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Serum hepcidin levels are elevated in the metabolic syndrome

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To the Editor:

Valenti et al. report increased MCP-1 and hepcidin-25 levels in patients with non alcoholic fatty liver disease (NAFLD) along with metabolic alterations and found them to be an independent predictor of the presence of carotid plaques, indicating an advanced atherosclerotic process. (1)

We performed a case-control study on hepcidin levelsin a differently defined population with the metabolic syndrome (MetS). Patients and controls were drawn from the Nijmegen Biomedical Study (NBS), a population-based survey among 22,454 randomly selected inhabitants from the city of Nijmegen, The Netherlands. (2) We evaluated the presence of MetS by means of a self-administrated questionnaire among the 6,468 responders. Cases had to report hypertension, hypercholesterolemia, and diabetes diagnosed by a physician and a BMI $\geq$ 30 kg/m^2 (n=16); per case we selected 2 sex- and age-matched controls with a BMI between 20-25 kg/m^2, who did not report hypertension, hypercholesterolemia or diabetes. We measured serum hepcidin levels by our mass spectrometry-based assay, that is able to separately quantify the 25 amino acid (aa) hepcidin-25 and the smaller hepcidin isoform of 20 aa (hepcidin-20). (3)

We found levels of hepcidin-25 in MetS patients to be significantly higher than those of controls (median 6.1 nM vs. 4.9 nM; $p < 0.05$) (Table 1, Fig. 1 - http://www.hepcidinanalysis.com/documents/Figure1ATVBlettertoeditor_Krootetal2011.pdf). Of note, in addition to hepcidin-25, also hepcidin-20 levels of the MetS patients were elevated compared to controls (median 1.5 nM vs. 1.1 nM; $p < 0.01$) (Table 1, Fig. 1 - http://www.hepcidinanalysis.com/documents/Figure1ATVBlettertoeditor_Krootetal2011.pdf). The biological significance of hepcidin-20 in serum is unknown. It appears not to be involved in iron metabolism, (4, 5) although it may have antimicrobial activity. (6)

Previous studies showed an increased risk for atherovascular diseases in MetS, (7, 8) however the cause of this increased risk is not known yet. Our results of increased hepcidin levels in patients with MetS, in combination with the relation of increased hepcidin levels with atherosclerosis

reported by Valenti et al., (1) might implicate serum hepcidin as a determinant for the increased prevalence of atherosclerosis in patients with MetS.

These observations indirectly add to the evidence for the hypothesis that elevated hepcidin levels may contribute to the development of atherosclerotic vascular disease, probably by causing macrophages to sequester iron, increasing oxidative stress and inducing their transformation into foam cells. (9, 10) Furthermore, our data in conjunction with those reported by Valenti *et al*. suggestthat anti-hepcidin therapy might be beneficial in the prevention of atherosclerotic plaque forming in these patients. (1, 11)

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Table 1. Characteristics and hepcidin levels of the study population.

	Controls (N=32)	Cases (n=16)	
	Mean (sd) Median	Mean (sd) Median	p-value
Age (years)	63.4 (7.9) 64.9	63.3 (7.8) 64.9	0.98
BMI (kg/m^2)	23.1 (1.3) 23.4	33.2 (2.5) 32.8	<0.001
Transferrin saturation (%)	27.9 (8.3) 29.0	28.6 (6.5) 28.2	0.38
Ferritin (µg/L)	131 (82) 120	199 (101) 210	<0.01
ALAT (U/L)	11 (6) 11	18 (12) 14	<0.01
hsCRP (mg/L)	1.19 (1.24) 0.83	2.64 (2.17) 2.28	<0.01
Hepcidin-25 (nmol/L)	5.0 (2.6) 4.9	6.6 (2.6) 6.1	<0.05
Hepcidin-20 (nmol/L)	1.1 (0.3) 1.1	1.5 (0.5) 1.5	<0.01
Hepcidin total (nmol/L)	6.1 (2.7) 6.6	8.1 (2.8) 7.4	<0.05

BMI, body mass index; hsCRP, high sensitive C-reactive Protein

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