Atherosclerosis 251 (2016) 192–196

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Serum levels of Mac-2 binding protein increase with cardiovascular risk and reflect silent atherosclerosis

Tomonori Sugiura [a, *], Yasuaki Dohi [b], Hiroyuki Takase [c], Sumiyo Yamashita [a], Shunsuke Murai [a], Yuji Tsuzuki [d], Shintaro Ogawa [d], Yasuhito Tanaka [d], Nobuyuki Ohte [a]

[a] Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
[b] Department of Internal Medicine, Faculty of Rehabilitation Science, Nagoya Gakuin University, Seto, Japan
[c] Department of Internal Medicine, Enshu Hospital, Hamamatsu, Japan
[d] Department of Virology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

ARTICLE INFO

Article history:
Received 14 March 2016
Received in revised form
14 June 2016
Accepted 15 June 2016
Available online 16 June 2016

Keywords:
Mac-2 binding protein
Cardiovascular risk factor
Oxidative stress
Augmentation index
Atherosclerosis

ABSTRACT

Background and aims: Mac-2 binding protein (M2BP) was reported to be a useful biomarker for liver fibrosis and malignant tumors. We hypothesized that expression of M2BP might also change in the process of atherosclerosis.
Methods: This study included subjects who visited our hospital for a physical checkup.
Results: The M2BP levels in subjects with hypertension, dyslipidemia, or abnormal glucose metabolism were higher than those in subjects without such risk factors. Moreover, the M2BP levels were associated with severity of cardiovascular risk. Subdivision of M2BP levels into quartiles revealed that M2BP was significantly associated with reactive oxygen metabolites, central systolic blood pressure, and radial augmentation index (AI). Logistic regression analysis with the endpoint of high radial AI (above mean value) showed that high radial AI was independently associated with high M2BP.
Conclusions: Although the spectrum was narrow as compared to that in cases of hepatic fibrosis, serum M2BP may reflect silent atherosclerosis in apparently healthy subjects.

1. Introduction

Mac-2 binding protein (M2BP), also known as 90K glycoprotein, is a ligand for galectin-3 and E-selectin that plays an important role in cell adhesion [1,2]. M2BP is secreted into serum from many cell types and levels of M2BP in serum were proposed as diagnostic biomarker for hepatic fibrosis and several types of malignant tumor [2–6]. Recent developments have enabled the measurement of M2BP levels as a fibrosis-specific form of glycosylated M2BP (M2BPGi) using a chemiluminescence enzyme immunoassay system (Sysmex Co., Kobe, Japan) [7].

Hypertension, dyslipidemia, and diabetes mellitus are established cardiovascular risk factors, and the proportion of individuals with such risk factors has been increasing relative to changes in life style [8–10]. Atherosclerosis is a chronic and progressive disease of the vascular wall and the mechanism underlying the initiation and progression of atherosclerosis is closely associated with increased oxidative stress and inflammation of the vascular wall [9–11]. Thus, oxidative stress and chronic inflammation might be a common basic pathway in the development of atherosclerosis and malignant neoplasm, suggesting that expression of M2BP might change in the process of atherosclerosis [8–10,12]. Therefore, the present study investigated a possible association between serum M2BP level and cardiovascular risk.

2. Materials and methods

Detailed methods are described in Supplementary Methods.

2.1. Study subjects

The present study included subjects who visited our hospital for a yearly physical checkup. Subjects under medication or with liver dysfunction, fatty liver diagnosed by ultrasonography, renal insufficiency (creatinine ≥ 1.5 mg/dl), malignant neoplasm, active inflammatory disease, history of obvious hepatic disease, and a

* Corresponding author. Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate School of Medical Science, Kawasumi 1, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan.
E-mail address: tomosugi@med.nagoya-cu.ac.jp (T. Sugiura).

http://dx.doi.org/10.1016/j.atherosclerosis.2016.06.027
0021-9150/

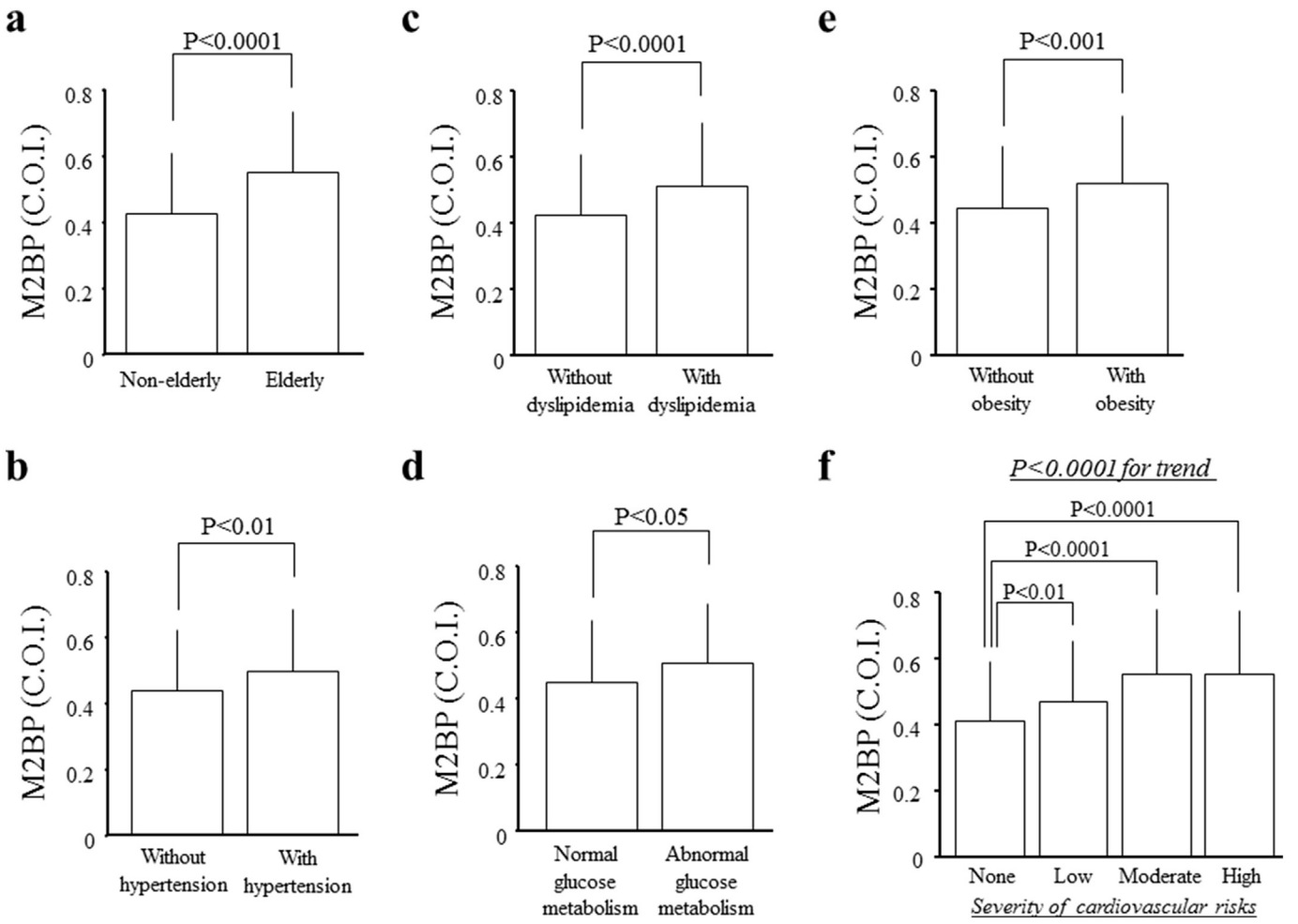

Fig. 1. Impact of old age (A), cardiovascular risk factors (B, hypertension; C, dyslipidemia; D, abnormal glucose metabolism; E, obesity), and severity of cardiovascular risk (F) on Mac-2 binding protein (M2BP) levels in total subjects. Data are expressed as mean value ± standard deviation.

history of cardiovascular events were excluded from analysis, as were current smokers. Hypertension or dyslipidemia were defined according to the relevant Japanese guidelines [13,14]. Subjects with a fasting plasma glucose ≥ 126 mg/dl or using anti-diabetic medications were defined as having diabetes mellitus, and subjects with a fasting plasma glucose ≥ 111 mg/dl and < 126 mg/dl were defined as having impaired glucose tolerance. Obesity was defined as body mass index (BMI) > 25 kg/m^2 [13]. For further analysis, the severity of cardiovascular risk in individuals was assessed by the risk stratification described in The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014) and patients were categorized into low, moderate, and high cardiovascular risk groups [13].

The study was approved by the Ethical Committee and was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each subject.

2.2. Biochemical analysis

Biochemical tests including serum lipid levels were determined by standard laboratory assays. The estimated glomerular filtration rate (eGFR) was calculated using a modified formula from the Modification of Diet in Renal Disease study for the Japanese population [15]. To assess oxidative stress, serum levels of derivatives of reactive oxygen metabolites (d-ROM) were measured [16].

2.3. Detection of M2BP

Serum levels of M2BP were measured using M2BPGi reagent as previously described, and the levels were expressed as cut off index (C.O.I.) units [7].

2.4. Measurement of central blood pressure and radial augmentation index

Measurement of radial artery pressure waveforms and estimation of central blood pressure was performed using a fully automated device (HEM-9000AI) as previously described [17,18]. The radial augmentation index (AI), which was reported to be a marker of arterial stiffness and subclinical atherosclerosis, was calculated by the following equation:

$$\mathrm{AI}(\%) = \left(\frac{\mathrm{P2}}{\mathrm{PP}}\right) \times 100,$$

where P2 and PP are the height of the late systolic shoulder/peak pressure and the pulse pressure of the radial arterial pressure contour, respectively [17,18].