MHR

J. T. TAMSMA, ET AL. [2005] MED HYPOTHESES RES 2: 567-571.

METABOLIC SYNDROME AND ATHEROSCLEROSIS: THE LDL RECEPTOR-RELATED PROTEIN HYPOTHESIS

J. T. TAMSMA*, L. HU, B. J. M. VAN VLIJMEN, L. M. HAVEKES AND M. V. HUISMAN

VASCULAR MEDICINE, DEPARTMENT OF GENERAL INTERNAL MEDICINE AND ENDOCRINOLOGY, LEIDEN UNIVERSITY MEDICAL CENTER, LEIDEN, THE NETHERLANDS (J.T.T., L.H., M.V.H.); TNO-PREVENTION AND HEALTH, GAUBIUS LABORATORY, LEIDEN, THE NETHERLANDS (L.H., B.J.M.V., L.M.H.); DEPARTMENT OF HEMATOLOGY AND HEMOSTASIS, LEIDEN UNIVERSITY MEDICAL CENTER, LEIDEN, THE NETHERLANDS (B.J.M.V.)

REVIEW ◊ HYPOTHESIS

ABSTRACT. THE PROPOSED HYPOTHESIS will address the pathophysiologic link between the metabolic syndrome (MS) and atherosclerosis. Visceral obesity is a prominent feature of the syndrome and has been shown to associate with hepatic insulin resistance. Based on epidemiologic, clinical and experimental data we propose that the metabolic syndrome if associated with hepatic insulin resistance results in a dysfunction of the hepatic low-density lipoprotein receptor-related protein (LRP) clearance pathway. This pathway is responsible for the clearance and regulation of plasma levels of more than 35 pro-atherothrombotic and antifibrinolytic proteins. Many of these factors are known to be increased, or to play a role in MS and diabetes on the one hand, and on atherosclerosis on the other. Examples are apolipoprotein E, a key apoprotein in the clearance of very low density lipoprotein, metalloprotease-9 important in plaque vulnerability, and PAI-1 a key regulator of fibrinolysis. In addition, hepatic LRP deficiency resulted in increased measures of atherosclerosis in an experimental setting. Dysregulation and accumulation of LRP ligands in MS-associated hepatic insulin resistance likely is a pathophysiologic link to atherosclerosis.

*ADDRESS ALL CORRESPONDENCE TO: DR. J. T. TAMSMA, VASCULAR MEDICINE, DEPARTMENT OF GENERAL INTERNAL MEDICINE AND ENDOCRINOLOGY, LEIDEN UNIVERSITY MEDICAL CENTER, P. O. BOX 9600, 2300 RC LEIDEN, THE NETHERLANDS.
E-MAIL: jttamsma@lumc.nl

• MEDICAL HYPOTHESES AND RESEARCH • THE JOURNAL FOR INNOVATIVE IDEAS IN BIOMEDICAL RESEARCH •

1. THE METABOLIC SYNDROME AND HEPATIC INSULIN RESISTANCE

Metabolic syndrome (MS) is a clustering of cardiovascular risk factors. The working definitions of the syndrome are a compilation of antropometry (waist circumference or waist-to-hip ratio), dyslipidemia characterized by high triglyceride levels and low high density lipoprotein (HDL) cholesterol levels, hypertension, and increased fasting glucose or a measure of insulin resistance [1]. MS is often characterized by increased visceral fat stores. This visceral adiposity may well be the driving force behind the syndrome [2,3]. Visceral fat stores are known to be metabolic active and are for instance the source of many adipocytokines. Not surprisingly, visceral fat accumulation can contribute to insulin resistance [4]. In the case of hepatic insulin resistance this will result in for instance increased hepatic glucose and very low density lipoprotein (VLDL) production [2]. The early development of hepatic insulin resistance can be experimentally studied. Mice fed with high fat diets develop hepatic insulin resistance early in their natural history eventually leading to full blown diabetes [5].

2. THE MS CONTRIBUTES TO INCREASED CARDIOVASCULAR MORTALITY

The metabolic syndrome is associated with an increase of cardiovascular morbidity and mortality. Patients with the syndrome have been shown to have more atherosclerosis [6]. Furthermore, at the same levels of atherosclerosis they suffer from increased rates of cardiovascular events [7,8]; also designated as an increase of atherothrombosis. The adverse effects of the MS phenotype even persist in patients with diabetes [9]. Lastly, MS results in a higher incidence of Type 2 diabetes, further contributing to its devastating vascular effects. From a pathophysiologic point of view, the syndrome is considered to be causally related to atherosclerosis and thrombosis. The impact on atherosclerosis is straight forward for some MS components such as the atherogenic dyslipidemia and hypertension. However, the pathophysiologic link of MS to atherosclerotic phenomena such as plaque evolution, vulnerability, rupture and resultant thrombosis has not been fully elucidated. These areas are an important focus of research: from the vulnerable plaque to the vulnerable patient [10].

3. PRO-ATHEROTHROMBOTIC AND ANTIFIBRINOLYTIC FACTORS ARE ASSOCIATED TO THE MS

Pro-atherothrombotic and antifibrinolytic factors associate with the MS. Examples are increased plasma levels of MMP-9, FVIII, tPA and PAI-1 [11-13]. Of these, especially PAI-1 has been proposed as syndrome-defining criteria. The molecular mechanism(s) underlying the increased plasma levels of these proteins remain largely unknown, although for some increased expression or production has been found. However, in general plasma protein levels are the result of a delicate balance between production and clearance. Intriguingly, many of the pro-atherothrombotic and anti-fibrinolytic proteins of MS share one characteristic, and they are ligands for the same receptor LRP.

4. LOW-DENSITY LIPOPROTEIN (LDL) RECEPTOR-RELATED PROTEIN (LRP)

LRP is a member of the well-known LDL receptor gene family [14]. The receptor is a multiligand (>35 ligands) endocytic receptor involved in the tight regulation of its ligands in plasma. Among these ligands are proteins such as apolipoprotein E (ApoE, hepatic clearance VLDL-remnants), hepatic lipase (HL), lipoprotein lipase (LPL), tissue-type plasminogen activator (tPA), factor VIII, several metalloproteases (MMPs), tissue factor pathway inhibitor (TFPI), and plasminogen activator inhibitor 1 (PAI-1) [11,12,15-17]. A few examples are summarised in TABLE 1. Intruigingly, hepatic LRP clearance dysfunction resulted in increased measures of atherosclerosis as we have recently showed in LRP knockout mice [18].

5. HYPOTHESIS

We hypothesize that MS, if associated with hepatic insulin resistance, results in dysfunction of the LRP hepatic clearance pathway. As a conse-

TABLE 1. EXAMPLES OF LRP LIGANDS RELATED TO THE METABOLIC SYNDROME.

FACTOR	ASSOCIATION WITH LRP	ASSOCIATION WITH MS	FUNCTIONS
Apo E	LRP is an important ApoE clearance receptor.	Increased triglycerides levels are a MS defining criterium.	Apo E is necessary for hepatic clearance of proatherogenic VLDL- and chylomicron-remnants.
PAI-1	Clearance of PAI-1 by LRP. PAI-1 has a high affinity to LRP especially when complexed to tPA.	Increased PAI-1 levels are strongly related to the MS in epidemiolocal, clinical and experimental studies.	A very important inducible anti-fibrinolytic protein. Direct causal relation with insulin resistance.
tPA, uPA	Clearance of tPA/PAI-1 or uPA/PAI-1 complexes. LRP has has also been found to act as a receptor involved in cell-signalling for these ligands.	Increased tPA levels are strongly related to the MS in epidemiolocal, clinical and experimental studies, although to a lesser extent than PAI-1.	tPA and uPA also have been found in the atherosclerotic plaque and seem to have local pro-atherogenic functions.
MMP-9	MMP-9 is a LRP ligand.	Increased MMP-9 levels have been observed in DM2.	Metalloproteinase is important in matrix biology and observed in high levels at the vulnerable shoulder of the plaque. The temporal relation of expression and rupture suggests direct MMP involvement.
FVIII	LRP is the hepatic FVIII clearance receptor.	Increased fVIII levels have been related to the MS in epidemiolocal studies, although not as consistently as PAI-1 and tPA.	An important factor in the humoral hemostasis. Associated with increased arterial and venous thrombosis.

quence, chronic accumulation of pro-atherothrombotic and anti-fibrinolytic LRP ligands could accelerate atherosclerosis, have an adverse impact on plaque-structure, and worsen the outcome in case of an acute thrombotic event. Thus, LRP clearance pathway dysfunction would be a candidate pathophysiologic explanation linking MS to atherosclerosis and thrombosis adding to the direct effects of dyslipidemia, hypertension and slightly increased glucose levels.

6. EVIDENCE FROM LITERATURE IN FAVOUR OF THE HYPOTHESIS

Thus far, much of the evidence is indirect or circumstantial. Nevertheless, when reviewing literature there are data supporting the hypothesis:

- A strong correlation exists between several LRP-ligands and the MS in epidemiologic, clinical and experimental studies as exemplified in TABLE 1.
- LRP has been found to be under PPAR control in adipocytes. The LRP gene contains a peroxisome proliferator-activated receptor (PPAR) responsive element in its promotor region that can be activated by the insulin-sensitising agent rosiglitazone in vitro [19].
- LRP expression could be modulated by insulin in vitro [20,21].

In addition, preliminary observations from our laboratory are in support of the hypothesis. Six weeks administration of a high-fat diet readily induced hepatic insulin resistance in mice, like previously shown [5]. Insulin resistance coincided with chronic increased plasma levels of the LRP ligands factor VIII and tPA, which was the result of a decreased clearance rate from plasma, as determined by intravenously infused purified proteins. The observed effects approached the results obtained with our mouse model of conditional LRP-deficiency, under normal feeding conditions

[22].

Why would the hypothesis be attractive? The hypothesis connects MS to atherothrombosis via an alternative pathophysiologic route. It can add to the explanation of a variety of proatherothrombotic and antifibrinolitic serologic alterations frequently observed in association with the syndrome. Changes include key features such as increased levels of VLDL remnants and other associated features such as for instance PAI-1. The hypothesis, including over 35 LRP ligands may point at sofar not identified markers of disease. Furthermore, the hypothesis adds to the biologic basis of the increased vulnerability of metabolic syndrome patients, and to their seemingly adverse outcome when faced with an event. Lastly, the hypothesis may be of help to get insight in the complexity and difficulties encountered in the MS research. Regarding MS defining or associated factors, not only production variables should be accounted for. Their blood and tissue levels are also defined by clearance characteristics: each LRP ligand has specific characteristics and LRP binding affinities. In addition, ligand competition at the hepatic LRP-site and the patency of hepatocyte surface anchored HSPG's may be of importance. Differences in ligand expression by specific genetic or environmental backgrounds can modify the phenotypic appearances even further. In this perspective, an interesting gene polymorphism has recently been associated with metabolic syndrome in cardiovascular patients [23]. It regarded RAP an important intracellular regulatory protein of LRP expression.

7. CONCLUSION

Thus, based on epidemiologic, clinical and experimental data, we propose that the MS, if associated with hepatic insulin resistance, would result in a dysfunction of the hepatic LRP clearance pathway. This pathway is responsible for the clearance and regulation of plasma levels of over 35 pro-atherothrombotic and antifibrinolytic proteins. Many of these factors are known to be increased, or to play a role in MS on the one hand and in atherosclerosis on the other hand. Dysregulation and accumulation of such factors could contribute to the pathophysiology of atherosclerosis in MS patients. Intriguingly, hepatic LRP deficiency has indeed been shown to result in increased measures of atherosclerosis in mice.

REFERENCES

[1] BALKAU B AND CHARLES MA [1999] Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabet Med 16:442-443.

[2] MONTAGUE CT AND O'RAHILLY S [2000] The perils of portliness: Causes and consequences of visceral adiposity. Diabetes 49: 883-888.

[3] CARR DB, UTZSCHNEIDER KM, HULL RL, KODAMA K, RETZLAFF BM, BRUNZELL JD, SHOFER JB, FISH BE, KNOPP RH AND KAHN SE [2004] Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. Diabetes 53: 2087-2094.

[4] GARG A [2004] Regional adiposity and insulin resistance. J Clin Endocrinol Metab 89:4206-4210.

[5] MUURLING M, JONG MC, MENSINK RP, HORNSTRA G, DAHLMANS VE, PIJL H, VOSHOL PJ AND HAVEKES LM [2002] A low-fat diet has a higher potential than energy restriction to improve high-fat diet-induced insulin resistance in mice. Metabolism 51: 695-701.

[6] BONORA E, KIECHL S, WILLEIT J, OBERHOLLENZER F, EGGER G, BONADONNA RC AND MUGGEO M [2003] Carotid atherosclerosis and coronary heart disease in the metabolic syndrome: Prospective data from the Bruneck study. Diabetes Care 26: 1251-1257.

[7] HSIA J, BITTNER V, TRIPPUTI M AND HOWARD BV [2003] Metabolic syndrome and coronary angiographic disease progression: The Women's Angiographic Vitamin & Estrogen trial. Am Heart J 146: 439-445.

[8] ANAND SS, YI Q, GERSTEIN H, LONN E, JACOBS R, VUKSAN V, TEO K, DAVIS B, MONTAGUE P AND YUSUF S [2003] Relationship of metabolic syndrome and fibrinolytic dysfunction to cardiovascular disease. Circulation 108: 420-425.

[9] ALEXANDER CM, LANDSMAN PB, TEUTSCH SM AND HAFFNER SM [2003] NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes 52: 1210-1214.

[10] NAGHAVI M, LIBBY P, FALK E, CASSCELLS SW, LITOVSKY S, RUMBERGER J, ET AL. [2003] From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. Circulation 108: 1772-

1778.

[11] MEIGS JB, MITTLEMAN MA, NATHAN DM, TOFLER GH, SINGER DE, MURPHY-SHEEHY PM, LIPINSKA I, D'AGOSTINO RB AND WILSON PW [2000] Hyperinsulinemia, hyperglycemia, and impaired hemostasis: The Framingham Offspring Study. JAMA 283: 221-228.

[12] SAKKINEN PA, WAHL P, CUSHMAN M, LEWIS MR AND TRACY RP [2000] Clustering of procoagulation, inflammation, and fibrinolysis variables with metabolic factors in insulin resistance syndrome. Am J Epidemiol 152: 897-907.

[13] HAFFNER SM, GREENBERG AS, WESTON WM, CHEN H, WILLIAMS K AND FREED MI [2002] Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. Circulation 106: 679-684.

[14] WILLNOW TE, NYKJAER A AND HERZ J [1999] Lipoprotein receptors: new roles for ancient proteins. Nature Cell Biol 1: E157-E162.

[15] MARX N, FROEHLICH J, SIAM L, ITTNER J, WIERSE G, SCHMIDT A, SCHARNAGL H, HOMBACH V AND KOENIG W [2003] Antidiabetic PPAR gamma-activator rosiglitazone reduces MMP-9 serum levels in type 2 diabetic patients with coronary artery disease. Arterioscler Thromb Vasc Biol 23: 283-288.

[16] HAFFNER SM, GREENBERG AS, WESTON WM, CHEN H, WILLIAMS K AND FREED MI [2002] Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. Circulation 106: 679-684.

[17] MORANGE PE, RENUCCI JF, CHARLES MA, AILLAUD MF, GIRAUD F, GRIMAUX M AND JUHAN-VAGUE I [2001] Plasma levels of free and total TFPI, relationship with cardiovascular risk factors and endothelial cell markers. Thromb Haemost 85: 999-1003.

[18] ESPIRITO SANTO SM, PIRES NM, BOESTEN LS, GERRITSEN G, BOVENSCHEN N AND VAN DIJK KW [2004] Hepatic low-density lipoprotein receptore related protein deficiency in mice increases atherosclerosis independent of plasma cholesterol. Blood 103: 3777-3782.

[19] GAUTHIER A, VASSILIOU G, BENOIST F AND MCPHERSON R [2003] Adipocyte low density lipoprotein receptor-related protein gene expression and function is regulated by peroxisome proliferator-activated receptor gamma. J Biol Chem 278: 11945-11953.

[20] DESCAMPS O, BILHEIMER D AND HERZ J [1993] Insulin stimulates receptor-mediated uptake of ApoE-enriched lipoproteins and activated alpha 2-macroglobulin in adipocytes. J Biol Chem 268: 974-981.

[21] MISRA UK, GAWDI G, GONZALEZ-GRONOW M AND PIZZO SV [1999] Coordinate regulation of the α_2-macroglobulin signaling receptor and the low density lipoprotein receptor-related protein/α_2-macroglobulin receptor by insulin. J Biol Chem 274: 25785-25791.

[22] BOVENSCHEN N, HERZ J, GRIMBERGEN JM, LENTING PJ, HAVEKES LM, MERTENS K AND VAN VLIJMEN BJ [2003] Elevated plasma factor VIII in a mouse model of low-density lipoprotein receptor-related protein deficiency. Blood 101: 3933-3939.

[23] MCCARTHY JJ, MEYER J, MOLITERNO DJ, NEWBY LK, ROGERS WJ AND TOPOL EJ [2003] Evidence for substantial effect modification by gender in a large-scale genetic association study of the metabolic syndrome among coronary heart disease patients. Hum Genet 114:87-98.

\

RECEIVED ON 7-5-2005.

ACCEPTED ON 9-2-2005.