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EXPEDITED REVIEWS

Obesity Is Associated With Increased Levels of Circulating Hepatocyte Growth Factor

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OBJECTIVES	This study evaluated whether obesity in humans was associated with an increase in circulating hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF) levels.
BACKGROUND	Obesity acts as a cardiovascular risk factor by mechanisms that are not fully understood. Adipose tissue is able to secrete multiple cytokines and growth factors <i>ex vivo</i> . We hypothesized that the increased presence of adipose tissue in obese subjects results in systemic elevations of the mitogenic factors HGF and VEGF.
METHODS	Blood samples were obtained from lean ($n = 21$) and obese ($n = 44$) volunteers. Serum HGF and VEGF levels were assessed by enzyme-linked immunosorbent assay. Insulin and fasting glucose levels were measured to evaluate insulin sensitivity. Conditioned medium of adipose cells was assayed for HGF secretion.
RESULTS	Serum HGF levels in obese subjects were more than three-fold higher than those of lean subjects ($2,462 \pm 184$ pg/ml vs. 765 ± 48 pg/ml, $p < 0.0001$). The VEGF levels were not significantly elevated in obese subjects (135 ± 31 pg/ml vs. 128 ± 37 pg/ml). The HGF concentrations, but not VEGF concentrations, were significantly correlated with body mass index (BMI) ($p < 0.0001$, $r = 0.74$). The observed increases in HGF concentrations of obese subjects were not secondary to insulin resistance or hypertension. Freshly isolated human adipose cells secreted HGF.
CONCLUSIONS	Our results indicate that obesity is associated with a marked increase in circulating HGF levels, which correlate linearly with BMI. Because vascular growth factors have been associated with the pathogenesis of atherosclerosis, the possible role of such humoral factors as a link between obesity and cardiovascular disease is very intriguing. (J Am Coll Cardiol 2003;41:1408–13) © 2003 by the American College of Cardiology Foundation

Multiple epidemiologic studies have shown that obesity markedly increases the risk of cardiovascular morbidity and mortality and is a significant risk factor for coronary artery disease and congestive heart failure (1–3). A recent study demonstrated that obesity promotes atherosclerosis even in adolescent and young adult men (4). This cardiovascular risk of obesity is in part mediated by the increased prevalence of risk factors such as hypertension or insulin resistance, which are frequently associated with obesity (5). This combination of obesity and cardiovascular risk factors is commonly referred to as Syndrome X or metabolic syndrome. However, in addition to influencing other risk factors, obesity also acts as a cardiovascular risk factor, independent of changes in blood pressure (BP), insulin resistance, or cholesterol levels (1,6). While the hemodynamic changes associated with obesity are thought to contribute to the ventricular dysfunction observed in obese

patients (7), less is known about the independent mechanisms by which obesity promotes atherosclerosis.

The adipose tissue is now recognized as an endocrine organ that secretes multiple cytokines and growth factors (8,9). Vascular endothelial growth factor (VEGF), for example, is an angiogenic growth factor which is secreted by rat adipose tissue *ex vivo* (10). It has also been found to cause progression of atherosclerosis, presumably by promoting endothelial proliferation and neovascularization in the atherosclerotic plaque (11). Hepatocyte growth factor (HGF) is another endothelial growth factor with potent angiogenic and mitogenic effects (12,13) that can synergistically augment the angiogenic effects of VEGF *in vivo* and *in vitro* (14). Serum HGF levels are elevated not only in patients with hepatic disease (15), malignancies (16), or end-stage renal disease (17), but also in patients with atherosclerosis and proliferative diabetic retinopathy (18–20). It has also been shown that the 3T3-L1 adipocyte cell line can secrete HGF *in vitro* (21), thus suggesting that primary adipocytes may also be able to synthesize and secrete HGF *in vivo*.

We hypothesized that the increased presence of secretory adipose tissue in obese subjects would result in systemic elevations of the angiogenic factors VEGF and HGF. Therefore, we studied the serum levels of VEGF and HGF

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Abbreviations and Acronyms

ASC	= adipose stromal cells
BMI	= body mass index
BP	= blood pressure
DBP	= diastolic blood pressure
HGF	= hepatocyte growth factor
HOMA	= Homeostatic Model Assessment
LFT	= liver function tests
SBP	= systolic blood pressure
VEGF	= vascular endothelial growth factor

in lean and obese subjects. Because obesity is frequently associated with insulin resistance and hypertension (5,22), we also examined whether the postulated obesity-related increases in growth factor concentrations were independent of these comorbidities.

METHODS

Patient selection and characteristics. Blood samples were obtained from healthy lean subjects (body mass index [BMI] ≤ 25 kg/m²; n = 21) or obese subjects (BMI ≥ 35 kg/m²; n = 44) undergoing bariatric surgical procedures or outpatient adipose tissue biopsies. Blood samples were taken in the morning before surgery after an overnight fast, and serum was separated after coagulation. Blood pressures and liver function tests (LFT) comprised of serum glutamic-pyruvic transaminase and serum glutamic-oxaloacetic transaminase measurements were obtained on most subjects at the time of blood collection. Systolic blood pressure (SBP) >140 mm Hg or diastolic blood pressure (DBP) >90 mm Hg at the time of blood draw were considered elevated. The LFT were elevated if either serum glutamic-oxaloacetic transaminase or serum glutamic-pyruvic transaminase levels were >50 IU/l. No subjects had any known acute infectious process at the time of enrollment in the study. The protocol was approved by the Institutional Review Boards of Indiana University-Purdue University at Indianapolis and St. Vincent's Hospital. All subjects provided informed consent.

Insulin resistance. Fasting serum insulin was quantitated by radioimmunoassay (Linco Research, St. Charles, Missouri), and glucose was determined using a YSI 2300 STAT plus glucose analyzer (YSI Inc., Yellow Springs, Ohio). The Homeostatic Model Assessment (HOMA) score, as a surrogate measure of insulin resistance (23) was calculated as: fasting insulin (μ U/ml) \times fasting glucose (mmol/l)/22.5, to determine the degree of insulin resistance. For analysis of insulin resistance effects on HGF levels, obese subjects were subdivided into three groups according to their degree of insulin resistance using the HOMA score: 1) obese normal (HOMA <3 , n = 13); 2) obese with moderate resistance ($3 < \text{HOMA} < 5$, n = 11); and 3) obese with severe resistance (HOMA >5 , n = 20).

Serum HGF and VEGF level determination. Serum HGF and VEGF levels were determined by using the HGF

Quantikine ELISA kit and the VEGF Multi-Analyte Profiting kit (both R&D Systems, Minneapolis, Minnesota) according to the manufacturer's instructions. Circulating HGF levels were assayed in all subjects (n = 65); VEGF levels were obtained in 61 of the 65 subjects. Data are presented in pg/ml as mean \pm SEM.

HGF expression by human adipose tissue ex vivo. Adipocytes and adipose stromal cells (ASC) were obtained by collagenase digestion of human subcutaneous adipose tissue samples and separation of the cells by centrifugation of the tissue samples as described (24). The HGF messenger ribonucleic acid in tissues and cells was determined by reverse transcription-polymerase chain reaction using reagents from Applied Biosystems (Foster City, California). Ribonucleic acid was isolated by standard techniques (25), and 2 μ g was reverse transcribed for 60 min. The reverse transcription reaction was split in half for amplification of HGF and glyceraldehyde-3-phosphate dehydrogenase. The polymerase chain reaction conditions were 95° \times 30 s, 55° \times 30 s, and 72° \times 60 s for 35 cycles. Upstream primer for HGF was 5'-ATGTGGGTGACCAAACTCCTG-3', and downstream primer was 5'-CTATTGAAGGGGA-ACCAGAGG-3' based on Genbank sequence XM_052253. The primers for HGF span an intron located between bases 122 and 123 of the complementary deoxyribonucleic acid sequence, therefore eliminating amplification of genomic deoxyribonucleic acid in the ribonucleic acid preparation. Primers for human glyceraldehyde-3-phosphate dehydrogenase were from Applied Biosystems. To assess secretion of HGF by cultured cells, freshly isolated adipocytes and ASC were each cultured in Dulbecco's modified Eagle medium with 10% fetal bovine serum for 48 h. Human aortic endothelial cells (Clonetics, Walkersville, Maryland) were cultured in endothelial basal media-2 (EBM-2, Clonetics) with 5% fetal bovine serum. Neither Dulbecco's modified Eagle medium with 10% fetal bovine serum nor EBM-2 with 5% fetal bovine serum had detectable endogenous HGF. The conditioned medium from each sample was collected and assayed for HGF using enzyme-linked immunoadsorbent assay.

Statistical analysis. To determine lean versus obese group differences, the data were analyzed by Fisher exact test for categorical variables and the *t* test for continuous variables. The *t* test correction for unequal variances was used where necessary. A one-way analysis of variance was performed for the comparison of more than two groups. Linear regression analysis was used to evaluate for a correlation between growth factor levels and BMI or HOMA score. The log of the HOMA score was used to provide a normal distribution for this variable. There was no difference in the linear regression statistics using the log of the HOMA score instead of the HOMA score. For all analyses, a value of *p* > 0.05 was considered not significant (NS).

Table 1. Subject Characteristics

	Lean	Obese	p Value
Total number	21	44	
Female/male	13/8	32/12	NS
Age (yrs)	36 ± 3	39 ± 2	NS
BMI (kg/m ²)	21 ± 0.5	48 ± 1	< 0.0001
Systolic BP (mm Hg)	121 ± 4	139 ± 3	0.0055
Diastolic BP (mm Hg)	69 ± 3	80 ± 1	0.0009
HOMA score	2.3 ± 0.1	5.3 ± 0.6	< 0.0001
Patients with ↑ LFT	2	2	NS
Known atherosclerosis	0	2	NS
ESRD	0	0	NS
Malignancy	0	0	NS

Characteristics of subjects in the two groups are presented as mean ± SEM. The third column denotes statistical significance as assessed by the *t* test for continuous variables or Fisher exact test for categorical variables. In the case of BMI and HOMA scores, a *t* test with correction for unequal variances between the two groups was used. A value of *p* > 0.05 was considered not significant (NS).

BMI = body mass index; BP = blood pressure; ESRD = end-stage renal disease; HOMA = Homeostatic Model Assessment; LFT = liver function tests.

RESULTS

Patient characteristics. There was no significant difference between the lean and obese subject groups in terms of their age or gender distribution (Table 1). Only two subjects in each group had elevated LFT. By design, the BMI was significantly higher in the obese group. As expected from published data (5,22), SBP, DBP, and the HOMA score as a marker of insulin resistance were all significantly higher in the obese group.

Elevated levels of circulating HGF in obese subjects correlate with BMI. As shown in Figure 1, obese subjects had significantly higher serum HGF levels than lean subjects (2,462 ± 184 pg/ml vs. 765 ± 48 pg/ml, *p* < 0.0001 by *t* test with correction for unequal variances). Serum VEGF levels, on the other hand, were not significantly elevated in obese versus lean subjects (135 ± 31 pg/ml vs. 128 ± 37 pg/ml, *p* = NS by *t* test).

Circulating HGF levels were significantly correlated with BMI (*r* = 0.74; *p* < 0.0001) (Fig. 2). On the other hand, circulating VEGF levels did not show any significant correlation with BMI (*r* = 0.18, *p* = NS).

Lack of correlation between circulating HGF levels and insulin resistance. Because increased insulin resistance is associated with obesity, we determined whether insulin resistance correlated with the elevated HGF levels in obesity. We subdivided the obese subjects into three groups according to their degree of insulin resistance and found no significant difference in mean HGF concentrations between the three groups (*p* = 0.34 by analysis of variance) (Fig. 3A). Instead, increasing insulin resistance, as assessed by the HOMA score, showed a nonsignificant trend of lower HGF concentrations in obese patients (Fig. 3B).

Obesity-related increases in circulating HGF levels are independent of increases in BP. Linear regression analysis between BP and HGF concentrations using all patients showed no correlation between SBP and HGF levels (*r* = 0.1, *p* = NS) but did show a significant correlation between

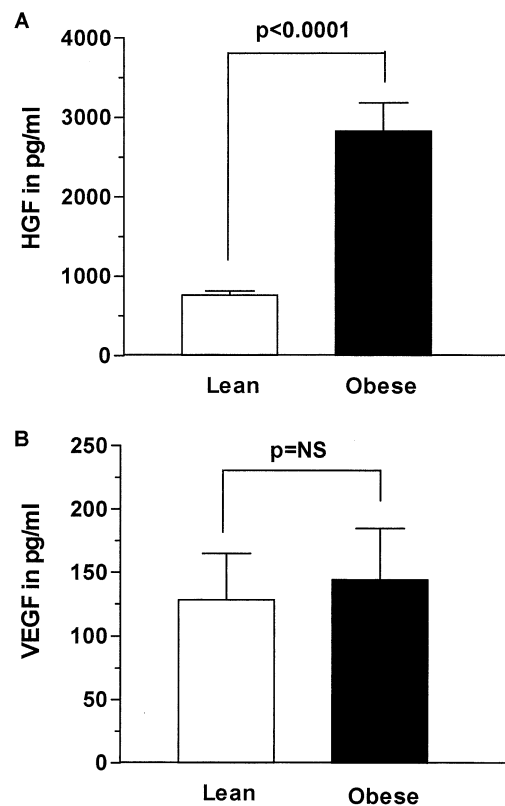


Figure 1. Obesity was associated with significant elevations of circulating hepatocyte growth factor (HGF) (A) but not of circulating vascular endothelial growth factor (VEGF) (B) in obese subjects when compared with lean subjects. Data are presented as mean ± SEM, and the analysis was performed using a *t* test. A value of *p* > 0.05 was considered not significant (NS).

DBP and HGF levels (*r* = 0.46, *p* = 0.0005). Because the obese subjects had significantly elevated BP (Table 1), it was not clear whether the observed obesity-related increases in HGF concentrations were primarily related to hypertension, which is known to be associated with increased HGF levels (26).

Therefore, we excluded all subjects in the lean and obese groups with either known hypertension or with elevated BP at the time of the blood draw for serum HGF determination. The remaining obese subjects had a mean SBP of 124 ± 3 mm Hg and a DBP of 74 ± 2 mm Hg, which were not significantly different from the SBP and DBP of the remaining lean subjects (*p* = NS). After the exclusion of the hypertensive subjects, HGF levels were still significantly elevated in the obese subjects when compared with the lean subjects (2,328 ± 360 pg/ml vs. 782.9 ± 51.36, *p* = 0.0008 by *t* test with correction for unequal variances) (Fig. 4A). Exclusion of the hypertensive subjects actually resulted in an even stronger correlation of HGF concentrations with BMI (*p* < 0.0001, *r* = 0.78) (Fig. 4B), thus suggesting that the correlation was not mediated by hypertension. In this normotensive population, DBP was no longer significantly correlated with HGF levels (*r* = 0.25, *p* = NS).

Ex vivo expression of HGF by human adipose tissue. To determine whether freshly isolated human adipose tissue

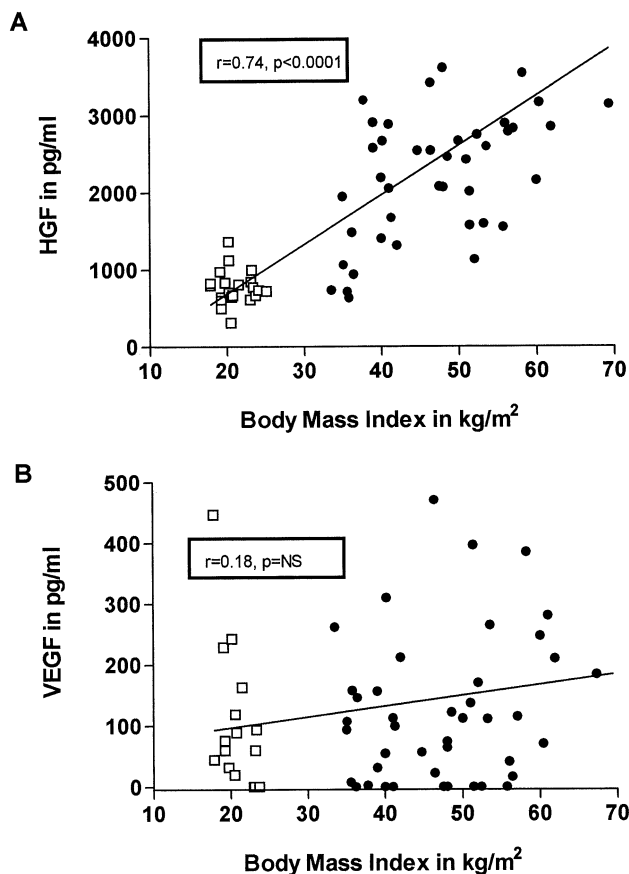


Figure 2. The serum levels of hepatocyte growth factor (HGF) (A) were significantly correlated with body mass index (BMI) as determined by linear regression analysis. To maintain the scale of the graph, three obese patients with HGF concentrations in the 4,000 to 6,500 pg/ml range are omitted from this graph. However, they are included in the statistical analysis. Circulating vascular endothelial growth factor (VEGF) levels (B), on the other hand, were not correlated with the degree of obesity. A value of $p > 0.05$ was considered not significant (NS). **Open squares** = lean subjects; **solid circles** = obese subjects.

could express HGF and thus may contribute to the systemic elevation of HGF in obese subjects, we separated adipocytes from ASC and assessed HGF messenger ribonucleic acid expression as well as secretion of HGF in culture. As shown in Figure 5, adipocytes and ASC both express HGF messenger ribonucleic acid, and the level of expression appears to be lower than that of human liver tissue. Furthermore, both adipocytes and ASC can secrete HGF in culture and achieve biologically active HGF concentrations, which are substantially higher than those found in the conditioned media of endothelial cells (Fig. 5B).

DISCUSSION

Obesity and HGF. To our knowledge, this is the first report of a systemic vascular growth factor elevation in obese patients. Our results indicate that obesity is associated with a more than three-fold increase in circulating HGF levels, correlating with the BMI. Some of the obese subjects in our study were hypertensive, and hypertension has been associated with elevated circulating HGF levels (26). However,

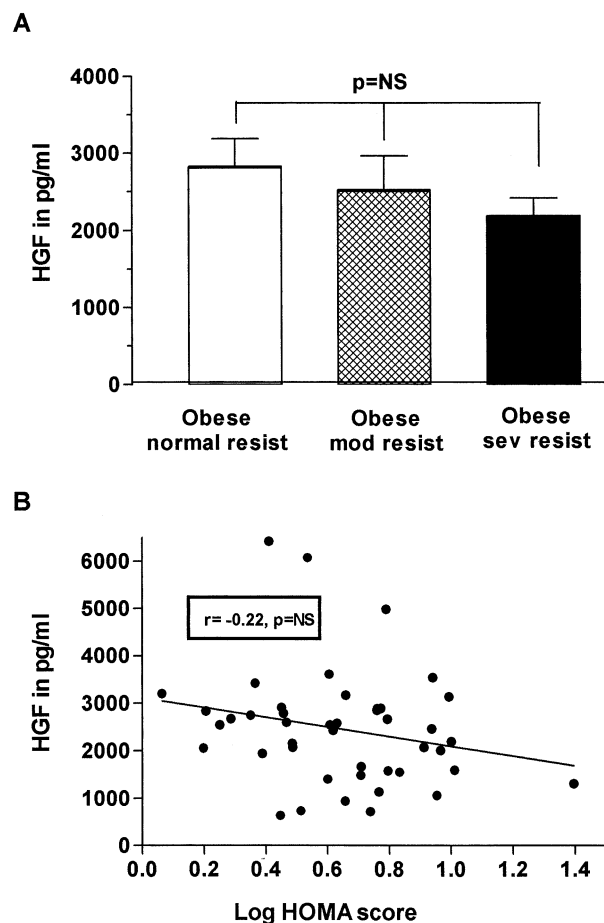


Figure 3. Obese patients were subdivided into three groups according to their insulin sensitivity using a Homeostatic Model Assessment (HOMA) score (normal insulin sensitivity with HOMA score <3 ; moderate insulin resistance with HOMA score between 3 and 5; and severe insulin resistance with HOMA score >5). The mean serum HGF levels of these three groups did not differ significantly using analysis of variance (A). There was also no significant correlation between the degree of insulin resistance (HOMA score) and hepatocyte growth factor (HGF) concentrations (B). There was a nonsignificant trend toward lower HGF levels with higher insulin resistance. A value of $p > 0.05$ was considered not significant (NS).

after exclusion of hypertensive subjects, circulating HGF levels were even more highly correlated with BMI. Furthermore, this increase in HGF levels was independent of the extent of insulin resistance. Therefore, our data suggest that the systemic HGF elevation observed in obese patients is primarily correlated with the extent of obesity rather than other components of the metabolic syndrome such as hypertension or insulin resistance.

One possible interpretation for the correlation between BMI and HGF concentrations is that the increased presence of adipose tissue may be responsible for the observed elevations in HGF levels. This is further supported by our observation that specific cellular components of human adipose tissue can secrete HGF *ex vivo*. The expression of HGF appeared to be lower than that of liver tissue. However, considering that adipose tissue is very abundant in obese subjects, these data suggest that adipose tissue may

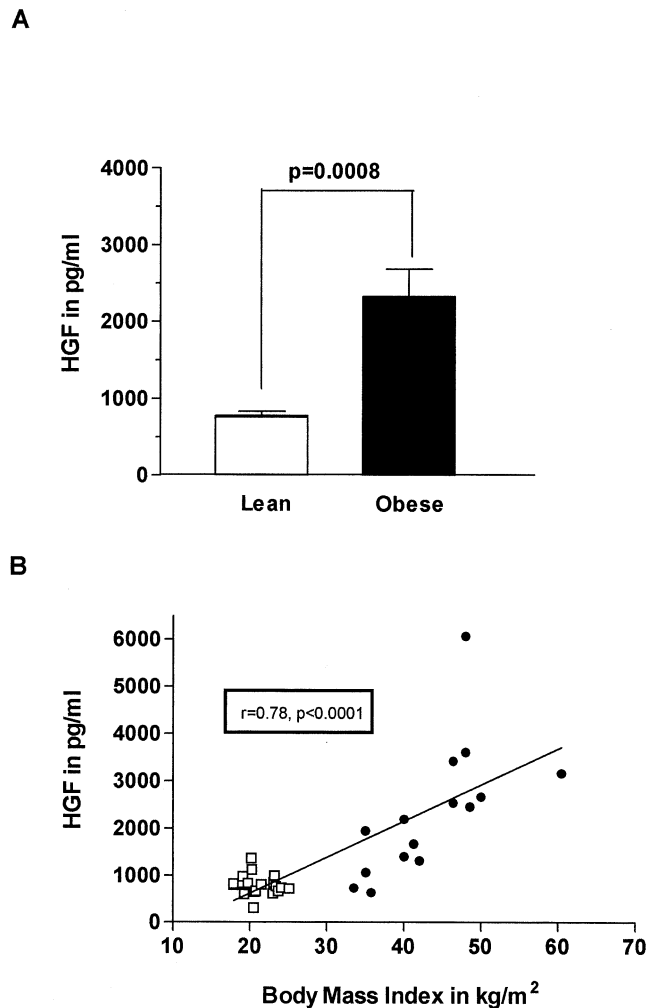


Figure 4. Because hypertension can affect hepatocyte growth factor (HGF) levels and hypertension has a higher prevalence among obese subjects, hypertension could act as a confounding factor. Therefore, we excluded all subjects with either known hypertension or documented hypertension at the time of blood draw (either systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg). The difference in mean serum HGF levels between the remaining obese and lean subjects continued to be highly significant (A). Furthermore, the correlation between body mass index and HGF levels was even stronger in this group of subjects (B). **Open squares** = lean subjects; **solid circles** = obese subjects.

substantially contribute to systemic HGF levels in obesity. The serum levels of VEGF, on the other hand, were not elevated in obese patients. Even though it has previously been shown that adipose tissue can secrete VEGF (10), the overall contribution of adipose tissue to systemic circulating levels may be substantially greater for HGF than for VEGF. **HGF as a link between obesity and coronary artery disease.** The elevated concentrations of HGF observed in our study are in the range in which HGF exerts its angiogenic and mitogenic effects on endothelial cells as well as its synergistic enhancement of VEGF effects (14). There is no clear evidence yet that HGF can directly contribute to the progression of atherosclerosis by plaque neovascularization as has been shown for VEGF (11); however, the similarity and synergy of angiogenic and mitogenic effects

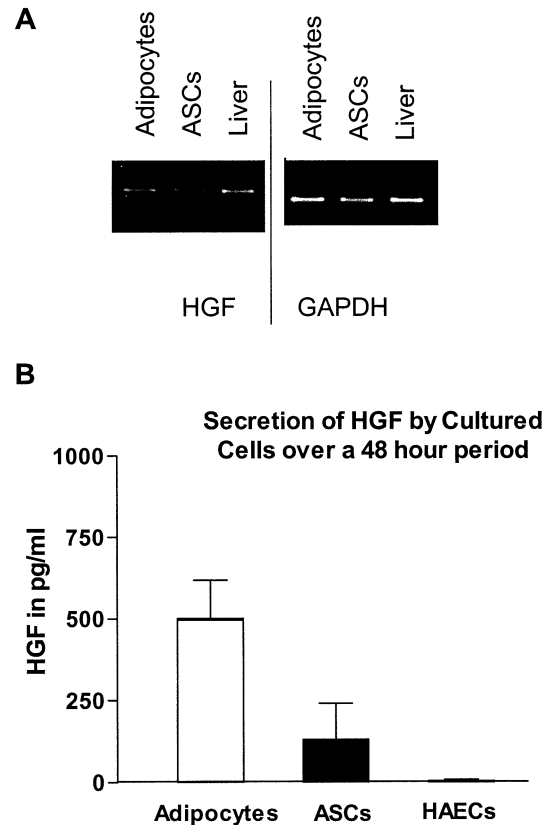


Figure 5. (A) The reverse transcription-polymerase chain reaction technique demonstrates that freshly isolated human adipocytes and non-adipocyte adipose stromal cells (ASCs) express hepatocyte growth factor (HGF). The expression appears to be less than that of liver tissue, when comparable amounts of total deoxyribonucleic acid (see glyceraldehyde-3-phosphate dehydrogenase as control) are used. (B) Adipocytes and ASCs can also secrete HGF protein into conditioned media, and achieve biologically active HGF concentrations in the media, which are substantially higher than those of cultured human aortic endothelial cells (HAECs).

with VEGF (14) suggest that this could be the case. In addition to the known association of circulating HGF levels with atherosclerotic disease (18–20), a recent study demonstrated the presence of HGF in atherosclerotic plaques (27).

On the other hand, HGF is also seen as a significant cardioprotective factor because of its potent angiogenic properties (13,28) and because HGF can reduce restenosis after balloon injury by enhancing re-endothelialization (29). Our findings may also contribute to understanding the previously described “obesity paradox” that obese patients actually have reduced mortality after percutaneous coronary intervention (30). The systemic elevation of HGF in obesity might increase the progression of atherosclerosis by plaque neovascularization, while at the same time reduce post-percutaneous coronary intervention mortality by enhancing re-endothelialization.

Study limitations and future directions. One limitation of our study is that the findings are limited to demonstrating an association between obesity and HGF concentrations, but do not prove that HGF acts in a pro-atherogenic manner in obese patients. Because HGF also has multiple

beneficial effects on the vasculature, the elevation of HGF in obese patients may instead be a vasculoprotective and cardioprotective response to subclinical atherosclerotic disease. Transgenic mouse models could be used in future studies to explore the effects of HGF on the progression of atherosclerosis.

Another limitation is that the obese subjects in our study were extremely obese, and that less obese subjects may not have such marked HGF elevations, although the linear correlation between HGF and BMI would suggest that patients with a BMI ≥ 30 kg/m² would also demonstrate significant HGF elevations. Owing to the nature of the study, we were not able to discern whether increased caloric intake and reduced physical activity, which are common in obese patients, contributed to the elevated HGF levels. Little is known about the effects of both exercise and caloric intake on HGF levels, and this could be addressed in future studies. Other related questions that can be investigated are whether HGF elevation in obese patients can affect such processes as therapeutic angiogenesis, tumor angiogenesis, or proliferative diabetic retinopathy, and whether specific inhibitors or modulators of HGF production and signaling pathways might indeed serve as targets for vascular therapies. Future studies may also identify additional humoral growth factors with vascular activity, which are secreted by adipose tissue *ex vivo* and systemically elevated in obese patients. We believe these data, as well as future related studies, will contribute to understanding the complex mechanisms that link obesity and cardiovascular disease.

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REFERENCES

1. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 1983;67:968–77.
2. Massie BM. Obesity and heart failure—risk factor or mechanism? *N Engl J Med* 2002;347:358–9.
3. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. *N Engl J Med* 2002;347:305–13.
4. McGill HC, Jr., McMahan CA, Herderick EE, et al. Obesity accelerates the progression of coronary atherosclerosis in young men. *Circulation* 2002;105:2712–8.
5. Abbasi F, Brown BW Jr., Lamendola C, McLaughlin T, Reaven GM. Relationship between obesity, insulin resistance, and coronary heart disease risk. *J Am Coll Cardiol* 2002;40:937–43.
6. Jousilahti P, Tuomilehto J, Vartiainen E, Pekkanen J, Puska P. Body weight, cardiovascular risk factors, and coronary mortality: 15-year follow-up of middle-aged men and women in eastern Finland. *Circulation* 1996;93:1372–9.
7. Kopelman PG. Obesity as a medical problem. *Nature* 2000;404:635–43.

8. Coppack SW. Pro-inflammatory cytokines and adipose tissue. *Proc Nutr Soc* 2001;60:349–56.
9. Trayhurn P, Beattie JH. Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ. *Proc Nutr Soc* 2001;60:329–39.
10. Mick GJ, Wang X, McCormick K. White adipocyte vascular endothelial growth factor: regulation by insulin. *Endocrinology* 2002;143:948–53.
11. Celletti FL, Waugh JM, Amabile PG, Brendolan A, Hilfiker PR, Dake MD. Vascular endothelial growth factor enhances atherosclerotic plaque progression. *Nat Med* 2001;7:425–9.
12. Nakagami H, Morishita R, Yamamoto K, et al. Mitogenic and antiapoptotic actions of hepatocyte growth factor through ERK, STAT3, and AKT in endothelial cells. *Hypertension* 2001;37:581–6.
13. Morishita R, Sakaki M, Yamamoto K, et al. Impairment of collateral formation in lipoprotein(a) transgenic mice: therapeutic angiogenesis induced by human hepatocyte growth factor gene. *Circulation* 2002;105:1491–6.
14. Van Belle E, Witzensbichler B, Chen D, et al. Potentiated angiogenic effect of scatter factor/hepatocyte growth factor via induction of vascular endothelial growth factor: the case for paracrine amplification of angiogenesis. *Circulation* 1998;97:381–90.
15. Shiota G, Umeki K, Okano J, Kawasaki H. Hepatocyte growth factor and acute phase proteins in patients with chronic liver diseases. *J Med* 1995;26:295–308.
16. Seidel C, Borset M, Turesson I, Abildgaard N, Sundan A, Waage A. The Nordic Myeloma Study Group. Elevated serum concentrations of hepatocyte growth factor in patients with multiple myeloma. *Blood* 1998;91:806–12.
17. Rampino T, Libetta C, De Simone W, et al. Hemodialysis stimulates hepatocyte growth factor release. *Kidney Int* 1998;53:1382–8.
18. Nishimura M, Nakano K, Ushiyama M, et al. Increased serum concentrations of human hepatocyte growth factor in proliferative diabetic retinopathy. *J Clin Endocrinol Metab* 1998;83:195–8.
19. Tateishi J, Waku S, Masutani M, Ohyanagi M, Iwasaki T. Hepatocyte growth factor as a potential predictor of the presence of atherosclerotic aorto-iliac artery disease. *Am Heart J* 2002;143:272–6.
20. Yoshitomi Y, Kojima S, Umemoto T, et al. Serum hepatocyte growth factor in patients with peripheral arterial occlusive disease. *J Clin Endocrinol Metab* 1999;84:2425–8.
21. Rahimi N, Saulnier R, Nakamura T, Park M, Elliott B. Role of hepatocyte growth factor in breast cancer: a novel mitogenic factor secreted by adipocytes. *DNA Cell Biol* 1994;13:1189–97.
22. Cefalu WT. Insulin resistance: cellular and clinical concepts. *Exp Biol Med* (Maywood) 2001;226:13–26.
23. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–9.
24. Considine RV, Nye MR, Morales LM, et al. Paracrine stimulation of preadipocyte-enriched cell cultures by mature adipocytes. *Am J Physiol* 1996;270:E895–9.
25. Chomczynski P, Sacchi N. Single-step method of RNA isolation by acid guanidinium thiocyanate-phenol-chloroform extraction. *Anal Biochem* 1987;162:156–9.
26. Nakamura Y, Morishita R, Nakamura S, et al. A vascular modulator, hepatocyte growth factor, is associated with systolic pressure. *Hypertension* 1996;28:409–13.
27. Ma H, Calderon TM, Fallon JT, Berman JW. Hepatocyte growth factor is a survival factor for endothelial cells and is expressed in human atherosclerotic plaques. *Atherosclerosis* 2002;164:79–87.
28. Taniyama Y, Morishita R, Hiraoka K, et al. Therapeutic angiogenesis induced by human hepatocyte growth factor gene in rat diabetic hind limb ischemia model: molecular mechanisms of delayed angiogenesis in diabetes. *Circulation* 2001;104:2344–50.
29. Yasuda S, Noguchi T, Gohda M, et al. Single low-dose administration of human recombinant hepatocyte growth factor attenuates intimal hyperplasia in a balloon-injured rabbit iliac artery model. *Circulation* 2000;101:2546–9.
30. Gruberg L, Weissman NJ, Waksman R, et al. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol* 2002;39:578–84.

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