Hepatocyte Growth Factor and Clinical Diabetes in Postmenopausal Women

Swapnil N. Rajpathak, mbbs, drph[1,2]
Sylvia Wassertheil-Smoller, phd[1]
Jill Crandall, md[2]
Simin Liu, md, scd[3]
Gloria Y.F. Ho, phd[1]

OBJECTIVE — To investigate the association between circulating levels of hepatocyte growth factor (HGF), a mesenchymal-derived pleiotrophic factor that is elevated in obesity, and the prevalence of type 2 diabetes.

RESEARCH DESIGN AND METHODS — A cross-sectional analysis among 892 postmenopausal women within the Women's Health Initiative Observational Study (WHI-OS).

RESULTS — HGF levels positively correlated with BMI and homeostasis model assessment for insulin resistance. In the multivariable analysis comparing the highest tertile with the lowest tertile of HGF, the odds ratio for prevalent diabetes was 2.47 (95% CI [1.12–5.47], *P* for trend = 0.014) after accounting for age, race, BMI, and other risk factors for diabetes.

CONCLUSIONS — HGF levels are associated with the presence of type 2 diabetes in postmenopausal women. Future studies should consider the prospective evaluation of the association of HGF with the development of type 2 diabetes.

Diabetes Care 33:2013–2015, 2010

Hepatocyte growth factor (HGF) is a mesenchymal-derived pleiotropic factor that regulates growth, motility, and morphogenesis of various cells (1). HGF is highly expressed in white adipose tissue (2,3), and it stimulates glucose uptake in cultured adipocytes (4). In humans, circulating HGF positively correlates with insulin and glucose (5) and is reported to be elevated in obesity (6), metabolic syndrome (5), hypertension (7), and coronary heart disease (8). Although HGF levels are observed to be elevated in these diabetes-associated conditions, the specific HGF-diabetes association has not yet been investigated. Hence, we conducted a study to examine the cross-sectional relationship between HGF and diabetes in a representative sample of postmenopausal women (n = 892) within the Women's Health Initiative Observational Study (WHI-OS).

RESEARCH DESIGN AND METHODS

— The WHI-OS is an ongoing prospective study of 93,676 postmenopausal women aged 50–79 years (9). At baseline, the women were queried about lifestyle factors, medical history, and personal habits, and a physical examination was performed to obtain height, weight, and blood pressure. Fasting blood samples were collected, centrifuged, frozen on site at −70°C, and stored in the specimen repository.

We conducted a study using data from a case-cohort study within the WHI-OS that aimed to evaluate the association of several adipokines and risk of cancers of the breast, colorectum, and endometrium (10). The study population for the current analysis included 892 women selected from the subcohort, a representative sample of WHI-OS women without cancer at baseline. Diabetes was defined as a history of treated diabetes or fasting glucose ≥126 mg/dl. Plasma HGF levels were measured by a multiplex assay (Human Adipokine Panel B; Millipore, Billerica, MA) based on Luminex xMAP technology (http://www.luminexcorp.com). The interassay coefficient of variation for HGF assay was 11.7%. We performed unconditional logistic regression analysis to evaluate the association between HGF tertiles and prevalent diabetes while accounting for potential confounders. Tests of linear trend across HGF tertiles were conducted by assigning a score for each tertile and including this variable as a continuous variable in the model. All statistical analyses were performed using SAS version 9.1 (Cary, NC), and *P* values <0.05 were considered statistically significant.

RESULTS

— In this population, HGF levels showed modest correlation with age (r = 0.20; $P < 0.0001$), BMI (r = 0.18; $P < 0.0001$), waist circumference (r = 0.19; $P < 0.0001$), and insulin resistance as measured by homeostasis model assessment for insulin resistance (r = 0.21; $P < 0.0001$). In addition, current postmenopausal hormone use and alcohol intake were associated with lower HGF levels (data not shown). In the age- and race-adjusted logistic regression model, the odds ratio (OR) for prevalent diabetes comparing women in the highest tertile of HGF with those in the lowest tertile was 3.63 (95% CI [1.83–7.19], *P*-trend <0.0001), which was attenuated to 2.78 (1.36–5.69), *P*-trend = 0.003 after additional adjustment for BMI (Table 1). This association remained significant when we further accounted for smoking, physical activity, family history of diabetes, alcohol intake, postmenopausal hormone use, and plasma levels of C-reactive protein (2.47 [1.12–5.47], *P*-trend = 0.014). To control for potential residual confounding by adiposity, we evaluated the effect of additional inclusion of waist circumference in the model. The results, however, were similar (2.34 [1.04–5.28], *P*-trend = 0.024). Additional adjustment for circulating insulin levels in the final multivariable model attenuated the results to borderline significance (1.95 [0.87–4.40], *P*-trend = 0.078). There

From the [1]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, New York; the [2]Department of Medicine (Division of Endocrinology), Albert Einstein College of Medicine, Bronx, New York; and the [3]Center for Metabolic Disease Prevention, University of California at Los Angeles, Los Angeles, California.
Corresponding author: Swapnil N. Rajpathak, swapnil.rajpathak@einstein.yu.edu.
Received 19 April 2010 and accepted 20 May 2010. Published ahead of print at http://care.diabetesjournals.org on 2 June 2010. DOI: 10.2337/dc10-0710.

Table 1—*Logistic regression analysis for the association of HGF with diabetes*

	Tertiles of HGF			
	Low	Medium	High	*P*-trend
n	298	298	296	
Mean	307.0	622.1	1,369.4	
Range (pg/ml)	(2.6–474.7)	(474.8–779.8)	(779.9–31,535.5)	
Number of cases	12	17	42	
Model 1	Reference	1.40 (0.65–3.02)	3.63 (1.83–7.19)	<0.001
Model 2	Reference	1.38 (0.62–3.03)	2.78 (1.36–5.69)	0.003
Model 3	Reference	1.27 (0.54–2.98)	2.47 (1.12–5.47)	0.014

Data are OR (95% CI) unless otherwise indicated. Model 1, adjusted for age and race; Model 2, Model 1 + adjusted for BMI; and Model 3, Model 2 + adjusted for smoking, physical activity, family history of diabetes, hormone use, alcohol intake, and C-reactive protein.

was no effect modification of the association by age, race, BMI, hormone use, or C-reactive protein levels.

CONCLUSIONS — We found that high HGF levels were associated with prevalence of type 2 diabetes. HGF is a mesenchymal-derived pleiotropic factor that regulates growth, motility, and morphogenesis of various cells (1). Although HGF was known initially as a potent mitogen for hepatocytes, it has recently been shown to have effects on other cells, including epithelial and endothelial cells. It is expressed in several tissues including lung, kidney, heart, brain, and especially fat (11). Circulating levels of HGF are up to threefold elevated in obese individuals, demonstrate strong correlation with BMI ($r = 0.68$; $P < 0.0001$), and substantially decline following weight loss (2,6).

In addition to obesity, several studies have linked HGF to other diabetes-associated disease conditions. HGF levels are elevated in patients with acute myocardial infarction and predict mortality following coronary intervention (8). Furthermore, circulating HGF levels are also associated with metabolic syndrome (5) and hypertension (7), reinforcing the potential role they may play in cardiometabolic disease. We recently reported that circulating HGF levels predicted the development of ischemic stroke among postmenopausal women in a large nested case-control study within the WHI-OS (12).

All these observations support the notion that HGF may also be involved in the pathogenesis of diabetes. The biological mechanisms linking HGF to the development of diabetes, however, are not well understood. It has been shown that HGF is highly expressed in adipose tissue where it exerts insulin-like effects and stimulates glucose uptake by augmenting the activity of phosphatidylinositol 3-kinase–dependent protein kinase B (4). It is possible that obese individuals exhibit HGF resistance, much like insulin resistance, which then affects the efficiency of glucose metabolism and leads to endothelial dysfunction, a known risk factor for diabetes. Alternatively, HGF may not be directly associated with diabetes risk, but it could be merely a bystander correlated with or induced by diabetes risk factors. Circulating HGF levels may rise in obesity as a compensatory mechanism for the increased insulin resistance. The elevated HGF levels in obesity may be secondary to a fatty liver as reported in a study of patients with nonalcoholic steatohepatitis (13); however, another study suggests that the high HGF levels in obesity occur even in the absence of any apparent liver dysfunction (5). In our study, the HGF-diabetes association was significant even after control of both BMI and waist circumference, suggesting that it is independent of obesity. The attenuation of the association after controlling for insulin possibly suggests that HGF may increase diabetes risk by increasing insulin resistance. However, only prospective studies can confirm this possibility. Our study is limited by its cross-sectional design, and we cannot determine the cause and effect between HGF and diabetes. Additional studies, especially prospective investigations, are warranted to further explore the role of HGF in the development of type 2 diabetes.

Acknowledgments — This research was funded by contract N01-WH-74310 (G.Y.F.H.) with the National Heart, Lung, and Blood Institute (NHLBI). The Hormones and Biomarkers Predicting Stroke Study (HaBPS) was supported by National Institute of Neurological Disorders and Stroke, and the WHI program is funded by NHLBI.

No potential conflicts of interest relevant to this article were reported.

S.N.R. researched the data, contributed to the discussion, and wrote/reviewed/edited the manuscript. S.W.-S. contributed to the discussion and reviewed/edited the manuscript. J.C. contributed to the discussion and reviewed/edited the manuscript. S.L. reviewed and edited the manuscript. G.Y.F.H. researched the data, contributed to the discussion, and reviewed/edited the manuscript.

The authors thank Dan Wang, Albert Einstein College of Medicine, New York, for assistance in data analysis.

References

1. Zarnegar R, Michalopoulos GK. The many faces of hepatocyte growth factor: from hepatopoiesis to hematopoiesis. J Cell Biol 1995;129:1177–1180
2. Bell LN, Ward JL, Degawa-Yamauchi M, Bovenkerk JE, Jones R, Cacucci BM, Gupta CE, Sheridan C, Sheridan K, Shankar SS, Steinberg HO, March KL, Considine RV. Adipose tissue production of hepatocyte growth factor contributes to elevated serum HGF in obesity. Am J Physiol Endocrinol Metab 2006;291:E843–E848
3. Fain JN, Madan AK, Hiler ML, Cheema P, Bahouth SW. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. Endocrinology 2004;145:2273–2282
4. Bertola A, Bonnafous S, Cormont M, Anty R, Tanti JF, Tran A, Le Marchand-Brustel Y, Gual P. Hepatocyte growth factor induces glucose uptake in 3T3–L1 adipocytes through A Gab1/phosphatidylinositol 3-kinase/Glut4 pathway. J Biol Chem 2007;282:10325–10332
5. Hiratsuka A, Adachi H, Fujiura Y, Yamagishi S, Hirai Y, Enomoto M, Satoh A, Hino A, Furuki K, Imaizumi T. Strong association between serum hepatocyte growth factor and metabolic syndrome. J Clin Endocrinol Metab 2005;90:2927–2931
6. Rehman J, Considine RV, Bovenkerk JE, Li J, Slavens CA, Jones RM, March KL. Obesity is associated with increased levels of circulating hepatocyte growth factor. J Am Coll Cardiol 2003;41:1408–1413
7. Nakamura S, Moriguchi A, Morishita R, Aoki M, Yo Y, Hayashi S, Nakano N, Katsuya T, Nakata S, Takami S, Matsumoto K, Nakamura T, Higaki J, Ogihara T. A novel vascular modulator, hepatocyte growth factor (HGF), as a potential index of the severity of hypertension. Biochem Biophys Res Commun 1998;242:238–243
8. Matsumori A, Furukawa Y, Hashimoto T, Ono K, Shioi T, Okada M, Iwasaki A, Nishio R, Sasayama S. Increased circulat-

ing hepatocyte growth factor in the early stage of acute myocardial infarction. Biochem Biophys Res Commun 1996;221:391–395
9. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. Control Clin Trials 1998;19:61–109
10. Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE, Li J, Ho GY, Xue X, Anderson GL, Kaplan RC, Harris TG, Howard BV, Wylie-Rosett J, Burk RD, Strickler HD. Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. J Natl Cancer Inst 2009;101:48–60
11. Boros P, Miller CM. Hepatocyte growth factor: a multifunctional cytokine. Lancet 1995;345:293–295
12. Rajpathak SN, Wang T, Wassertheil-Smoller S, Strickler HD, Kaplan RC, McGinn AP, Wildman RP, Rosenbaum D, Rohan TE, Scherer PE, Cushman M, Ho GY. Hepatocyte growth factor and the risk of ischemic stroke developing among postmenopausal women: results from the Women's Health Initiative. Stroke 2010;41:857–862
13. Balaban YH, Sumer H, Simsek H, Us D, Tatar G. Metabolic syndrome, non-alcoholic steatohepatitis (NASH), and hepatocyte growth factor (HGF). Ann Hepatol 2006;5:109–114