Table 7).

Table (1): Demographic data of the patients and the controls

	Patients	Control
Age	43.4±10.4	43.5±8.6
Gender Male Female	45 (75%) 15 (25%)	14 (70%) 6 (30%)

Table (2): Echocardiographic and CIMT data of the patients and control group

	Patients	Control	*P* value
LA mm	38.4±5.1	34.7±3.1	0.007
AO mm	30.4±3.1	28.5±2.4	0.04
IVST cm	1.0±0.2	0.9±0.1	0.01
PWT cm	1.0±0.1	0.9±0.1	0.006
EDD cm	4.9±0.7	4.6±0.4	NS
ESD cm	3.1±0.6	2.8±0.4	0.03
EF %	66.7±8.6	70.8±6.8	NS
LV mass gm	183.0±52.1	136.8±29.2	0.001
CIMT mm	1.0±0.1	0.6±0.1	0.001

$P < 0.05$= significant, $P < 0.01$= highly significant

LA: left atrium diameter, Ao: aortic diameter, IVST: interventricular septum thickness, PWT: posterior wall thickness, LVM: left ventricular mass.

EDD: end diastolic dimension, ESD: end systolic dimension, EF: ejection fraction, LA: left atrium dimension, CIMT: carotid intima-media thickness.

Table (3): Laboratory data of the patients and control group

	Patients	Control	*P* value
Na mEq/L	131.3±4.8	141.0±2.5	0.001
K mEq/L	4.8±0.5	4.0±0.2	0.001
Creat mg/dL	1.1±0.5	1.0±0.2	NS
BUN mg/dL	23.4±17.2	30.0±10.3	NS
ALT U/L	31.9±33.9	13.6±2.1	0.001
AST U/L	65.9±88.7	13.2±4.1	0.001
T bil mg/dL	3.4±4.3	0.5±0.1	0.001
D bil mg/dL	1.8±2.7	0.1±0.0	0.001
Alb g/dL	2.5±0.7	4.2±0.1	0.001

$P < 0.05$= significant, $P < 0.01$= highly significant

Creat: creatinine, BUN: blood urea nitrogen, Na: serum sodium, K: serum potassium, ALT: alanine aminotransferase, AST : aspartate aminotransferase,T bil. : Total bilirubin, D bil.: Direct bilirubin.

Table (4): Specific Laboratory data of the patients and control group

	Patients	Control	*P* value
VEGF ng/L	483.6±242.3	252.3±180.7	0.003
PDGF ng/L	73.4±25.7	49.27±.9	0.001

Table (5): Measurements of liver span and portal vein (PV) diameter

	Patients	Control	*P* value
Liver cm	6.4±0.5	15.0±1.6	0.001
PV mm	14.6±0.5	12.4±1.8	0.001

Table (6): Correlation between VEGF, PDGF and other parameters

	VEGF		PDGF	
	R	*P*	R	*P*
Ao	.236	.049		
IVST			.242*	.044
PWT			.289*	.015
LV mass			.331**	.005
CIMT	.252*	.036	.256*	.032
K	.322**	.007		
D bil.			.273*	.028
PV	0.306	0.017		

Ao: aortic diameter, IVST: interventricular septum thickness, PWT: posterior wall thickness, LVM: left ventricular mass, CIMT: carotid intima-media thickness, K: serum potassium, D bil.: Direct bilirubin, PV: portal vein. *: significant, **: highly significant.

Table (7): Correlation between Echocardiographic parameters, CIMT and laboratory parameters.

	IVS		PWT		LV mass		LA		CIMT	
	R	*P*	R	*P*	R	*P*	R	*P*	R	*P*
Na	-.255*	.033	-.260*	.030	-.260*	.030			-.465**	.000
K	.370**	.002	.268*	.025	.385**	.001			.416**	.000
D bil	-.046	.714								
Alb	-.319**	.007	-.258*	.031			-.310**	.009	-.605**	.000
PV	.280*	.030	.371**	.003	.310*	.016			.713**	.000
Liver span							-.239*	.048	-.326**	.006

*: significant, **: highly significant.

4.Discussion

Liver fibrosis is an important pathological event in chronic hepatitis patients that eventually progresses to liver cirrhosis. Hepatic fibrosis has emerged as a highly relevant aspect of liver biology because of the significant progress in uncovering its mechanisms, combined with a growing realization that effective antifibrotic therapies may soon alter the natural history of chronic liver disease (22).

Liver cirrhosis is characterized by the hyper-accumulation of connective tissue components in the liver. Although the pathogenic mechanisms of cirrhosis are not fully understood, the over-production of extracellular matrix (ECM) in the liver, besides chronic parenchymal injury, is likely to initiate cirrhosis. The net result of an imbalance between enhanced matrix synthesis and diminished breakdown of connective tissue proteins is the

increased deposition of ECM (23). In this concept, hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF) may play an important role, as their activation is largely responsible for matrix breakdown (4).

In the early phase of liver regeneration, proliferating hepatocytes show hypoxia-induced VEGF expression which initiates a process aiming at achieving the proper flow of blood through the liver. Hepatocytes then proliferate to the greatest extent around the portal vein (the area around the portal), which rarely is accompanied by reconstruction of the hepatic sinusoids (24).

The role of VEGF in liver regeneration, however, is broader than a simple stimulation of cell proliferation (25, 26).

Brodsky et al. showed that VEGF expression in the cirrhotic liver is very diverse. Namely, VEGF expression in the regenerative nodules is smaller than in the surrounding tissues and in the healthy liver tissue, whereas in liver tissue modified by fibrosis, that surrounds regenerative nodules, VEGF expression is higher compared to the nodule tissues and the healthy liver tissue (27).

In our study, we examined circulating VEGF level in patients with liver cirrhosis to assess their clinical significance. We found that VEGF concentration was significantly higher in cirrhotic patients than in normal controls (P <0.01) and it was positively correlated with aortic diameter, CIMT, portal vein diameter.

There are conflicting results concerning the serum VEGF in liver cirrhosis. An upregulation of VEGF in cirrhotic livers was previously demonstrated in animal models (28) as well as in human clinical studies (29, 30) and linked with ongoing angiogenesis and portal hypertension.

Our results are also in consistent with the study of *Tekkesin et al.,* 2011 that was conducted on mice and they found that VEGF concentration was significantly higher in cirrhotic than in non-cirrhotic livers (4). Also*, Enjoji et al.*, and *Li et al*. reported higher levels of VEGF in cirrhotics (31,32).

Abdelmoaty et al., observed increased VEGF in liver cirrhosis compared to healthy controls. The highest concentrations of VEGF were observed in patients with advanced stages of liver cirrhosis, which was reflected by a positive correlation with Child-Pugh score specially score C and they suggest that VEGF might be involved in cirrhosis associated angiogenesis as well as portal hypertension (33).

On the other hand, the study of *Assy et al.,* clearly indicate that serum VEGF levels decreased in patients with liver cirrhosis which did not correlate with the disease severity (34). Also, the study of *Kraft et al. (35)* and that of *Chow et al. (36)* showed decreased serum VEGF levels in patients with cirrhosis.

In our study, the level of VEGF was positively correlated with portal vein diameter (PV) that was significantly increased in patients with liver cirrhosis than in normal controls (P<0.001).The potential usefulness of duplex sonography in the diagnosis of portal hypertension has been assessed previously by *Iwao et al*. (37). A portal vein diameter greater than 13cm or a portal vein flow velocity less than 15cm/sec indicated portal hypertension with a sensitivity and specificity of over 80%. As in our study VEGF correlates positively well with the portal vein diameter, this indicates that VEGF is increased in patients with portal hypertension. This was in agreement with the study of *Abdelmoaty et al*. (33) who suggested that VEGF might be involved in cirrhosis associated angiogenesis as well as portal hypertension. On the other hand, the results of *Assy et al*. indicated that expression of VEGF in the serum is down-regulated in the presence of moderate to severe portal hypertension and they concluded that the reasons for this remain unclear and the decreased VEGF serum levels are related to not only increased portal hypertension but also reduced regenerative capacity (34).

In our study, the level of VEGF was positively correlated with aortic diameter. This can be explained by the fact that VEGF is an endothelium-specific secreted protein that induces vasodilation and increases endothelial release of nitric oxide that has been shown to induce endothelium-dependent vasodilation (38). Direct measurement of NO demonstrated a threefold increase in basal NO release from aortic tissue of rats injected with VEGF, at 4 and 24 h post-treatment (39). Also, *Ku et al.* demonstrated that vasodilatation was induced by intravenous injection of VEGF in rats (40). The VEGF-induced vasodilation and its effect on vascular permeability are inhibited by nitric oxide (NO) synthase inhibitors (41). *Brock et al.* (41) demonstrated that VEGF increases cytosolic calcium, which is known to promote calmodulin binding to the endothelial isoform of nitric oxide synthase (NOS) and stimulate NO production (43). Similarly, VEGF has been shown to increase NO release in bovine (44), rabbit (45), and human endothelial cells (46). More recently, this effect of VEGF on NO production has been associated with up-regulation of endothelial cell nitric oxide synthase (ecNOS) activity (47).

In our study, we also found significant increase in CIMT in patients with liver cirrhosis compared to normal controls (P<0.01) and there was positive correlation between VEGF level and the sonographically measured CIMT which is an indicator of atherosclerosis and cardiovascular risk.

Hence, our findings suggest that VEGF may have some role in the progression of coronary atherosclerosis in humans. This finding is in keeping with previous report of *Inoue et al*., who suggested that VEGF may have some role in the progression of human coronary atherosclerosis, as well as in recanalization processes in obstructive coronary diseases (48).

In fact, it has already been reported that the in vivo introduction of human VEGF cDNA into rabbit carotid arteries by the hemagglutinating virus of Japan/liposome method induced prominent angiomatoid proliferation of (endothelial cells) ECs and thickening of the intima due to fibromuscular hyperplasia (7*). Lazarous et al.* also reported that VEGF administration exacerbated neointimal thickening after vascular injury in dogs (6). These reports suggest that VEGF is indeed capable of inducing neointimal angiogenesis and intimal hyperplasia. This is more likely because VEGF has been recognized not only to stimulate EC proliferation, increase vascular permeability, and alter thrombogenicity (49) but also to induce migration of human mononuclear phagocytes/monocytes and stimulate their expression of tissue factor (50).

Celletti et al. in their study conducted on cholesterol-fed mice concluded that VEGF can promote angiogenesis but may also exert certain effects to alter the rate of atherosclerotic plaque development (51).

Platelet-derived growth factor (PDGF) is a major mitogen for connective tissue cells and certain other cell types. Activation of PDGF receptors leads to stimulation of cell growth and to changes in cell shape and motility. Overproduction of PDGF has been implicated in malignant and nonmalignant conditions characterized by an increased cell proliferation, such as atherosclerosis and fibrotic conditions (8).

Platelet-derived growth factor has also been implicated in liver cirrhosis. After liver injury, the amounts of PDGF and PDGF receptors in the liver increase (52). An immunohistochemical analysis revealed that PDGF A- and B-chain are present in infiltrating inflammatory cells and along vascular structures in fibrous septa and PDGF receptors in mesenchymal cells, fibrous septa and around sinuses; the expression of receptors correlated with the severity of the lesion (53).

Our results revealed significant increase of serum PDGF level in patients with liver cirrhosis compared to normal controls (P <0.01). This is in agreement with the study of *Grigorescu* who concluded that PDGF is the main stimulus of (hepatic stellate cell (HSC) proliferation and migration and is upregulated following liver injury and the serum level of PDGF–BB was found to have the highest value for assessment of hepatic fibrosis, when compared to other markers of fibrosis (54).

In our study we found that PDGF was positively correlated with IVS, PWT, LVM and CIMT. Our data raise the possibility that this growth factor (PDGF) may be involved in cardiac fibrosis and atherosclerosis. These results are in agreement with the study of *Ponten et al* who generated transgenic mice over expressing the active core domain of PDGF-D in the heart and they found that transgenic PDGF-D stimulates proliferation of cardiac interstitial fibroblasts and arterial vascular smooth muscle cells (vSMCs) which results in cardiac fibrosis followed by dilated cardiomyopathy and subsequent cardiac failure. Transgenic mice also display vascular remodeling, including dilation of vessels, increased density of SMC-coated vessels, and proliferation of vSMCs, leading to a thickening of tunica media (55).

Also, the study of *Tuuminen et al* revealed that PDGF-A, PDGF-C, or PDGF-D, when introduced into the heart using adenovirus-mediated delivery, significantly upregulated profibrotic TGFβ1 mRNA and accelerated cardiac fibrosis and arteriosclerosis, indicating that PDGF may also act to promote fibrosis by elevating TGFβ levels (56).

The involvement of PDGF in the atherosclerosis process has been confirmed experimentally using balloon catheterization of rat carotid arteries as a model. In the denuded artery, an increased amount of activated PDGF receptors is seen in the vessel wall (57). The intimal thickening that follows this treatment was inhibited by administration of neutralizing PDGF antibodies (58). In addition, a low-molecular-weight PDGF receptor kinase inhibitor, AG-1295, was recently shown to inhibit neointima formation in a porcine restenosis model (59). Moreover, infusion of PDGF-BB into rats after carotid injury (60), or expression of recombinant PDGF-BB in porcine arteries (61), caused increased intimal thickening. The role of PDGF in the atherosclerotic lesions may be to stimulate smooth muscle cells to migrate from the media of the vessel to the intima layer and to proliferate and produce matrix molecules at this site (62). Platelet-derived growth factor is also involved in neointima formation in other model systems including human saphenous vein cultured *in vitro* (63).

These observations together with our findings may suggest that PGDF may be a good target for antifibrotic therapy in the liver and heart.

Conclusion:

Our study concluded that liver cirrhosis may be associated with increased VEGF level and as it was

positively correlated with portal vein diameter, Hence, VEGF might be involved in cirrhosis associated with portal hypertension. The level of VEGF was positively correlated with aortic diameter as it is an endothelium-specific secreted protein that induces vasodilation and increases endothelial release of nitric oxide. VEGF was also positively correlated with the sonographically measured CIMT which is an indicator of atherosclerosis and cardiovascular risk. Hence, our findings suggest that VEGF may have some role in the progression of coronary atherosclerosis in humans.

The present study revealed significant increase of plasma level of PDGF in patients with liver cirrhosis that was positively correlated with IVS, PWT, LVM and CIMT. So, our data raise the possibility that PDGF may be involved not only in liver fibrosis but also in cardiac fibrosis and atherosclerosis and hence, it may have a role in cirrhotic cardiomyopathy and in the progression of coronary atherosclerosis in humans. Also, our findings may suggest that PGDF may be a good target for antifibrotic therapy both in the liver and in the heart.

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