Forward to the English Edition of Our Society Journal
Chikako Ito ................................................................. 3

Minoru Yamakado ................................................................. 5

High-molecular-weight Adiponectin and Ningen Dock:
Useful Biomarker of Metabolic Syndrome and Related Disorders
Hiroshi Hirose ................................................................. 7

Evaluation of Severity and Complication in Nonalcoholic Fatty Liver Disease
Yasuji Arase ................................................................. 16

How to Detect Early Stage Rheumatoid Arthritis (RA)
in Persons Undergoing Ningen Dock (Health Evaluation and Promotion)
Junichi Kaburaki, Masataka Kuwana ................................................................. 24

Comparison of Serum Lipid Management According to Japan Atherosclerosis Society 2007 and 2012 Guidelines:
Analysis of Data from Ningen Dock Database
Eiko Takahashi, Kengo Moriyama, Minoru Yamakado ................................................................. 34

Bone Turnover Markers and Risk Factors Associated with Osteoporosis and Decreased Bone Mass
Tomoko Shiga, Yuriko Moriyoshi, Hikaru Nagahara ................................................................. 40

Effect of Perceived Economic Status on Knowledge about Cancer Prevention, Healthy Behaviors,
and Cancer Check-up Rate in Japan
Junko Umihara, Mariko Nishikitani ................................................................. 47

Relationships of High-density Lipoprotein 2 and 3 Cholesterols with Lifestyle Habit Factors
in Japanese Adults
Kengo Moriyama, Eiko Takahashi ................................................................. 54

Comparison Among Body Mass Index, Waist Circumference, Waist-to-height Ratio,
and Percent Body Fat as Predictors of Incident Diabetes in a Japanese Health Screening Population
Eiji Oda ................................................................. 63

Lifestyle and Blood Pressure Control in Japanese Adults Receiving Hypertension Treatment:
Analysis of 2009 Japan Society of Ningen Dock Database
Eiko Takahashi, Kengo Moriyama, Minoru Yamakado and the Ningen Dock Database Group ................................................................. 70

Acknowledgments ................................................................. 79
Regulations of ISND ................................................................. 80
Instructions for Authors ................................................................. 85
Forward to the English Edition of Our Society Journal

Chikako Ito
Vice Chairman, Japan Society of Ningen Dock

The prevalence of lifestyle-related diseases has continued to increase throughout the world. With regard to diabetes mellitus, a typical lifestyle-related disease, the International Diabetes Federation (IDF) has reported its prevalence rate to be 8.3% in 2013 with a predicted prevalence rate of 8.8% in 2035 and that there would be an increase of 55% in the number of people with the disease by 2035. Thus, it is a major task facing our very aged society to determine how to prevent such diseases in order to maintain the QOL of the people. Furthermore, there has been an increase in malignant neoplasm with an aggravation of environmental factors to bring rise to not only increase of medical care cost but also to decrease in QOL.

It is needless to state that prevention and early detection of lifestyle-related diseases are important. From more than half a century ago, Japan Society of Ningen Dock has been engaged in the early detection and prevention of diseases in order to contribute toward the maintenance of the health of the people. These efforts have steadily borne fruit and produced a great deal of evidence. During the past 55 years our scientific meeting has been held annually to share the information thus obtained to the members and to the general public.

In Japan from 2008 focusing our target to metabolic syndrome, we have conducted and continued specific health examination and specific health guidance with the aim of preventing atherosclerotic diseases. Japan Society of Ningen Dock has also been engaged in successfully training professional staff qualified to conduct such health guidance with the use of evidence that have been accumulated over the years.

In addition, Japan Society of Ningen Dock has established a rigorous inspection criterion for the recognition of health examination facilities qualified to conduct high-level health examination and as of this date 300 facilities have so recognized. In 2012, a total of 3.16 million persons have undergone Ningen Dock health examination at these recognized facilities to show a 7.6-fold increase during the last 30 years. Malignant neoplasm have been detected annually in more than 8,000 cases with the proportion of early stage malignancy being very high. These results can be considered to attributable to the constant review being made in the examinations and their methodology.

It may be considered that these fruitful results of our efforts should not be confined for use only in Japan. Many peoples around the world have shown their interest and expectation in preventive medicine. As there is a common need for Ningen Dock throughout the world, it is considered that the information on the organization, mission and findings of Japanese Ningen Dock should be provided and disseminated to those involved in health care and to the general public through-
out the world.

Japan Society of Ningen Dock held its first World Congress on Ningen Dock in 2006 in Okinawa with the Congress being once every three years, that is in Tokyo, and Taipei to date. However, information and knowledge could only be shared with those who have attended these congresses. Thus there has been a need to disseminate our evidences internationally to a wider scope of people on the significance and importance of Japanese Ningen Dock.

It was with this objective in mind that decision was made to publish an English version of the official journal of Japanese Society of Ningen Dock with the belief that it will provide greater impetus for our activities aimed to contribute to the wellbeing and happiness of mankind based on the results that we have managed to collect during a period of half a century in Japan.
Preface to “Ningen Dock International”,
New English Version of Society Journal

Minoru Yamakado
Editor-in-Chief, Japan Society of Ningen Dock

The first edition of the English version of “Ningen Dock”, the Official Journal of Japanese Society of Ningen Dock, was published as Volume 19, No. 6 of the journal in 2005 but following publication of Volume 26 No. 6 in English in 2012, publication of the English version was temporarily suspended. Since then, papers in English have been published together with those in Japanese in the Japanese version of “Ningen Dock” and have comprised 2 forewords, 5 reviews, 58 original papers, 2 case reports and 5 proceedings of world congresses. The decision to include English papers in the Japanese version of the journal was based on the guarantee of an international audience through the listing of Ningen Dock in J-STAGE, the possibility of listing in PubMed for papers having English summaries as well as the fact that that with the former English version of the journal it could take a long as 12 months from the original submission of the paper to publication in the English version, thereby losing novelty, as publication was only once a year.

However, we were informed by Thomson Reuters that in order to obtain an Impact Factor, the global evaluation standard, for the society journal and have it listed in PubMed and Citation Index, it would be necessary to publish English articles in an independent English journal, not as part of the Japanese version. We therefore decided to revive the English version of the journal and publish it as Ningen Dock International.

Ningen Dock is a type of health check-up system unique to Japan and Ningen Dock-style health check-ups have contributed to prolonging a healthy life for Japanese as documented by “Japan: Universal Health Care at 50 Years” a special feature on Japan published in the Lancet (September 2011). In view of this, we feel that it is the role of Japan Society of Ningen Dock to inform people worldwide of the usefulness of Ningen Dock health check-ups and have them introduced globally, which would make a significant contribution to the longevity of the people all over the world.

Regarding longevity, it is not just enough to increase life expectancy, we have to prolong the period of healthy life as well. For this purpose, we must go beyond secondary prevention, the purpose of conventional Ningen Dock which involves the early detection and treatment of cancer and primary prevention that calls for reducing morbidity and mortality rates of cerebrovascular diseases and cardiovascular diseases, and establish preemptive medicine whose aims are predicting and preventing lifestyle-related diseases, i.e. preemptive medical care, and disseminate this worldwide. In order to achieve this objective, in Ningen Dock International it will be necessary to publish a large number of high quality papers that will be well-received by people working in health care all over the world.

We take this opportunity to extend a request to submit papers, not just to members of Japan Society
of Ningen Dock but to non-society members worldwidely as well. As regards articles carried by the Japanese version of Ningen Dock that are suitable for sharing with people abroad, the Editorial Committee will provide help in translating them into English. As members a global community, we feel that it is our duty to make the people of the world healthier through Ningen Dock health check-ups.
High-molecular-weight Adiponectin and Ningen Dock: Useful Biomarker of Metabolic Syndrome and Related Disorders

Hiroshi Hirose¹ ²

Abstract
Adiponectin was discovered to be the most abundant transcript in human adipose tissue in 1996. Animal studies have revealed that administering adiponectin improves insulin resistance and blood glucose levels, and inhibits atherosclerosis. In this review, I re-assess the significance of measuring serum high-molecular-weight (HMW) adiponectin levels in health check-ups, ‘Ningen Dock’. Cross-sectional studies using ELISA have revealed that the serum HMW-adiponectin concentration in healthy Japanese females was 1.9 times that of males and that there was a strong positive correlation between it and HDL-C but there were negative correlations with BMI and the homeostasis model assessment insulin resistance (HOMA-R). These studies also indicated that the serum HMW-adiponectin concentration was more strongly associated with HOMA-R and numbers of subjects with MetS than the total adiponectin concentration. Some subjects may inherit a lower serum adiponectin concentration and may have a higher risk of developing cardiovascular diseases (CVDs). Our longitudinal study, a 6-year follow-up study of Japanese men, revealed that decreased HMW-adiponectin is a predictor of progression to MetS. In another study, on 16 Japanese male subjects with MetS, lifestyle modification for 3 months induced a decrease in BMI and waist circumference and an increase in serum HMW-adiponectin but not total adiponectin.

A chemiluminescent enzyme immunoassay (CLEIA) developed for HMW-adiponectin is reportedly faster and more accurate than other assays. Also, serum levels are closely correlated with parameters related to MetS and CVDs and findings have suggested that HMW-adiponectin is a useful biomarker of MetS and related disorders in ‘Ningen Dock’.

Keywords high-molecular-weight adiponectin, MetS, insulin resistance, Ningen Dock

According to ‘Vital Statistics of 2012’ published by the Ministry of Health, Labour and Welfare of Japan, the leading cause of death in Japan is malignant neoplasm (28.8% of 1,256,000 subjects), followed by heart disease (15.9%), pneumonia (9.9%) and cerebrovascular disease (9.7%). Thus, the mortality of cardiovascular diseases (CVDs), which include heart and cerebrovascular diseases, is close to that of cancer. With the spread of a westernized diet and reduced physical activity due to increased automation and car use, the prevalence of lifestyle-related diseases such as type 2 diabetes mellitus (DM), hypertension, dyslipidemia, and atherosclerotic diseases has increased and become a social problem in Japan. As these conditions often develop concurrently via visceral fat accumulation and/or insulin resistance¹, they have been called syndrome X², the deadly quartet¹, insulin resistance syndrome⁴, and visceral fat syndrome⁴ but more recently, they have come to be called MetS. The above conditions are important risk factors for atherosclerosis and CVDs, and comorbidity of these factors is known to increase the risk of CVDs, not additively, but synergistically⁵. Therefore, in order to prevent and control MetS and CVDs in health check-ups, it is very important to have people recognize the need to correct visceral (abdominal)-type obesity and insulin resistance. Fig. 1 shows the intermediate factors involved in the progression from obesity to atherosclerotic diseases, including those which induce insulin resistance.

It was formerly considered that adipose tissue only regulated energy storage but recent studies have revealed that it is a site for the synthesis and secretion of

¹ Health Center, Keio University ; ² Center for Preventive Medicine, Keio University Hospital
Contact : Hiroshi Hirose, Health Center, and Center for Preventive Medicine, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. Tel: +81–3–3353–1211 ; Fax: +81–3–5363–3635
various bioactive substances, such as free fatty acids (FFAs), tumor necrosis factor (TNF)-α, resistin, leptin, adiponectin, plasminogen activator inhibitor-1 (PAI-1), and angiotensinogen.

Adiponectin was discovered by researchers at Osaka University (Osaka, Japan) in 1996 as the most abundant transcript in adipose tissue. It was found to be the same substance as a 28-kD gelatin-binding protein (GBP28) extracted from human serum by the Faculty of Pharmaceutical Sciences, Showa University (Tokyo, Japan) in the same year. In vitro experiments, adiponectin was shown to inhibit signals triggering inflammation in vascular endothelial cells and the growth of vascular smooth muscle cells. Animal studies revealed that adiponectin attaches to injured blood vessel walls. Also, Yamauchi et al. and Berg et al. reported separately, using various types of obese mice and diabetic mice, that the administration of adiponectin improves both insulin resistance and blood glucose levels. Another study reported that circulating adiponectin levels decreased in rhesus monkeys with DM as insulin resistance worsened. Studies using knockout mice indicated that a high-fat diet induces insulin resistance and atherosclerosis in such mice. Furthermore, adiponectin was found to inhibit hepatic fibrosis and growth of cancer cells, and provide survival benefits in animal studies.

Recent gel filtration analyses have revealed that adiponectin does not exist as a monomer in serum, and that high-molecular-weight (HMW) forms of adiponectin, such as a dodecamer (4 × 3 mer) and octadecamer (6 × 3 mer), are more closely associated with the onset of coronary artery diseases (CADs) and weight reduction, and play the role of insulin sensitizers. Several in vitro studies have reported that HMW-adiponectin mainly activates adenosine monophosphate (AMP) kinase, prevents apoptosis of vascular endothelial cells, and has cytostatic effects, and is therefore an active form of adiponectin. In this review, I explain the significance of measuring serum HMW-adiponectin from viewpoints of assessment of subjects with MetS and/or related disorders and providing care for them.

Cross-sectional studies using conventional ELISA method

Studies in healthy subjects

Although adiponectin is secreted from adipocytes, adiponectin concentrations are lower in obese subjects and in patients with type 2 DM, and much lower in those with both type 2 DM and CAD. Furthermore, a significant positive correlation was observed between the plasma adiponectin concentration and insulin sensitivity in Pima Indians with severe obesity and DM.

Clinical study data has confirmed that HMW-adiponectin levels are selectively reduced in type 2 diabetic patients with CAD and weight reduction preferentially increases the HMW form of adiponectin but not the lower molecular complexes. Furthermore, Waki et al. revealed that human adiponectin with rare missense mutations (G84R and G90S) does not form HMW multimers. These mutations were associated with insulin resistance and type 2 DM and they concluded that the proportion of adiponectin oligomeric complex is important for the anti-diabetic and anti-atherogenic activities of this protein. Several studies have found that HMW-adiponectin is more useful than total adiponectin. In addition, in type 2 diabetic patients receiving medications including thiazolidinediones (TZDs), the
HMW/total adiponectin ratio was more useful than the serum total adiponectin level. In this regard, Pajvani et al.\textsuperscript{17} reported that the HMW/total adiponectin ratio was significantly more useful for monitoring improvements in insulin sensitivity in response to TZDs in type 2 DM and Hara et al.\textsuperscript{23} reported that the HMW/total adiponectin ratio was better for predicting insulin resistance and MetS than the plasma total adiponectin level. Furthermore, Aso et al.\textsuperscript{21} reported that calculating the HMW/total adiponectin ratio was more useful for evaluating CAD in type 2 diabetic patients than simply measuring the serum total adiponectin level.

We conducted a cross-sectional study in healthy Japanese male subjects taking no medication and found that the HMW-adiponectin level was as effective as the HMW/total adiponectin ratio for predicting insulin resistance and/or MetS\textsuperscript{26}. In this study, 945 healthy Japanese males and females aged 30 to 65 years who underwent regular health check-ups were enrolled as subjects, in order to examine relationships between the serum HMW-adiponectin concentration and BMI, blood pressure, lipid profile, plasma glucose, serum insulin level and other parameters. The serum adiponectin concentration was determined using a kit (Chugai Diagnostics Science Co., Ltd, Tokyo) available at the time\textsuperscript{27–29}, which used IH7, the same antibody as that used in the ELISA kit specific for HMW-adiponectin (Fujirebio Inc., Tokyo)\textsuperscript{30,31}. This antibody (IH7) specifically identifies HMW-adiponectin, rendering heat treatment unnecessary\textsuperscript{30}. For the present review, the serum HMW-adiponectin concentrations determined using the former ELISA kit\textsuperscript{27–29} were converted to data that would have been obtained using the latter ELISA kit\textsuperscript{31}.

The serum HMW-adiponectin concentration was 1.9 times higher in female subjects than in male subjects\textsuperscript{27}. It was negatively correlated with homeostasis model assessment insulin resistance (HOMA-R) and positively correlated with HDL-C in both male and female subjects, even after adjusting for age and BMI\textsuperscript{27}. There was also a significant negative correlation between HMW-adiponectin concentration and blood pressure, but it was not significant (NS) after adjusting for age and BMI. Stepwise multiple regression analysis revealed that the serum HMW-adiponectin concentration was independently associated with gender ($r' = 0.250$), HDL-C ($r' = 0.295$), HOMA-R ($r' = -0.138$), and BMI ($r' = -0.148$) ($p < 0.001$ for all)\textsuperscript{27}. The strongest correlation, between HMW-adiponectin concentration and HDL-C, was observed in both male and female subjects, but details of the mechanism remain unclear. The total adiponectin concentration was also measured using a commercially available kit (Otsuka Pharmaceutical Co., Ltd, Tokyo) in our cross-sectional study, whose results showed that the HMW-adiponectin concentration was more strongly associated with HOMA-R and numbers of subjects with MetS than the total adiponectin concentration\textsuperscript{26}.

Some subjects may inherit a lower serum adiponectin concentration\textsuperscript{32–36}, and may have a higher risk of developing CVDs.

Studies in patients with type 2 DM

Our previous studies\textsuperscript{37} and others have shown that when troglitazone, an insulin sensitizer, is administered to type 2 diabetic patients for 3 to 6 months (400 mg/day), their body weight and skinfold thickness increase, but intra-abdominal fat decreases. Since intra-abdominal fat is a well-known risk factor for insulin resistance and atherosclerosis\textsuperscript{1}, reducing intra-abdominal fat could be important for preventing atherosclerosis.

We also studied the effects of 3 months administration of pioglitazone (30 mg/day) to 10 Japanese male patients with type 2 DM (57.7 ± 7.4 years)\textsuperscript{28}, using the same protocol as for troglitazone\textsuperscript{37}. Three months of pioglitazone significantly decreased the subjects' fasting plasma glucose, insulin, blood pressure, and HbA1c levels, while it significantly increased BMI, LDL-C, and leptin levels. The serum HMW-adiponectin concentration increased in all subjects to 3 times the initial concentration (from 3.2 ± 1.1 to 9.6 ± 1.4 μg/mL). A CT scan revealed that the subcutaneous fat area (S) significantly increased, from 155 ± 69 to 179 ± 81 cm$^2$, and the visceral fat area (V) tended to increase as well (from 165 ± 38 to 180 ± 46 cm$^2$, V/S ratio from 1.2 ± 0.3 to 1.1 ± 0.3, NS for both), unlike the case of troglitazone.

In this study, the administration of pioglitazone to type 2 diabetic patients improved their plasma glucose level and blood pressure and increased the serum HMW-adiponectin concentration, suggesting that pioglitazone might be useful for preventing the onset and progression of atherosclerosis in type 2 diabetic patients, as shown in the PROActive Study\textsuperscript{38}.

In keeping with the results of previous studies reporting an association between TZDs and the serum adiponectin concentration, administration of troglitazone\textsuperscript{39}, pioglitazone\textsuperscript{39}, or rosiglitazone\textsuperscript{40} increased the total adiponectin concentration approximately 2-fold and the serum HMW-adiponectin concentration 3-fold.

“Good adiponectin” and “bad TNF-α” are thought to inhibit the secretion and effects on muscles of each other, suggesting that TZDs may exert beneficial effects by inhibiting TNF-α via an increase in adiponectin concentration. Although many studies have indicated that TZDs increase LDL-C levels, adiponectin has been shown to inhibit atherosclerosis in in vitro and in vivo animal studies, suggesting that adiponectin might prevent the onset and progression of CVDs in diabetic patients and also in patients with MetS.
Longitudinal and intervention studies on adiponectin

In a longitudinal study, we investigated factors causing worsening of glucose tolerance in non-diabetic Japanese. Subjects were enrolled from among persons undergoing annual health check-ups in both 2004 and 2010. Subjects consisted of 390 Japanese male and 147 female teachers and other workers of 25 to 60 years of age at baseline. Subjects diagnosed as having type 2 DM at baseline were excluded. Height, weight, blood pressure, fasting plasma glucose, HbA1c, serum lipids, insulin and HMW-adiponectin levels were measured after an overnight fast. Subjects were divided into 3 groups in 2004 and 2010: DM, Pre-DM and normal glucose tolerance. Serum insulin concentrations were measured by EIA and serum HMW-adiponectin by ELISA. After the worsening of glucose tolerance in non-diabetic adults (Table 3 of Reference 41), no correlations were observed with baseline smoking, alcohol consumption, exercise status (data not shown). Stepwise multiple regression analysis of [Unchanged / Worsened] as a dependent variable showed that there were significant independent correlations for baseline glucose, HMW-adiponectin (F=11.5, r=−0.165) and age in males (Table 2). The findings of this 6-year longitudinal study suggested that low baseline HMW-adiponectin, together with baseline glucose level and age, are predictive of worsening glucose tolerance in non-diabetic Japanese men.

Table 1. Relationships between Glucose Tolerance Status [Unchanged=0 / Worsened=1] and Various Metabolic Parameters in 388 Japanese Male Subjects and 147 Female Subjects

<table>
<thead>
<tr>
<th>vs. Unchanged / Worsened</th>
<th>Males (n=388)</th>
<th>Adjusted for age and glucose</th>
<th>Females (n=147)</th>
<th>Adjusted for age and glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.181 0.0003</td>
<td>0.129 0.0096 NS</td>
<td>0.279 0.0006 NS</td>
<td>0.065 NS</td>
</tr>
<tr>
<td>BMI</td>
<td>0.223 &lt;0.001</td>
<td>0.126 0.1344 NS</td>
<td>0.239 0.0306 NS</td>
<td>0.008 NS</td>
</tr>
<tr>
<td>SBP</td>
<td>0.237 &lt;0.001</td>
<td>0.093 NS</td>
<td>0.099 NS</td>
<td>0.022 NS</td>
</tr>
<tr>
<td>DBP</td>
<td>0.220 &lt;0.001</td>
<td>--- NS</td>
<td>0.386 &lt;0.001 NS</td>
<td>--- NS</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.342 &lt;0.001</td>
<td>0.047 NS</td>
<td>0.023 NS</td>
<td>0.079 NS</td>
</tr>
<tr>
<td>Glycoalbumin</td>
<td>0.124 0.0148</td>
<td>0.047 NS</td>
<td>0.301 0.0002 NS</td>
<td>0.234 0.0021 NS</td>
</tr>
<tr>
<td>TG (log)</td>
<td>0.134 0.0081</td>
<td>0.049 NS</td>
<td>0.023 NS</td>
<td>0.079 NS</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.144 0.0045</td>
<td>0.007 NS</td>
<td>0.288 0.0004 NS</td>
<td>0.194 0.0133 NS</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.125 0.0140</td>
<td>0.026 NS</td>
<td>0.041 NS</td>
<td>0.026 NS</td>
</tr>
<tr>
<td>ALT (log)</td>
<td>0.149 0.0032</td>
<td>0.175 0.0337 NS</td>
<td>0.081 NS</td>
<td>0.149          0.0133 NS</td>
</tr>
<tr>
<td>γ-GTP (log)</td>
<td>0.205 &lt;0.001</td>
<td>0.097 0.0538 NS</td>
<td>0.177 0.0396 NS</td>
<td>0.069 NS</td>
</tr>
<tr>
<td>Uric acid</td>
<td>0.124 0.0146</td>
<td>0.087 NS</td>
<td>0.115 NS</td>
<td>0.032 NS</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.111 0.0282</td>
<td>0.080 NS</td>
<td>0.308 &lt;0.0017 NS</td>
<td>0.123 0.0023 NS</td>
</tr>
<tr>
<td>WBC</td>
<td>0.142 0.0049</td>
<td>0.088 NS</td>
<td>0.001 NS</td>
<td>0.024 NS</td>
</tr>
<tr>
<td>RBC</td>
<td>0.137 0.0067</td>
<td>0.165 0.0007 NS</td>
<td>0.035 NS</td>
<td>0.051 NS</td>
</tr>
<tr>
<td>Hb</td>
<td>0.151 0.0028</td>
<td>0.142 0.0031 NS</td>
<td>0.056 NS</td>
<td>0.105 NS</td>
</tr>
<tr>
<td>HOMA-R (log)</td>
<td>0.258 &lt;0.001</td>
<td>0.138 0.0094 NS</td>
<td>0.252 0.0021 NS</td>
<td>0.181 0.0240 NS</td>
</tr>
<tr>
<td>HMW adiponectin (log)</td>
<td>-0.196 &lt;0.001</td>
<td>-0.165 0.0005 NS</td>
<td>-0.127 NS</td>
<td>-0.030 NS</td>
</tr>
<tr>
<td>Total adiponectin (log)</td>
<td>-0.077 NS</td>
<td>-0.044 NS</td>
<td>-0.157 0.0581 NS</td>
<td>-0.075 NS</td>
</tr>
</tbody>
</table>

Slightly modified from Table 3 of Reference 41, with permission. HOMA-R: homeostasis model assessment insulin resistance, HOMA-β: homeostasis model assessment insulin secretion. r: regression coefficient, NS: p > 0.05.

Table 2. Stepwise Multiple Regression with [Unchanged=0/Worsened=1] as Dependent Variable in 388 Japanese Male Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardized regression coefficient</th>
<th>F value</th>
<th>p value</th>
<th>Change in R^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>0.300</td>
<td>51.2</td>
<td>&lt;0.0001</td>
<td>11.9%</td>
</tr>
<tr>
<td>HMW-adiponectin (log)</td>
<td>-0.165</td>
<td>11.5</td>
<td>&lt;0.0001</td>
<td>2.6%</td>
</tr>
<tr>
<td>Age</td>
<td>0.110</td>
<td>5.1</td>
<td>&lt;0.0001</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

Slightly modified from Table 4 of Reference 41, with permission. BMI, SBP, log[TG], LDL-C, uric acid, log[γ-GTP], log[HOMA-R] were also permitted to enter the regression mode. R^2 = (0.395)^2 = 0.156
The findings of a longitudinal study conducted by Daimon et al. in Funagata, Yamagata Prefecture indicated that hypoadiponectinemia might be a risk factor for the development of type 2 DM. Another study conducted in 18,225 American men aged 40 to 75 years reported that nonfatal myocardial infarction or fatal CVDs developed in 226 subjects during a 6-year follow-up period and indicated that a low blood concentration of adiponectin might be a predictor of myocardial infarction. Even after adjusting for age, study enrollment time, smoking, and other factors, the incidence of myocardial infarction in the lowest quintile of the adiponectin concentration was 2.5 times higher than that in the top quintile ($p < 0.001$).

Longitudinal data concerning HMW-adiponectin have also been reported. For example, decreased HMW-adiponectin was found to be an independent risk factor for progression to type 2 DM in Japanese Americans during a 5.4-year follow-up study, and Inoue et al. reported that the serum HMW-adiponectin level ($\leq 2.6 \mu g/mL$) was a predictor of future CVDs in patients with CAD during a 7-year follow-up study.

We also investigated whether decreased HMW-adiponectin is a predictor of progression to MetS during a 6-year follow-up period in Japanese men. This study included 416 Japanese men without MetS, aged 30 to 59 years at baseline, who had undergone annual health check-ups in both 2000 and 2006. The study found that a low concentration of HMW-adiponectin ($\leq 2.6 \mu g/mL$) was associated with a substantially higher hazard ratio for progression to MetS even after adjusting for age and BMI (hazard ratio 1.56, 95% confidence interval 1.05 – 2.29, $p = 0.028$). The numbers of subjects who progressed to MetS in each tertile based on the baseline HMW-adiponectin concentration was significantly different among 3 groups (HMW-adiponectin, $\chi^2 = 7.473, p = 0.0238$; total adiponectin, $\chi^2 = 4.477, p = 0.1066$; HMW/total ratio, $\chi^2 = 1.676, p = 0.4325$).

In an intervention study, 16 Japanese male subjects with MetS aged 54.8 ± 7.2 years were enrolled in our program. Each subject was instructed regarding lifestyle modifications consisting of increasing physical activity and decreasing calories by public health nurses and a nutritionist at our institute (Health Center, Keio University), and as a result subjects mainly increased the amount of exercise they did. Such lifestyle modification for 3 months brought about decreases in BMI, waist circumference (WC), serum TG and post-prandial insulin levels, as well as an increase in the serum HMW-adiponectin level (from 2.5 ± 1.8 to 3.4 ± 2.6 $\mu g/mL$, $p = 0.0045$) but not in total adiponectin level (from 4.1 ± 1.7 to 4.3 ± 2.1 $\mu g/mL$, $p > 0.15$). The HMW-adiponectin level was most strongly correlated with the change in BMI ($r = -0.656, p = 0.0046$) but it was not correlated with the change in WC at all ($r = -0.085, p = 0.7586$). Although mechanisms for this discrepancy were not clear, there is a possibility that BMI reflected reduction in body fat more precisely than the WC. WC was measured by several examiners in this study.

It has been reported that the serum HMW-adiponectin concentration increases slightly with the administration of some angiotensin receptor blockers (ARBs), statins, and insulin secretagogues. Losartan, an ARB, is widely used as an anti-hypertensive agent, and its metabolite is reported to have partial peroxisome proliferator-activated receptor gamma (PPARγ) activity in vitro. Several studies have demonstrated that losartan treatment increases the serum HMW-adiponectin concentration, although the effects of losartan on metabolic parameters in clinical practice are controversial.

In this regard, we observed that administering telmisartan, which also has partial PPARγ activity, increased the serum HMW-adiponectin concentration in Japanese male subjects with hypertension and abdominal obesity. On the other hand, treatment with diuretics, including hydrochlorothiazide (HCTZ) and indapamide, was reported to decrease the adiponectin level.

Studies using recently-developed CLEIA method

The chemiluminescent enzyme immunoassay (CLEIA) for HMW-adiponectin has been shown to be faster and more accurate than the conventional ELISA. In a recent study, we measured the serum level of HMW-adiponectin by CLEIA in the health check-up setting in our institute to investigate relationships between it and various metabolic parameters. Subjects consisted of 1,036 male and 416 female Japanese teachers and other working individuals, 40 to 71 years of age, from whom informed consent was obtained. Data from those receiving anti-diabetic medication or with suspected inflammation (CRP level $> 1$ mg/dL) were excluded from the analyses. Since adiponectin measurement is not yet covered by the Japanese health insurance system, we requested SRL, Inc. (Tokyo) to do the measurement.

Median levels of serum HMW-adiponectin measured by CLEIA were 2.5 $\mu g/mL$ in males and 4.95 $\mu g/mL$ in females. The serum HMW-adiponectin level in males with MetS ($2.13 \pm 1.14, n = 173$) was significantly lower than that in those without MetS ($3.02 \pm 3.43, n = 860, p < 0.0001$). HMW-adiponectin levels were correlated positively with serum HDL-C in both males and females, and inversely with BMI, WC, SBP, plasma glucose, serum TG, uric acid, CRP, HOMA-R, etc. (Table 3). Stepwise multiple regression analysis revealed that the serum HMW-adiponectin level was correlated inde-
pendently with serum HDL-C, gender, HOMA-R and CRP ($F > 20$, $p < 0.0001$, $R^2 = 0.392$) (Table 4).

The HMW-adiponectin levels measured by CLEIA were close to half of those measured by the conventional ELISA due to changes in the calibrator concentration. HMW-adiponectin (CLEIA) = HMW-adiponectin (ELISA) $\times 0.504 + 0.172$, and the correlation between the levels was very high ($r = 0.993$, $n = 185$) in our hospital (Laboratory Medicine). The intra-assay coefficient of variation (CV) was 1.0% to 2.2%, and the inter-assay CV was 1.7% to 3.3% for CLEIA, and these parameters were 2.4% to 3.0%, and 4.2% to 5.1% for ELISA. Therefore, the CLEIA is more accurate and faster than the conventional ELISA (Table 5).

These results suggest that measuring serum HMW-

| Table 3. | Relationships between High-molecular-weight (HMW) Adiponectin Level and Various Metabolic Parameters in 1036 Japanese Male Subjects and 416 Female Subjects |
| --- | --- | --- | --- |
| vs. HMW-adiponectin measured by CLEIA | Males (n = 1036) | After adjustment for age and BMI | Females (n = 416) | After adjustment for age and BMI |
| | | | | |
| Age | 0.083 | 0.0078 | -- | -- | 0.083 | NS | -- | -- |
| BMI | -0.319 | <0.0001 | -- | -- | -0.328 | <0.0001 | -- | -- |
| Waist circumference | -0.301 | <0.0001 | -0.113 | NS | -0.306 | <0.0001 | -0.147 | NS |
| SBP | -0.100 | 0.0112 | -0.016 | NS | -0.122 | 0.0130 | -0.006 | NS |
| DBP | -0.100 | 0.0012 | -0.013 | NS | -0.093 | NS | 0.001 | NS |
| Glucose | -0.129 | <0.0001 | -0.061 | 0.0478 | -0.170 | 0.0005 | -0.097 | NS |
| HbA1c | -0.159 | <0.0001 | -0.097 | 0.0019 | -0.072 | NS | 0.003 | NS |
| TG | -0.334 | <0.0001 | -0.252 | <0.0001 | -0.321 | <0.0001 | -0.257 | <0.0001 |
| HDL-C | 0.410 | <0.0001 | 0.334 | <0.0001 | 0.375 | <0.0001 | 0.276 | <0.0001 |
| LDL-C | -0.205 | <0.0001 | -0.164 | <0.0001 | -0.221 | <0.0001 | -0.203 | <0.0001 |
| AST | -0.173 | <0.0001 | -0.079 | 0.0104 | 0.038 | NS | 0.068 | NS |
| ALT | -0.285 | <0.0001 | -0.169 | <0.0001 | -0.101 | 0.0402 | -0.019 | NS |
| γ-GTP | -0.214 | <0.0001 | -0.129 | <0.0001 | -0.129 | <0.0001 | -0.116 | 0.0227 |
| Uric acid | -0.224 | <0.0001 | -0.145 | <0.0001 | -0.234 | <0.0001 | -0.177 | 0.0005 |
| Creatinine | -0.011 | NS | 0.011 | NS | -0.079 | NS | -0.076 | NS |
| WBC | -0.195 | <0.0001 | -0.128 | <0.0001 | -0.162 | 0.0009 | -0.079 | NS |
| RBC | -0.247 | <0.0001 | -0.169 | <0.0001 | -0.159 | 0.0011 | -0.091 | NS |
| Hb | -0.246 | <0.0001 | -0.161 | <0.0001 | -0.170 | 0.0005 | -0.151 | 0.0013 |
| BNP | 0.172 | <0.0001 | 0.162 | <0.0001 | 0.170 | 0.0005 | 0.127 | 0.0065 |
| PSA (n = 589) | -0.054 | NS | -0.051 | NS | -- | -- | -- | -- |
| HOMA-R (n = 845 & 342) | -0.334 | <0.0001 | -0.225 | <0.0001 | -0.361 | <0.0001 | -0.245 | <0.0001 |
| CRP (n = 845 & 342) | -0.281 | <0.0001 | -0.186 | <0.0001 | -0.299 | <0.0001 | -0.173 | 0.0042 |

Slightly modified from Table 2 of Reference 62, with permission.

BNP: brain natriuretic peptide, HOMA-R: homeostasis model assessment insulin resistance.

<p>| Table 4. | Stepwise Multiple Regression with High-molecular-weight (HMW) Adiponectin (log) Measured by CLEIA as Dependent Variable in 1452 Japanese Subjects |
| --- | --- | --- | --- |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardized regression coefficient</th>
<th>$F$ value</th>
<th>$p$ value</th>
<th>Change in $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C</td>
<td>0.276</td>
<td>371.2</td>
<td>&lt;0.0001</td>
<td>23.9%</td>
</tr>
<tr>
<td>Gender</td>
<td>0.308</td>
<td>179.3</td>
<td>&lt;0.0001</td>
<td>10.0%</td>
</tr>
<tr>
<td>HOMA-R (log)</td>
<td>-0.183</td>
<td>74.6</td>
<td>&lt;0.0001</td>
<td>3.9%</td>
</tr>
<tr>
<td>CRP (log)</td>
<td>-0.130</td>
<td>27.7</td>
<td>&lt;0.0001</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

Slightly modified from Table 3 of Reference 62, with permission.

Gender: male = 0, female = 1.

Age, BMI, SBP, HbA1c, log[ALT] and WBC were also permitted to enter the regression mode.

$R^2 = (0.626)^2 = 0.392$

| Table 5. | Comparison between the 2 HMW-adiponectin assay methods: ELISA (X) and Chemiluminescent Enzyme Immunoassay (CLEIA) (Y) |
| --- | --- | --- |
| | Conventional ELISA | Newly-developed CLEIA |
| Intrassay CV (%) | 2.4 – 3.0 | 1.0 – 2.2 |
| Interassay CV (%) | 4.2 – 5.1 | 1.7 – 3.3 |
| Time Consuming | Saving |
| Reference | 30, 31 | 61 |

CV: coefficient of variation. $Y = 0.504 \times X + 0.172$ ($r = 0.993$, $n = 185$).

Concentration of 2.6 μg/mL by ELISA corresponds to 1.5 μg/mL by CLEIA.
adiponectin by CLEIA is useful, and that the serum HMW-adiponectin level is closely correlated with parameters related to MetS and/or CVDs.

**Conclusion**

Previous *in vitro* and *in vivo* animal studies indicated that adiponectin inhibits atherosclerosis, suggesting that it might prevent the onset and progression of CVDs in patients with MetS and in those with type 2 DM. Our findings suggest that HMW-adiponectin is a useful biomarker for the evaluation and care of subjects with MetS and related disorders.

**Acknowledgments**

The studies presented here were conducted according to the principles expressed in the Declaration of Helsinki. Informed consent was obtained from each subject or patient after full explanation of the purpose, nature, and risk of all procedures used. The protocols were approved by the ethical review committees of the Health Center and the School of Medicine, Keio University, Tokyo.

**Grant support**

These studies were supported in part by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan (No. 23500855), and by research grants from Keio University, Tokyo.

**Potential Conflict of Interest**

Fujirebio, Inc. (Tokyo) and Keio University have a patent for HMW-adiponectin measurement.

**References**


52. Guo LL, Pan Y, Jin HM: Adiponectin is positively associated


(Received December 25, 2013; Accepted January 24, 2014)
Evaluation of Severity and Complications of Nonalcoholic Fatty Liver Disease

Yasuji Arase

Abstract
Nonalcoholic fatty liver disease (NAFLD) has been increasing dramatically in Japan and many other nations over the past few decades. At present, according to Japanese annual health check-up reports, 10–40% of Japanese adults show evidence of NAFLD in ultrasonography. Also, 10–20% of these people with NAFLD have nonalcoholic steatohepatitis (NASH). Ultrasonography is more useful for detecting NAFLD than laboratory tests, such as liver enzymes. Physicians detecting NAFLD in their patients should evaluate its severity by imaging methods, histological scoring systems, and/or liver biopsy. They should also evaluate NAFLD-related complications in NAFLD patients, such as type 2 diabetes mellitus, vascular disease and hepatocellular carcinoma, as well as the factors involved in these complications.

Keywords  nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, diagnosis, complication

Nonalcoholic fatty liver disease (NAFLD), considered to be one of the more common causes of chronic liver disease in worldwide1–6, consists of the following two clinicopathological entities: 1) non-alcoholic steatohepatitis (NASH) which may progress to cirrhosis and hepatocellular carcinoma (HCC); 2) simple steatosis which has a benign non-progressive clinical course. Simple steatosis is called non-NASH fatty liver (NNFL).

NAFLD is considered to be the liver component of metabolic syndrome7. According to data from annual health check-ups, 10–40% of Japanese adults have ultrasonography (US)-diagnosed NAFLD8 and NASH is observed in 10–20% of NAFLD cases. Thus, NAFLD is often encountered in routine clinical practice. Also, NAFLD is associated with obesity, dyslipidemia, pituitary dysfunction, hypertension, sleeping apnea, chronic kidney disease, and type 2 diabetes mellitus (T2DM)9–13, and it often causes cardiovascular disease and cerebral stroke14,15. Its progress to cirrhosis enhances the onset of HCC and hepatic insufficiency.

Thus, NAFLD has become an important public health issue because of its high prevalence and the various kinds of complication associated with it. The purpose of this review is to describe the diagnosis, complications and prognosis of NAFLD for physicians who are involved in its daily management in Ningen Dock.

Diagnosis algorithms in NAFLD
NAFLD patients are usually asymptomatic until it progresses to liver cirrhosis. Among non-alcoholic individuals, it is therefore often detected from the presence of hepatic steatosis on abdominal US during routine health check-ups or clinical visits for other diseases. One of problems in detecting NAFLD is that serum transaminase is not useful for diagnosing of steatosis. About 60–70% of patients diagnosed with NAFLD in Toranomon Health Management Center have normal transaminase levels. The actual rates for normal transaminase levels in patients with NAFLD at our Center were 62.7% (7,600/12,129) in men and 69.4% (1,451/2,090) in women, respectively. Therefore US examination is more useful for detecting NAFLD than laboratory tests, such as liver enzymes.

Fig. 1 shows an algorithm for the diagnosis of NAFLD. The diagnosis of NAFLD should meet all of the following three requirements: 1) ethanol (EtOH) consumption of <20 g/day; 2) detection of steatosis either by imaging or by histology; 3) appropriate exclusion of other liver diseases, such as alcoholic liver diseases, viral hepatitis, autoimmune liver diseases, and metabolic or hereditary liver diseases. Regarding detection of hepatic steatosis by imaging, abdominal US examination is currently the most common method employed for its qualitative assessment in Ningen Dock because it is non-invasive. Presence of hepatic steatosis on abdominal US is usually...
detected on the basis of a pattern consistent with bright liver (brightness, deep attenuation and vascular blurring) and stronger echoes in the hepatic parenchyma than in the renal or spleen parenchyma (Fig. 2). For the quantification of steatosis, CT and magnetic resonance imaging (MRI) seem to be more objective and sensitive techniques. In the diagnosis of steatosis by CT, the liver-to-spleen attenuation ratio is measured, and the diagnosis of steatosis is made when the ratio is $<0.9$. MRI diagnosis uses the liver-specific contrast material gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA), whose safety and usefulness in the detection of HCC has been reported. Also, magnetic resonance laparoscopy (MRL) may be achieved through the creation of images of the hepatobiliary phase in Gd-EOB-DTPA-enhanced MRI. Since MRL is non-invasive, patients with contraindications for conventional laparoscopy (e.g. bleeding tendency, old age) can be examined safely using it, as long as there is no contraindication for Gd-EOB-DTPA-enhanced MRI. Liver images obtained by MRL are shown in Fig. 3.

Several other imaging techniques have been advocated as non-invasive diagnostic tests for NASH. US-based transient elastography, or FibroScan, has produced promising results in assessment of the severity of liver fibrosis and degree of steatosis. However, such modalities are expensive and not widely available.

**Liver biopsy in NAFLD**

The principal histological features of NASH are as follows: 1) presence of macrovesicular fatty change, 2) ballooning degeneration, 3) lobular inflammation, 4) fibrosis. Mallory Denk bodies, giant mitochondria, and nuclear glycogen are often also seen. Therefore, biopsy is considered the “gold standard” for a definitive diagnosis. However, liver biopsy by means of laparoscopy has several drawbacks; it is an invasive procedure and is fraught with the possibility of sampling error. Accordingly, at present, liver biopsy should only be considered in NAFLD patients who are considered to be at increased risk of developing NASH with advancing fibrosis or are suspected to have other coexisting chronic liver diseases.

**Scoring systems for NAFLD**

Table 1 shows scoring systems used for NAFLD. Many use recently reported biochemical markers that are predictive of NASH and NNFL in NAFLD. The NAFLD fibrosis score is a widely validated scoring system for predicting the severity of fibrosis that is based on six readily assessable clinical variables (age, BMI, hyperglycemia, platelet count, albumin, AST/ALT).
A major problem with the NAFLD fibrosis score is that calculating the score is complicated. The BARD score (which includes the three following variables: BMI, (AST/ALT) Ratio, and Diabetes) is used in western countries. Although the BARD scores is easy to calculate, it might not be appropriate for assessing Japanese NAFLD patients because they have a lower BMI than Westerners.

The NAFIC score, a simple scoring system to differentiate NASH from NAFLD, is based on serum ferritin, fasting insulin and type IV collagen 7S. The 3 variables in the NAFIC score are combined in an easily calculated weighted sum [serum ferritin ≥200 ng/mL (female) or ≥300 ng/mL (male) = 1 point, fasting insulin ≥10 U/mL = 1 point, and type IV collagen 7S ≥5.0 ng/mL = 2 points] for predicting NASH. The NAFIC score can predict NASH in Japanese NAFLD patients with sufficient accuracy and simplicity for clinical use.

### Table 1. Scoring Systems for NAFLD Patients

<table>
<thead>
<tr>
<th>Scoring system</th>
<th>Author</th>
<th>Calculation</th>
<th>Point(s)</th>
<th>Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD fibrosis</td>
<td>Angulo (2007)</td>
<td>$-1.65 + 0.03 \times \text{age (years)} + 0.094 \times \text{BMI} + 1.13 \times \text{DM (presence=1, absence=0)} + \text{AAR} - 0.013 \times \text{PLT (10^9/L)} - 0.66 \times \text{Alb (g/dL)}$</td>
<td></td>
<td>Low :-1.455</td>
</tr>
<tr>
<td>BARD score</td>
<td>Harrison (2008)</td>
<td>BMI ≥ 28 kg/m², AAR=AST/ALT ≥ 0.8 Diabetes (+)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>NAFIC score</td>
<td>Sumida (2011)</td>
<td>Ferritin: male ≥ 300, female ≥ 200 Fasting insulin ≥ 10 μU/mL Type–4 collagen ≥ 5 ng/mL</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>FIB-4 index</td>
<td>Shah (2009)</td>
<td>$\text{Age} \times \text{AST (IU/L) / PLT (10^9/L) / (ALT (IU/L))}^{1/2}$</td>
<td></td>
<td>Low :-1.45</td>
</tr>
<tr>
<td>APRI score</td>
<td>Wai (2003)</td>
<td>$\text{(AST level/ULN)} \times 100 / \text{PLT (10^9/L)}$</td>
<td></td>
<td>High : ≥1.5</td>
</tr>
</tbody>
</table>

PLT, platelets; BARD score includes the three following variables: BMI, (AST/ALT) Ratio, and Diabetes; DM, diabetes mellitus; FIB-4 index is composed of the following 4 fibrosis factors: age, AST, ALT levels, and platelet counts; The NAFIC score, a simple scoring system to differentiate NASH from NAFLD, is composed of serum ferritin, fasting insulin and type IV collagen 7S.
The FIB-4 index, a scoring system to differentiate advanced hepatic fibrosis, includes the following 4 factors: age, AST and ALT levels, and platelet counts. The FIB-4 index was shown to be superior to other tested noninvasive markers of fibrosis in Japanese patients with NAFLD.

The AST to platelet ratio index (APRI), a non-invasive index for prediction of significant fibrosis in patients with chronic hepatitis C, was reported previously, and its utility in NAFLD has also been reported. APRI is a predictive factor for the development of HCC.

**Complications**

**Type 2 diabetes mellitus**

Generally, chronic liver disease enhances the onset of diabetes. In chronic HCV disease, HCV clearance reduces the onset of diabetes to one-third. On the other hand, the onset of T2DM is more enhanced by NAFLD than HCV.

It has been speculated that visceral fat plays a role in the onset of T2DM, and the possible mechanisms have been reported as follows: 1) activated macrophage and inflammatory cytokines/kemokines enhance insulin resistance (IR), 2) progression of hepatofibrosis reduces insulin clearance and causes hyperinsulinemia, 3) disturbance of hepatic insulin sensitivity worsens further with increasing hepatic fat accumulation, resulting in increased hepatic gluconeogenesis and increased hepatic glucose output. It has also been reported that development of T2DM is associated with lower insulin secretion.

Our previous studies suggested that pre-diabetes status, lack of physical activity, elevated γ-GTP and triglycerides during follow-up are important factors in enhancement of the onset of T2DM in patients with NAFLD (Fig. 4, Table 2). These findings suggest that improvement of pre-diabetes status, physical activity, normalization of mean γ-GTP and triglycerides during follow-up is important for preventing the onset of T2DM in patients with NAFLD.

In addition, Ogata et al. have reported that a BMI decrease of ≥1.5 and physical activity of ≥2 Metabolic Equivalent of Task (MET) h/day are predictive of regression from IGT to normal glucose regulation (NGR) in NAFLD patients.

T2DM has continued to increase in Asian countries over the last few decades, including Japan and many newly developed and developing nations. In this

![Fig. 4. Cumulative Development Rates of T2DM in NAFLD Patients](image-url)
country, 8–10% of adults have T2DM, a serious, costly disease. Treatment for T2DM may prevent some of its devastating complications, but does not usually restore normoglycemia or eliminate all the adverse consequences. Therefore, physicians treating patients with NAFLD who have a decreased insulinogenic index (IGI) and elevated IR should particularly pay attention to the development of T2DM.

**Vascular disease**

As mentioned in the diabetes mellitus (DM) section above, several researchers have reported that NAFLD enhances several vascular diseases, such as coronary heart disease and cerebral stroke. Table 3 presents studies on the incidence of vascular disease. NAFLD patients tend to have the complications of hypertension, diabetes and dyslipidemia. It is likely that these factors influence the progression of atherosclerosis and development of vascular disease.

Ogawa et al. have reported that the annual incidence of coronary heart disease, ischemic stroke, or hemorrhagic stroke in NAFLD patients with an age of ≥60 years old was 11.7% based on the cumulative development in the 10th year (Fig.5). They mentioned that physicians in charge of NAFLD patients with high glucose levels, hypertension and dyslipidemia should pay attention to the development and prevention of coronary heart disease or cerebral stroke (Table 2). However, hemorrhagic stroke tends to develop in advanced NAFLD patients. Poor control of blood pressure, aging, and high glucose levels were found to be risk factors for ischemic stroke in NAFLD patients. Also, poor control of blood pressure, aging, low albumin level and high APRI were risk factors for hemorrhagic stroke in NAFLD patients. Furthermore, a low albumin level and high APRI indicated advanced NAFLD. These findings indicate that hemorrhagic stroke tends to develop in advanced NAFLD (Table 4).

Our findings therefore indicate that physicians treating NAFLD patients with a high glucose level, hypertension and dyslipidemia should pay attention to the prevention and development of coronary heart disease or cerebral stroke. On the other hand, as mentioned above, hemorrhagic stroke tends to develop in advanced NAFLD patients.

**Hepatocellular carcinoma**

HCC is a common malignancy worldwide, and its incidence is increasing in Asia and in the United States. Chronic viral hepatitis and liver cirrhosis following infection with hepatitis B and C viruses play important roles in the development of HCC. However, a substantial proportion (5–10%) of Japanese patients with HCC are negative for markers of hepatitis B and C viruses. Besides viral infection, NAFLD is also considered to play a role in enhancing the development of HCC. Therefore, clarification of the pathogenesis and clinical features of HCC in patients with NAFLD is an urgent matter.

Table 4 shows the incidence of HCC in NAFLD. Incidence of HCC in patients with NAFLD in several longitudinal follow-up studies ranged from 0 to 0.5%.

Kawamura et al. reported that the rate of HCC was

---

Table 2. Factors Promoting Various Complications in NAFLD

<table>
<thead>
<tr>
<th>Complication</th>
<th>Promoting Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2DM</td>
<td>prediabetes, aging, γ-GTP, lack of exercise</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>hypertension, smoking, dyslipidemia, elevated Hba1c</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>aging, hypertension, dyslipidemia, elevated Hba1c</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>aging, hypertension, APRI ≥ 1.5, dyslipidemia, elevated Hba1c</td>
</tr>
<tr>
<td>HCC</td>
<td>aging, APRI ≥ 1.5, diabetes</td>
</tr>
</tbody>
</table>

APRI, AST to platelet ratio index; HCC: hepatocellular carcinoma; T2DM, type 2 diabetes mellitus

Table 3. Incidence of Vascular Disease in NAFLD

<table>
<thead>
<tr>
<th>NAFLD or NASH</th>
<th>End-point</th>
<th>Author</th>
<th>Published year</th>
<th>No of subjects</th>
<th>Observation years (mean)</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD</td>
<td>CHD</td>
<td>Targler</td>
<td>2007</td>
<td>2103</td>
<td>6.5</td>
<td>HR 1.87*</td>
</tr>
<tr>
<td>NAFLD</td>
<td>CHD</td>
<td>Hamaguchi</td>
<td>2007</td>
<td>1637</td>
<td>5.8</td>
<td>HR 4.12*</td>
</tr>
<tr>
<td>NAFLD</td>
<td>CHD</td>
<td>Haring</td>
<td>2009</td>
<td>4160</td>
<td>7.3</td>
<td>HR Men 6.22*, women 0.98*</td>
</tr>
<tr>
<td>NAFLD</td>
<td>CHD, IS, HS</td>
<td>Ogawa</td>
<td>2012</td>
<td>1798</td>
<td>7.6</td>
<td>11.7%†</td>
</tr>
</tbody>
</table>

CHD, coronary heart disease; IS, Hemorrhagic stroke; HR, hazard ratio; IS, Ischemic stroke; NAFLD, Nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; *HR in NAFLD to individuals without NAFLDC, † Cumulative incidence of three vascular diseases

---

Kawamura et al. reported that the rate of HCC was
0.51%/12 years for all NAFLD. Overall, the development of HCC from NAFLD is rare. As most NAFLD comes under the non-NASH fatty liver (NNFL) type, the rate of HCC is likely to be low in NAFLD subjects. However, the incidence of NASH ranged from 0 to 2.8 % over a follow-up period of ≥10 years42,43. It has been reported that cirrhotic NAFLD produces a high rate of HCC and the studies of Ascha et al. and Kodama et al. also observed this to be the case, with yearly onset rates of 0.4–2.5%41,44,45.

Cox hazards analysis has shown that older age, higher serum γ-GTP, diabetes and advanced liver fibrosis are risk factors of HCC (Table 2). Of these factors, liver fibrosis was the most important one for development of HCC (Fig.6)41. The 5-year survival and recurrence rates for NAFLD-HCC were very similar to those for HCV-HCC.

Conclusions

In this review, we have described the state of our current knowledge regarding diagnosed complications of NAFLD. In the daily management of patients with
NAFLD, physicians should pay attention to evaluating its severity. In addition, it is important to assess the risk factors of various complications, such as T2DM, vascular disease and HCC.

Conflict of Interest
Yasuji Arase is a member of the speakers’ bureau of MSD K.K.

References


(Received February 4, 2014; Accepted February 14, 2014)
How to Detect Early Stage Rheumatoid Arthritis (RA) in Persons Undergoing Ningen Dock (Health Evaluation and Promotion)

Junichi Kaburaki¹, Masataka Kuwana²

Abstract
Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease. It is most frequently seen in rheumatic diseases. Recent advances in the treatment of RA can prevent bone/cartilage destruction and improve the prognosis of RA patients. In view of this situation, the concept of ‘T2T’, ‘Treatment to target’, has been established to administer appropriate treatment, such as that with methotrexate and newly developed biological agents, which will attain clinical remission as well as radiographic and functional remission. Such biological agents have direct effects against pro-inflammatory cytokines such as TNF-α and IL-6 in RA synovial tissues. Smoking is a risk factor for RA in association with genetic factors. Although morning stiffness is not specific to RA, joint swelling and/or tenderness reflects synovitis and is an important clinical feature. Pulmonary involvement should be investigated as an extra-articular manifestation. Laboratory examinations, which include acute-phase reactants such as CRP and erythrocyte sedimentation rate (ESR), evaluate disease activity. IgM RF is also tested as a diagnostic tool, although it is also detected in other diseases. Anti-citrullinated protein antibodies (ACPA) are a new marker for the diagnosis of RA and predict articular destruction. It is necessary to obtain a definite diagnosis through classification in order to start suitable treatment for RA patients in the early stage. As the previously published American College of Rheumatology (ACR) 1987 revised criteria were not useful for identifying RA patients in the early stage, the ACR and European League against Rheumatism (EULAR) proposed new criteria for the classification of RA in 2010.

Keywords rheumatoid arthritis, rheumatic disease, classification criteria, Ningen Dock

One of the aims of Ningen Dock (health evaluation and promotion) is to detect diseases in the early stage and carry out interventions for them. Lifestyle-related diseases including malignant neoplasms are an example of such diseases mentioned in the annual report of the Japan Society of Ningen Dock¹.

It has been reported that rheumatic diseases are more frequently found in primary care in Japan than was previously supposed³. The findings of this research suggest that rheumatic diseases should also be kept in mind in Ningen Dock. The prevalence rate of rheumatoid arthritis (RA), the most common rheumatic disease, ranges between 0.5% and 1.0%³–⁵. It is estimated that there are at least 700,000 patients with RA in Japan. RA tends to occur in women in their 40s and 50s who frequently visit Ningen Dock in clinics or hospitals.

RA is a chronic autoimmune inflammatory disease that causes joint swelling, tenderness, and bone and/or cartilage destruction, leading to functional disability, and reduces QOL in patients with it⁶–⁷. However, recent advances in treatment, for instance with methotrexate and newly developed biological agents, can prevent bone and/or cartilage destruction, and has improved the QOL and prognosis of patients with RA⁶–¹⁴. At the present time, the treatment goals for RA are considered to be not only clinical remission but also radiographic and functional remission¹⁵.

Criteria for the classification of RA have been recently updated. Revised criteria for the classification of RA proposed in 1987 by the American College of Rheumatology (ACR) are still in use in clinical practice¹⁶ but these criteria were established based on data for RA patients with long disease duration (7.7 ± 8.6 years). Also, they consist of 7 criteria but among them, morning stiffness is not specific for RA, rheumatoid nodules are hardly ever found, and radiographic changes such as erosions

¹ Department of Internal Medicine, Shinjuku Kenshin-plaza ; ²Department of Internal Medicine, Division of Rheumatology, Keio University School of Medicine
Contact : Junichi Kaburaki, Department of Internal Medicine, Shinjuku Kenshin-plaza, 2-31-12, Kabukicho, Shinjuku-ku 160-0021, Tokyo, Japan. Tel: +81–3–3209–0217 ; Fax: +81–3–3209–1753 ; E-mail: j-kaburaki@nikkenkyo.or.jp
are not visible on X-ray films during the early stage of RA. Although the ACR 1987 revised criteria are suitable for the classification of RA after a disease duration of 10 years from onset, their sensitivity is only 50% and 80% when patients have only had symptoms for 6 months and 1 year, respectively\(^{10,17,18}\). Therefore, the ACR 1987 revised criteria are not useful for identifying individuals with early stage RA from a clinical perspective. In view of this situation, the ACR and the European League against Rheumatism (EULAR) proposed new criteria for the classification of RA in 2010\(^{17,18}\) and we suppose they are now being used by physicians and rheumatologists.

Clinical symptoms such as joint swelling or tenderness are the first indication that people might have RA in Ningen Dock. CRP, a test included in the basic examination of Ningen Dock\(^{19}\), can predict the presence of arthritis. In addition, RF, which are sometimes tested, are useful in the classification of RA\(^{20–22}\). The above clinical symptoms and laboratory data are necessary for discriminating between patients with RA and other diseases in Ningen Dock. Physicians should also pay attention to chest X-ray findings and hematological tests to determine if extra-articular features of RA are present. If examinees are suspected to have RA, physicians will conduct further tests, such as anti-citrullinated protein antibodies (ACPA) and anti-nuclear antibodies (ANA), and then consult with rheumatologists regarding the findings. In this review, we focus on the pathophysiology as well as the clinical and the laboratory features of RA in order to determine how early stage RA may be detected in Ningen Dock. We also discuss the new 2010 ACR/EULAR criteria for the classification of RA.

**Pathophysiology**

Three major types of cell in the synovial tissues play major roles in patients with RA\(^{3,7,23}\). They are blood vessel cells, lymphocytes and synovial cells (Fig. 1). Briefly, these cells are activated and pro-inflammatory mediators are released through interactions among them. This triggers activation of T and B cells, further proliferation of synovial cells, increased expression of adhesion molecules on endothelial cells, formation of blood vessels, degradation of cartilage and cartilage matrix, and activation of osteoclasts. The essential factor in this process has been identified as enhanced release of pro-inflammatory cytokines such as TNF-\(\alpha\) and IL-6.

Newly developed biological agents used in the management of RA patients target TNF-\(\alpha\) or IL-6 receptors. For example, etanercept, a soluble TNF receptor, neutralizes TNF-\(\alpha\) as well as TNF-\(\beta\) and has been successful in treatment\(^{11,12}\), while tocilizumab, an anti-IL-6 receptor antibody, blocks the function of IL-6\(^{13}\). Another is abatacept, a therapeutic agent developed to modulate T cell co-stimulatory signals mediated by the CTLA-4/CD28 molecule on activated T cells and CD80/86 molecules in the antigen presenting cells (APC) pathway\(^{14}\).

**Clinical manifestations**

Major rheumatology-related symptoms seen in Ningen Dock examinees are morning stiffness and joint swelling and/or tenderness. Physicians should also ask them if they smoke or not because smoking is an important risk factor for RA\(^{24–26}\). Swollen and/or tender joints should be investigated in a physical examination.

---

**Fig. 1. Mechanism of Rheumatoid Arthritis (RA) Involving Synovial Tissue**

Blood vessels, lymphocytes such as T cells and B cells with the surface molecule CD20, as well as antigen presenting cells (APC) and synovial cells are activated and play important roles in synovial proliferation, resulting in pannus formation, as the main features of RA. One of the therapeutic targets is the T cell co-stimulatory signal that is mediated by the CTLA-4/CD80/86 pathway. Three components are active in this mechanism at the same time. Firstly, pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-\(\alpha\) and interleukin (IL)-6, are released and augment the degree of inflammation. Secondly, osteoclasts are activated and cause bone destruction. Thirdly, matrix metalloproteinase (MMP)-3 is secreted and damages cartilage.
Smoking

The risk of RA increases with the quantity of cigarettes smoked and the duration of cigarette use. There is a strong association between smoking and ACPA-positive and RF-positive tests in patients with RA. Although the genetic background of RA has been clarified, genetic variation in the human leucocyte antigen (HLA) may explain only 30% of the population’s genetic susceptibility to the disease. However, a more precise association involving alleles encoding a “shared epitope” on the HLA-DRB1 molecule has been found. Smokers who carry the shared epitope have a 1.5-fold enhanced risk of developing ACPA-positive RA over non-smokers who do not carry copies of this shared epitope. In addition, smokers who have two copies of the shared epitope have a 21-fold higher risk of developing RA than non-smokers who do not carry this shared epitope. The studies producing these findings suggest a gene-environment interaction in developing RA.

Morning stiffness

Morning stiffness, defined as stiffness in and around the joints, lasting at least 1 hour before maximal improvement in the morning, was included in the ACR 1987 revised criteria. However, morning stiffness is excluded in the 2010 ACR/EULAR criteria. Morning stiffness is not specific for RA, and joints with swelling or tenderness may be a more important indicator of synovitis. Proliferation of synovial cells is essential in RA. When their proliferation becomes out of control and the synovium grows thicker, a rheumatoid pannus is formed and becomes palpable between the patient’s skin and the underlying bone and cartilage. This condition is referred to as synovitis. However, heat and redness, the classical signs of inflammation, are usually absent.

Joints with swelling and/or tenderness

Subjects who complain of swollen or tender joint are diagnosed as having RA or other diseases. The distribution of joints with swelling or tenderness is important in the classification of RA and making a differential diagnosis. Although all joints are involved, small joints, which include metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, second through fifth metatarsophalangeal (MTP) joints, thumb interphalangeal (IP) joint and wrist joint, are vulnerable to inflammation in RA. The MCP and PIP joints are almost always involved in RA. Typically the index and long fingers are more affected than the others. On the other hand, distal interphalangeal (DIP) joints are rarely involved in RA, because they have less synovium than the MCP joints and PIP joints. When people complain of pain and/or swelling of the DIP joint(s), the most probable diagnosis is osteoarthritis.

Extra-articular manifestations

a) Rheumatoid nodules

Rheumatoid nodules are specific for RA and occur in 20% and 50% of RA patients, generally those in whom the disease is more severe. However, it is uncommon for...
rheumatoid nodules to be present within the first year from onset and therefore it would be rare for physicians in Ningen Dock to detect them.

b) Pulmonary involvement

Pulmonary involvement in RA is frequent, although it is not always clinically recognized\(^{29}\). However, it is important to determine whether there is pulmonary involvement or not as treatment with methotrexate or biological agents may have adverse effects such as interstitial pneumonitis or opportunistic infections\(^{1,29}\).

Rheumatoid interstitial pulmonary disease has been found in 20% of RA patients\(^{29}\), and it is more frequent in men than in women, for smokers positive for RF. The clinical presentations of pulmonary fibrosis in RA have been reported to be similar to those of idiopathic pulmonary fibrosis, but it is considered that the response to immunosuppressive therapy is better if pulmonary fibrosis occurs in the context of RA\(^{30}\).

### Laboratory data

Two main categories of laboratory examination are conducted for RA. One is acute-phase reactants\(^{29}\), including CRP\(^{31,32}\) and erythrocyte sedimentation rate (ESR)\(^{33}\), which evaluates disease activity, and the other is RF and ACPA which is useful in classification and predicting the prognosis. Both RF and ACPA are listed as serological tests in the newly proposed 2010 ACR/EULAR criteria\(^{17,18}\). ANA tests are usually conducted to exclude other rheumatic diseases when subjects are suspected to have RA.

#### C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)

CRP, which is tested in the basic Ningen Dock examination\(^{33}\), is produced by hepatic cells due to stimulation by pro-inflammatory cytokines such as TNF and IL-6\(^{34}\). Elevation of serum CRP is not specific for RA; it is indicative of various diseases, including infections, malignancy and myocardial infarction\(^{29,31,32}\). ESR indicates the quantity of serum fibrinogen, and it is elevated in anemia or hypergammaglobulinemia\(^{30,35}\). However, both CRP and ESR are referred to as acute-phase reactants and are useful in determining the presence and degree of articular inflammation in RA. CRP and ESR are listed as acute-phase reactants in the newly proposed 2010 ACR/EULAR criteria, and a test result for at least one of them is needed for the classification of RA\(^{17,18}\).

#### Rheumatoid factors (RF)

RF are a family of autoantibodies which recognize antigenic determinants on the Fc portion of immunoglobulin G (IgG)\(^{20-22}\). The major RF species is the immunoglobulin M (IgM) isotype, and the IgG-RF and immunoglobulin A (IgA)-RF isotypes occur less frequently\(^{34,35}\). Therefore, RF tests involve the IgM isotype, previously by the agglutination method and more recently by turbidometric techniques such as laser nephelometry and ELISA\(^{25}\). A transient increase in IgM-RF can be seen in the normal immunoregulation process, for example in bacterial or viral infections and thus a low-titer IgM-RF is found in 5% of healthy individuals, which has led to the setting of 15 IU/mL as the cutoff point for RF in Japan\(^{20}\). IgM-RF is positive in 80% of RA patients, although it is detected in sera in various diseases (Table 1)\(^{20,31}\). Therefore, people positive for IgM-RF are not always diagnosed as having RA. Therefore, other clinical manifestations and laboratory data should also be investigated. The sensitivity of IgM RF has been estimated to be 66% for established RA and 56% for early RA, and its specificity to be 78% for established RA and 89% for early RA\(^{36,37}\).

Ig-G-RF is positive in 30% of RA patients and it is associated with extra-articular manifestations such as vasculitis and destructive joints\(^{3,37,38}\).

#### Anti-citrullinated protein antibodies (ACPAs)

Antibodies to filaggrin were first reported in sera from RA patients\(^{39}\). They are autoantibodies that are directed at citrullinated proteins resulting from deamination of arginyl residues by the enzyme peptidyl arginine deiminase. Originally, epitopes were made to artificially form a cyclic structure including citrullinated proteins, and then the antibodies, which were named anti-cyclic citrullinated peptide (CCP) antibodies, were measured by ELISA\(^{37,40,41}\). At present, anti-CCP antibodies are called ACPAs, as the epitopes are citrullinated protein\(^{20,37}\).

Testing for ACPA uses commercially available ELISA kits and is covered by health insurance in Japan. The sera

<table>
<thead>
<tr>
<th>Disease</th>
<th>RF</th>
<th>ACPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>69–80%</td>
<td>76%</td>
</tr>
<tr>
<td>within 1.5 year from onset</td>
<td>59%</td>
<td>62%</td>
</tr>
<tr>
<td>more than 1.5 year from onset</td>
<td>76–80%</td>
<td>87%</td>
</tr>
<tr>
<td>Other rheumatic diseases</td>
<td>23%</td>
<td>8%</td>
</tr>
<tr>
<td>Chronic inflammatory diseases</td>
<td>24%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Other rheumatic diseases include systemic lupus erythematosus, systemic sclerosis and Sjögren’s syndrome. Chronic inflammatory diseases are chronic hepatitis, chronic pulmonary diseases and malignant diseases.
of 76% of RA patients are ACPA positive (Table 1)\(^{20,37}\). At 95%, the specificity of ACPA is higher than that of RF for RA in early and established stage, while the sensitivity of ACPA is for RA is 67%.

The clinical significance of ACPA consists of 2 aspects. Firstly, ACPA are a new serological marker for RA, and have been adopted as an item in the 2010 ACR/EULAR criteria\(^{37,18}\). ACPA are reportedly useful for the detection of RA before disease onset\(^{35,37,42,43}\). When patients with undifferentiated arthritis visited a hospital, 52% of those with RF were diagnosed as having RA during the follow up period, though 77% of patients with ACPA developed RA afterwards\(^{37}\). Also, it has been reported that when patients whose serum contained RF in Ningen Dock visited a clinic for further examinations, patients who were ACPA positive were diagnosed as having RA\(^{44}\). However, it should be kept in mind that ACPA are positive in other diseases too, especially other rheumatic diseases such as Sjögren’s syndrome and systemic lupus erythematosus and pulmonary tuberculosis\(^3\). Secondly, measurement of serum ACPA is useful for predicting the prognosis of RA patients because a high ACPA titer is associated with articular destruction\(^{36,47}\) and RA activity\(^{45}\), and suggests the necessity of methotrexate treatment\(^{46}\).

**Anti-nuclear antibodies (ANA)**

ANA are tested in the next step once people who visit Ningen Dock are suspected to have RA, and are covered by Japanese health insurance. This is because individual anti-nuclear antibodies are useful diagnostic markers for rheumatic diseases\(^{20,47,48}\). ANA are tested by immunofluorescent assay, and positive staining includes a homogenous pattern, peripheral pattern, speckled pattern, nucleolar pattern, discrete speckled pattern and cytoplasmic pattern. Individual anti-nuclear antibodies and anticytoplasmic antibodies are usually measured by ELISA in Japan. The ANA positive rate for RA sera ranges between 20% and 40%, and such patients usually have Sjögren’s syndrome\(^3\). The clinical significance of ANA is summarized in Table 2.

**Hematological abnormalities as extra-articular manifestation**

The degree of anemia is correlated with disease activity in RA, particularly the degree of articular inflammation\(^3\). It is commonly normocytic and normochromic. The cause of anemia in RA is multifactorial. It has been emphasized that iron utilization is impaired due to cytokine-induced upregulation of hepcidin, leading to abnormal retention of iron from senescent red blood cells by the reticuloendothelial system and increased lactoferrin, which contributes to the binding of iron and its decrease in the serum. In addition, proinflammatory cytokines, such as TNF and IL-6, act directly on red cell precursors in bone marrow, leading to anemia\(^{49}\). Therefore, anemia due to RA-related inflammation will improve when RA treatment is successful.

Thrombocytosis is frequently seen in the active stage of RA and the degree of thrombocytosis is correlated with the number of involved joints.

When patients with RA present leucopenia in combination with splenomegaly, they are diagnosed as having Felty syndrome\(^{40}\). However, this syndrome may be rare in Ningen Dock since Felty syndrome characteristically occurs in patients with long-standing, seropositive, nodular deforming RA.

**2010 ACR/EULAR criteria**

As mentioned in Introduction, the ACR 1987 revised criteria are well accepted as a benchmark for disease definition\(^{16}\) but they are not helpful in achieving the goal of identifying patients for early intervention\(^{10}\). It has been recently reported that joint destruction occurs within a few years from onset, going against the previous concept which was that the process was more gradual (Fig. 3)\(^{51,52}\). These observations indicate that adequate treatment is necessary in the early stage of RA. Therefore, the concept of “T2T”, that is, “Treatment to target” has been developed\(^{15}\). Disease activity should be evaluated at least every 3 months in the active stage of RA, and management, including methotrexate and biological agents, should be directed at long-term health-related QOL through control of symptoms, prevention of structural damage, normalization of function and social participation. In view of this situation, a joint working group between ACR and EULAR was formed to develop a new approach to the

### Table 2. Clinical Significance of Anti-nuclear Antibodies in Rheumatic Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antibodies(Ab)</th>
<th>Frequency</th>
<th>Associated clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>Anti-dsDNA Ab</td>
<td>50–70%</td>
<td>active stage of SLE, nephritis</td>
</tr>
<tr>
<td></td>
<td>Anti-Sm Ab</td>
<td>15–25%</td>
<td>late-onset nephritis</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>Anti-Scl-70 Ab</td>
<td>30%</td>
<td>diffuse scleroderma, pulmonary fibrosis</td>
</tr>
<tr>
<td></td>
<td>Anti-centromereAb</td>
<td>20–30%</td>
<td>limited scleroderma</td>
</tr>
<tr>
<td></td>
<td>Anti-RNA polymerase III Ab</td>
<td>10%&gt;</td>
<td>renal crisis</td>
</tr>
<tr>
<td>Polymyositis/Dermatomyositis</td>
<td>Anti-aminocyt 1 RNA synthetase Ab</td>
<td>20–30%</td>
<td>pulmonary interstitial disease</td>
</tr>
<tr>
<td>Mixed Connective Tissue Disease(MCTD)</td>
<td>Anti-U1-RNP Ab</td>
<td>100%</td>
<td>Raynaud’s phenomenon</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>Anti-SS • B(La) Ab</td>
<td>20–30%</td>
<td>annular erythema, neonatal lupus, mucosal dryness</td>
</tr>
<tr>
<td></td>
<td>Anti-SS • A(Ro)Ab</td>
<td>50–70%</td>
<td>mucosal dryness</td>
</tr>
</tbody>
</table>
Recent investigations have clarified that articular destruction occurs within a few years from onset in RA, although it was previously thought that destruction proceeded more gradually.

Table 3. The 2010 Rheumatoid arthritis classification criteria proposed by American College of Rheumatology (ACR) and European League against Rheumatism (EULAR)(from references 17 and 18)

<table>
<thead>
<tr>
<th>Score</th>
<th>Target population (Who should be tested?): Patients who</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1) have at least 1 joint with definite clinical synovitis (swelling)</td>
</tr>
<tr>
<td></td>
<td>2) with the synovitis not better explained by another disease</td>
</tr>
<tr>
<td></td>
<td>Classification criteria for RA (score-based algorithm: add score of categories A-D; a score of ≥ 6/10 is needed for classification of a patient as having definite RA)</td>
</tr>
</tbody>
</table>

A. Joint involvement

<table>
<thead>
<tr>
<th>Score</th>
<th>A large joint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1 large joint</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2 – 10 large joint</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1 – 3 small joints (with or without involvement of large joints)</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>4 – 10 small joints (with or without involvement of large joints)</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 joints (at least 1 small joint)</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

B. Serology (at least 1 test result is needed for classification)

<table>
<thead>
<tr>
<th>Score</th>
<th>Negative RF and negative ACPA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Low-positive RF or low-positive ACPA</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>High-positive RF or high-positive ACPA</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

C. Acute-phase reactants (at least 1 test result is needed for classification)

<table>
<thead>
<tr>
<th>Score</th>
<th>Normal CRP and normal ESR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Abnormal CRP or abnormal ESR</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

D. Duration of symptoms

<table>
<thead>
<tr>
<th>Score</th>
<th>&lt; 6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>≥ 6 weeks</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history of compatible with prior fulfillment of the 2010 criteria should be classified as having RA.

Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted. Although patients with a score of < 6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

Large joints refers to shoulders, elbows, hips, knees, and ankles.

Small joints refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).

Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤ 3 times the ULN for the laboratory and assay; high-positive refers to IU values that are > 3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA= anti-citrullinated protein antibody.

Normal/abnormal is determined by local laboratory standards. CRP= C-reactive protein; ESR= erythrocyte sedimentation rate.

Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.
classification of RA, especially with a view to providing a reference tool for primary care physicians. This resulted in the proposal of the 2010 ACR/EULAR criteria for the classification of RA (Table 3)\(^\text{17,18}\). It is recommended that classification of RA according to these criteria is done by a rheumatologist.

Joint involvement refers to any swollen or tender joint on examination; except DIP joints, first carpometacarpal joints, and first MTP joints. At least 1 of the involved joints must be a small joint. Each category has a score with the total ranging from 0 to 10. Patients with a score of 6 or over are classified as having RA. Additional evidence for the presence of synovitis can be obtained from imaging techniques such as ultrasonography\(^\text{33,34}\) or MRI\(^\text{55,56}\) to confirm the clinical findings. Ultrasonographic assessments are reported to be particularly useful for detecting RA in patients after Ningen Dock\(^\text{57}\).

The 2010 ACR/EULAR criteria state that the final diagnosis should be made by rheumatologists or physicians in clinical practice\(^\text{17,18}\). False positive results may be seen. In view of this, the Japan College of Rheumatology has proposed a list of diseases for differential diagnosis\(^\text{58}\). The investigation for this purpose was conducted on the Japanese population. Differential diagnoses are summarized in Table 4.

Physicians in Ningen Dock consider at least three categories for differential diagnoses of RA because the listed diseases include acute inflammation and patients with such diseases do not visit Ningen Dock. The three categories are osteoarthritis, fibromyalgia and other rheumatic diseases, including systemic lupus erythematosus (SLE), scleroderma and Sjögren’s syndrome.

Osteoarthritis is the most common articular disease, especially in people over 40 years old\(^\text{19}\). The main symptoms are swollen and/or tender joint(s). DIP joints are typically involved (Fig. 2), with slowly growing bony enlargement called “Heberden nodes”. There are often associated hard or soft tissue changes in the PIP joints, which are called “Bouchard nodes”. Deformity of the PIP joints is most commonly seen in the second and third fingers. Osteoarthritis occurs in the knee, leading to pain, particularly with obesity and when ascending or descending stairs, enlargement, swelling and finally valgus deformity. X-rays of osteoarthritis usually do not show erosions like in RA. It has been noted that women with menopause may present arthralgia similar to RA\(^\text{58}\).

Fibromyalgia is a central pain syndrome, and caused by several factors such as environmental stressors, neuroendocrine abnormalities and autoimmune mechanisms\(^\text{60}\). Patients with fibromyalgia complain of widespread pain. Musculoskeletal pain is the most prominent feature. The pain often waxes and wanes, and is frequently migratory in nature. Guidelines for fibromyalgia in clinical practice have been published in Japan.

Other rheumatic diseases are those with specific features and criteria. Arthritis is observed in patients with systemic lupus erythematosus but it is usually non-deforming\(^\text{61}\). Skin sclerosis is found in patients with systemic sclerosis\(^\text{62}\). Non-erosive arthritis is seen in patients with Sjögren’s syndrome, who have mucosal dryness such as xerophthalmia (keratoconjunctivitis sicca) and xerostomia\(^\text{63}\).

**Table 4. Representative Differential Diagnoses for Detecting Rheumatoid Arthritis in Patients**

<table>
<thead>
<tr>
<th>(1) Ningen Dock, health evaluation and promotion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Osteoarthritis</td>
</tr>
<tr>
<td>2) Fibromyalgia</td>
</tr>
<tr>
<td>3) Other rheumatic diseases: Systemic lupus erythematosus, Systemic sclerosis</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(2) Outpatient clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Viral infections; Parvovirus B19, Rubella, Human immunodeficiency virus (HIV), Hepatitis B, Chronic hepatitis C infection</td>
</tr>
<tr>
<td>2) Other rheumatic diseases; Polymyalgia rheumatica, Behçet’s syndrome, Vasculitis, Adult-onset Still’s disease, Palidromic rheumatism, RS3-PE syndrome</td>
</tr>
<tr>
<td>3) Psoriatic arthritis</td>
</tr>
<tr>
<td>4) Crystal-induced arthritis; Gout, Pseudogout</td>
</tr>
<tr>
<td>5) Tenosynovitis, Tendinitis</td>
</tr>
<tr>
<td>6) Seronegative spondyloarthropathies;</td>
</tr>
<tr>
<td>7) Systemic diseases; Sarcoidosis, Amyloidosis</td>
</tr>
<tr>
<td>8) Malignancies; Leukemia, Multiple myeloma, Pulmonary carcinoma, Thymoma</td>
</tr>
</tbody>
</table>

What physicians in Ningen Dock should pay attention to when adequately managed patients with RA in clinical remission come to Ningen Dock

When patients with definite RA, which is adequately managed and in clinical remission, visit Ningen Dock, physicians should pay attention to whether they have cardiovascular diseases and osteoporosis.

Recent advances in treatment, such as that using...
methotrexate and newly developed biological agents, have improved the prognosis of RA. While the frequencies of vasculitis and renal failure due to amyloidosis have recently decreased as causes of death in RA, infection, interstitial pulmonary disease and malignancy are currently the main causes of death for RA in Japan. Therefore, people in the general population who visit Ningen Dock should be carefully examined for them. Furthermore, it has recently been estimated that 40 to 60% of deaths in RA are due to cardiovascular disease in the United States and Europe. Also, it has been suggested that systemic inflammation is associated with RA and atherosclerosis. Peters, et al. reported that the risk of cardiovascular disease in RA is significantly elevated compared with the general population, and comparable with the magnitude of risk of type 2 diabetes mellitus in the Netherlands. They state that the age- and the sex-adjusted hazard ratio for RA is 1.94, compared with the general population. In addition, Rho, et al. have published an interesting article indicating that leptin is associated with increased insulin resistance, and that increasing the concentration of serum leptin attenuates the association between insulin resistance and coronary calcification in patients with RA. Therefore, physicians in Ningen Dock should pay attention to risk factors for atherosclerosis in patients with RA.

Osteoporosis is caused by aging as well as RA. Osteoporosis in RA is mainly due to inflammatory cytokines and prednisolone if it is used. The clinical outcomes of fractures due to osteoporosis include increased morbidity, increased risk for subsequent fracture and increased mortality. As management of osteoporosis can prevent fractures, physicians in Ningen Dock should recommend a bone mineral density test, when patients with RA have not had one as an additional or optional test.

Conclusion

“Treatment to target (T2T)”, the concept for the management of RA, has been recently developed. It is necessary to treat RA patients in the early stage to prevent articular destruction and subsequent deterioration in QOL. With this in mind, the 2010 ACR/EULAR criteria for the classification of RA have been proposed. In view of this situation, physicians in Ningen Dock should be aware of the recent advances in the field of RA that will help find patients in the early stage. It is recommended that Ningen Dock physicians conduct appropriate tests for RA and consult with rheumatologists regarding appropriate treatment.

Conflict of Interest

The authors declare no conflict of interest.

References


53. Taylor PC, Steuer A, Gruber J, et al: Ultrasonographic and radiographic results from a two-year controlled trial of immediate or one-year-delayed addition of infliximab to

(Received January 29, 2014; Accepted February 17, 2014)
Comparison of Serum Lipid Management According to Japan Atherosclerosis Society 2007 and 2012 Guidelines: Analysis of Data from Ningen Dock Database

Eiko Takahashi¹², Kengo Moriyama², Minoru Yamakado¹³

Abstract

Objective: The Japan Atherosclerosis Society (JAS) recommended that serum lipid management goals based on a coronary heart disease (CHD) risk factor classification be included in its 2007 guidelines (GL 2007) for the diagnosis and prevention of atherosclerotic cardiovascular disease in the Japanese population, which were revised in 2012 (GL 2012). Using the Japan Society of Ningen Dock database, we compared the distributions of the risk categories according to GL 2007 and GL 2012.

Methods: A total of 17,991 adults taking dyslipidemia medications were enrolled. The JAS GL 2007 and GL 2012 were used for evaluation. The guidelines have 2 different objectives (secondary prevention for subjects with a prior history of CHD and primary prevention for those with other CHD risk factors) and we compared the distributions of risk categories in a primary prevention group. Serum low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula.

Results: Of the patients in Category I according to GL 2007, 6.6% came under Category III according to GL 2012. Of the patients in Category II according to GL 2007, 37.1%, 38.5%, and 24.3% came under Categories I, II, and III according to GL 2012, respectively. Most subjects (81.1%) in Category III according to GL 2007 were still in the same category according to GL 2012, while 4.3% and 14.7% were in Categories I and II, respectively.

Conclusion: According to GL 2012, 43.7% of the primary prevention patients were assigned to categories different from those based on GL 2007.

Keyword dyslipidemia, guideline, management goal

Important risk factors for coronary heart disease (CHD) include hypercholesterolemia (total cholesterol [TC]: ≥220 mg/dL, low-density lipoprotein cholesterol [LDL-C]: ≥140 mg/dL), hypertension, advanced age (≥45 years in men; ≥55 years in women), diabetes mellitus type 2 and/or impaired glucose tolerance (IGT), smoking, a family history of CHD, decreased serum high-density lipoprotein cholesterol (HDL-C), obesity, a history of cerebral infarction (CI) or arteriosclerosis obliterans (ASO) and a history of CHD. Major epidemiologic studies have established a significant correlation between hypercholesterolemia and an increased risk of CHD¹² and this correlation is corroborated by the finding that lowering serum TC and LDL-C levels reduces CHD risk³⁴.

In the United States, the National Cholesterol Education Program (NCEP) was promulgated as a set of evidence-based guidelines in 1988⁵. Thereafter, the NCEP underwent 2 major revisions, in 1993⁶ and 2001⁷, and was partially revised in 2004⁸. The Japan Atherosclerosis Society (JAS) Guidelines for the Diagnosis and Treatment of Hyperlipidemia in Japanese Adults were published in 1997⁹. However, as the Japan Lipid Intervention Trial (J-LIT)¹⁰, which studied a cohort of more than 50,000 patients with hypercholesterolemia who had been prescribed lipid-lowering therapy for the primary prevention of CHD found that the risk of CHD is higher when mean TC and LDL-C levels are ≥240 and ≥160 mg/dL, respectively¹⁰,¹¹, the JAS revised the guidelines in 2002¹². The guidelines recommend that patients with a high risk of CHD be subjected to strict regimens to achieve serum lipid management goals (SLMGs).

Despite JAS recommendations, there is a lack of con-
sensus among physicians in Japan regarding the choice of first-line therapy in patients with hyperlipidemia. The JAS revised the Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Disease in Japanese Patients in 2007 and in them, LDL-C rather than TC is used to evaluate cholesterol levels in order to predict the risk of atherosclerotic disease. The JAS Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases were promulgated in 2012. A comparison of the 2012 and 2007 JAS Guidelines shows that the newer guidelines include “absolute risk” based on CHD risk evaluation charts and emphasize the importance of comprehensive management for atherosclerotic disease including chronic renal disease (CKD) as a high risk. There is also a specific mention of familial hypercholesterolemia in them and attention is drawn to the value of using non HDL-C in the evaluation of dyslipidemia.

The present study compared distributions of risk categories according to the 2007 and 2012 JAS guidelines.

Methods

Study design

This was a cross-sectional observational study that assessed the percentage of patients in each CHD risk category and achievement rates of SLMGs according to the JAS guidelines published in 2007 (GL 2007) and 2012 (GL 2012).

Study population

This multicenter retrospective study was conducted using data from persons undergoing annual health examinations at 21 Ningen Dock institutes located throughout Japan in 2009. From the total of 286,246 persons who underwent health examinations, data were analyzed for 17,991 subjects aged between 20 and 79 years who were taking medications for dyslipidemia.

The study complied with the ethics regulations outlined in the Declaration of Helsinki. Anonymized health records were used for the analysis, and the privacy of the participants was completely protected. It was approved by the Ethics Committee of the Japan Society of Ningen Dock.

CHD risk categories

Subjects were assigned a CHD risk category on the basis of GL 2007 and GL 2012. They were further divided into 2 groups: those who had not developed CHD (primary prevention) and those with a history of CHD (secondary prevention). For secondary prevention, an intensive LDL-C lowering goal (<100 mg/dL) was proposed. For primary prevention, in order to prevent CHD, subjects were categorized into low-, intermediate-, and high-risk groups (Categories I, II, and III, respectively). For Category I, which included patients with no major coronary risk factors, the LDL-C level management goal was <160 mg/dL and those for Category II and III patients were <140 and <120 mg/dL, respectively.

In GL 2007, patients are categorized into the 3 groups depending on the number of major coronary risk factors other than LDL-C. The ones that have been confirmed to date are advanced age (≥45 years in men; ≥55 years in women), hypertension (under medication or blood pressure ≥140/90 mmHg), diabetes mellitus (including impaired glucose tolerance [under medication or fasting plasma glucose ≥110 mg/dL]), smoking, family history of CHD, and low HDL-C (<40 mg/dL). In classifying diabetic patients as Category III, greater weight is given to diabetes than other risk factors. Patients with CI or ASO are classified as Category III because they already have atherosclerotic lesion in arteries other than the coronary artery.

In GL 2012, patients are categorized into 3 groups depending on the ten-year CHD death probability (absolute risk of CHD death) according to the following risk factors: sex, age, smoking status, systolic blood pressure, and TC. Patient with diabetes mellitus, CI, peripheral arterial disease (PAD), or CKD are classified as Category III. Additional coronary risk factors are impaired glucose tolerance (fasting plasma glucose ≥110 mg/dL), family history of CHD, and low HDL-C (<40 mg/dL).

In this study, anthropometric measurements and blood samples were obtained after overnight fasting. Serum LDL-C levels were calculated using the Friedewald formula: LDL-C = TC − HDL-C − TG/5. ASO, PAD, and family history of CHD were not evaluated.

Results

Table 1 shows subject characteristics. Mean age, TC, LDL-C and HDL-C were significantly higher in women than in men (p<0.01).

Table 2 shows the distribution of LDL-C levels. More than half of the subjects had LDL-C levels <120 mg/dL. Overall, 23.1% of them (22.1% for men and 24.9% for women) had borderline LDL-C levels (120 to 139 mg/dL). The distribution of LDL-C levels was very similar in men and women.

Table 3 shows the prevalence of CHD risk factors. In the secondary prevention group, 9.8% of subjects had a history of CHD, while 19.1%, 15.9%, and 3.4% had diabetes, CKD, and a history of CI, respectively. Advanced age (≥45 years in men and ≥55 years in women) was the most frequently observed CHD risk factor (87.3%), followed by hypertension (50.6%). Overall, men possessed a greater proportion of the CHD risk factors than women.

Fig.1 shows a flow chart for coronary heart disease risk category assignment according to the JAS guidelines published in 2007 and 2012. The new guidelines...
include "absolute risk" based on CHD risk evaluation charts and emphasize the importance of comprehensive management for atherosclerotic disease including CKD as a high risk.

Fig. 2 shows distributions of subjects with respect to the CHD risk categories in the 2 guidelines. More patients were assigned to Categories I and III according to GL 2012 than to GL 2007. However, fewer patients were classified as Category II according to GL 2012 than to GL 2007. The percentages of patients in the secondary prevention group were the same for both guidelines.

Table 2 compares the percentages of patients and SLMG achievement rates for CHD risk categories in the primary prevention group according to GL 2007 and GL 2012. Most subjects (93.4%) in Category I according to GL 2007 were still in the same category according to GL 2012. However, 6.6% of patients in Category I according to GL 2007 were in Category III according to GL 2012. Of the patients in Category II according to GL 2012.
GL 2007, 37.1%, 38.5%, and 24.3% were assigned to Categories I, II, and III according to GL 2012, respectively. Most subjects (81.1%) in Category III according to GL 2007 were in the same category according to GL 2012, while 4.3% and 14.7% were in Categories I and II, respectively. Overall, 43.7% of subjects were assigned to different categories according to GL 2012.

CKD patients in Category I according to GL 2007 were in Category III according to GL 2012 (SLMG achievement rate = 53.1%). Among the patients in Category II according to the GL 2007, 24.3% were classified as Category III according to GL 2012 (SLMG achievement rate = 52.0%).

Fig. 1 Flow Chart for Coronary Heart Disease Risk Category Assignment according to GL 2007 and GL 2012

Fig. 2 Distributions of Subjects according to Respective Coronary Heart Disease Risk Categories
The rates of achieving LDL-C lowering goals are unsatisfactory. In our previous study\textsuperscript{17}, which analyzed 17,991 patients taking dyslipidemia medications, the LDL-C goals were achieved in 75.4% of patients in the primary prevention group (89.5% in Category I, 81.1% in Category II, 62.9% in Category III), and 44.5% of the patients in the secondary prevention group according to the JAS 2007 guidelines. The DYSIS (Dyslipidemia International Study), which evaluated 19,196 consecutive patients in Europe and Canada treated for dyslipidemia, found that LDL-C targets were not achieved by 43.3% of those in the highest-risk category, 35.7% of those with 2 or more risk factors, and 16.7% of those with no or only 1 risk factor\textsuperscript{18}, according to NCEP ATP III\textsuperscript{7}. Although the LDL-C goals recommended in GL 2002\textsuperscript{12} and GL 2007\textsuperscript{13} published by JAS are comparable to those outlined in the NCEP ATP III\textsuperscript{7}, the JAS guidelines provide more detailed risk categories based on lipid levels. The NCEP ATP III recommends LDL-C-lowering therapy for the primary prevention of CHD and a CHD risk classification that includes just 2 categories: 0–1 coronary risk factor (low to moderate) and ≥2 coronary risk factors (high).

The proportion of subjects classified as Category I according to the GL 2007 was 5.4%, but this increased to 26.4% according to GL 2012, which indicates that a substantial number of subjects had lowered management goals according to GL 2012. On the other hand, 30.8% of subjects were classified as Category III according to GL 2007 and this increased to 38.4% according to GL 2012. Approximately 15% (2428/16221) of subjects in the primary prevention group had decreased management goals. Therefore, the percentage of subjects who achieved management goals remained high for subjects who were classified as a lower category according to GL 2012 (i.e., management goals for LDL-C increased). Furthermore, subjects who were classified as a higher category according to GL 2012 (i.e., their management goals for LDL-C decreased) require careful attention to improve their achievement rates.

### Discussion

The results of this study on Japanese patients who were prescribed lipid-lowering therapy for CHD prevention according to the JAS recommendations in GL 2007 and GL 2012 indicated considerable changes in the distributions of subjects in each category. Overall, 43.7% (7,081/16,221) of patients in the primary prevention group were classified as different categories under the latter.

### Acknowledgment

We thank all those at the institutes who kindly provided the data for individuals receiving annual health examinations used in this pilot study.

The authors have no conflicts of interest to declare.

### References


(Received February 20, 2013; Accepted March 19, 2013)
Bone Turnover Markers and Risk Factors Associated with Osteoporosis and Decreased Bone Mass

Tomoko Shiga¹, Yuriko Moriyoshi¹, Hikaru Nagahara²

Abstract

Objective: The first aim of this study was to identify risk factors associated with osteoporosis and decreased bone mass in the general Japanese population. The second was to elucidate the relationship between bone mineral density and bone turnover markers.

Materials and Methods: We analyzed bone mineral density (BMD) and bone turnover markers - such as bone-specific alkaline phosphatase (BAP), urinary deoxypyridinoline (DPD) and N-terminal crosslinking telopeptide of type I collagen (NTX) - in 238 subjects who visited the Department of General Medicine, National Center for Global Health and Medicine from March 2005 through March 2007 for a Ningen Dock-style annual health check-up. Risk factors associated with osteoporosis and decreased bone mass were evaluated using multivariate logistic regression analysis, and the differences in BMD and bone turnover markers were examined between subjects with and without osteoporosis.

Results: Factors associated with osteoporosis were age, gender (female) and low BMI, and specifically in female subjects menopause, high serum level of total cholesterol and large alcohol intake \((p<0.05)\). BMD was strongly correlated with bone turnover markers. (NTX: \(R=–0.44, p<0.0001\), DPD: \(R=–0.42, p<0.0001\)).

Conclusion: Bone turnover markers were useful for estimating BMD. High serum level of total cholesterol and large alcohol intake were risk factors for osteoporosis.

Keywords: Ningen Dock, osteoporosis, bone turnover marker

Osteoporosis, a result of abnormal mineral metabolism, is one of the most common disorders in elderly people, and bone fractures caused by osteoporosis are a major public health problem. Patients with osteoporosis have no symptoms until they suffer a bone fracture, which will decrease their quality of life. Hence, prevention of osteoporosis is of great importance in maintaining the quality of life of elderly people and reducing medical expenditure on the treatment of fractures. In this study, we evaluated several risk factors associated with osteoporosis in order to develop an approach towards preventing bone fractures.

A number of experimental and clinical studies have demonstrated that markers of bone metabolism can be used to investigate skeletal remodeling under normal and abnormal conditions. Biochemical markers associated with bone metabolism have been employed as non-invasive and comparatively inexpensive tools for the diagnostic work-up and management of metabolic bone disease, such as postmenopausal osteoporosis. The markers presently used include osteoblast- and osteoclast-derived enzymes as well as structural peptides, precursors or fragments derived from the various compartments of the bone matrix. These components are usually categorized into 2 types of markers; one is related to bone formation and the other represents bone resorption for clinical and didactic purposes. In this study, we analyzed relationships between BMD and bone turnover markers to determine which markers are useful for predicting bone mass reduction.

BAP is a marker that represents bone formation because it is derived from osteoblasts. BAP is produced by osteoblasts at a relatively immature stage of differentiation and triggers calcification of bone tissue through the provision of phosphoric acid. BAP serum levels are not influenced by liver or kidney function. DPD and NTX are markers of bone resorption. Eighty five to 90% of bone matrix consists of type I collagen, in which DPD is incorporated abundantly. DPD is a cross-linker between type I collagen and telopeptides and is formed during extracellular maturation of fibrillar collagen and released during the dissociation

¹ Department of General Medicine, National Center for Global Health and Medicine; ² Aoyama Hospital, Tokyo Women’s Medical University

Contact: Tomoko Shiga, Department of General Medicine, National Center for Global Health and Medicine, 1–21–1 Toyama Shinjuku-ku, Tokyo 162–8655, Japan. Tel: +81–3–3202–7181; Fax: +81–3–3202–8007; E-mail: toshiga@hosp.ncgm.go.jp
process of mature collagen. DPD is present at high concentration in mature bone collagen, but is absent from cartilage and skin and thus it is a specific marker for bone tissue. DPD in serum is normally excreted into the urine with as much as 40% in the free form because of its low molecular weight (429–591 Dalton). Owing to this, serum levels of DPD are extremely low and undetectable in normal individuals. DPD concentrations are therefore estimated in urine.

NTX, a peptide derived from bone type I collagen degraded during bone resorption, is released into the circulation and excreted into urine. Both urinary and serum levels of NTX are measurable, and the urinary level can be corrected according to the patient’s renal function.

Subjects and methods
Study population
Two hundred thirty eight subjects (90 men aged 61.5 ±13.1 years and 148 women aged 58.2±12.6 years) who visited Department of General Medicine, National Center for Global Health and Medicine (Tokyo, Japan) from March 2005 through March 2007 for a Ningen Dock-style annual health check-up were analyzed. The individual’s BMD and bone turnover markers, such as BAP, DPD, NTX, were examined. We excluded subjects who were being treated for osteoporosis and/or with steroidal medicines, and those with bone metastasis of malignancies as well as subjects who had undergone gynecological operations, those with renal dysfunction, hyperthyroidism, and infection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV). Informed consent was obtained from all subjects.

Measurement of bone mineral density
BMD was measured at the L1–L4 level of the lumbar spine by dual energy X-ray absorptiometry (DXA) using a QDR-4500 bone densitometer (Hologic Inc. NY, USA). BMD was automatically calculated by dividing bone mineral content (BMC) (g) by bone area (cm²), expressing it in g/cm².

Definition of Osteoporosis and bone loss
In this study, osteoporosis and decreased bone mass were defined according to the Japanese diagnostic criteria: osteoporosis as BMD less than 70% of that of young adult mean (YAM) (age, 20–44 years) and decreased bone mass as 70%≤BMD<80% of YAM. The normal range is 80% of YAM or higher.

Bone turnover markers
We adopted serum BAP as a marker of bone formation and DPD and NTX as markers of bone resorption. These and other bone turnover markers are influenced by gender, aging and menopause as well as circadian rhythm; their serum levels are high in the morning and low in the afternoon for the most part. The measurement of bone turnover markers and determination of normal limits in urine are conducted on fasting samples obtained in the morning and venous blood samples for measurement are also collected in the morning under fasting conditions.

Serum BAP levels were measured by chemiluminescent enzyme immunoassay (CLEIA) while urinary DPD and NTX levels were measured by enzyme immunoassay (EIA) using first or second void morning urine samples, and corrected for serum creatinine levels.

Definition of risk factors
The Ningen Dock-style annual health check-up includes the following: physical characteristics (height, body weight and waist circumference), complete blood count, blood biochemistry, urinalysis, electrocardiogram, abdominal ultrasonography, chest radiography, barium meal examination of the upper gastrointestinal tract or upper gastrointestinal endoscopy, visual acuity test, tonometry, fundic examination (retinal photography) and hearing ability. Medical histories and information on alcohol consumption- and tobacco consumption-related lifestyle factors are obtained in a personal interview with a physician.

We defined the potential risk factors as follows: alcohol overuse (over 20 g of ethanol per day); smoking (Brinkman Index (B.I.) >200, number of cigarettes smoked per day multiplied by number of years of smoking); hypertension (systolic blood pressure≥130 mmHg, diastolic blood pressure≥85 mmHg), and/or presence of antihypertensive drug treatment; low BMI (body mass index (BMI) <18.5 kg/m²), calculated using weight in kilograms divided by the square of the subject’s height in meters); high levels of total cholesterol (total cholesterol≥220 mg/dL, and/or presence of drug treatment for lipid abnormalities); high levels of LDL cholesterol (LDL cholesterol≥140 mg/dL and/or presence of drug treatment for hyperlipidemia); low levels of HDL cholesterol (HDL cholesterol<40 mg/dL and/or presence of drug treatment for hyperlipidemia) and/or presence of drug treatment for dyslipidemia); abnormal lipid metabolism (total cholesterol<220 mg/dL, low density lipoprotein cholesterol (LDL-C)<140 mg/dL, high density lipoprotein cholesterol (HDL-C)<40 mg/dL, triglyceride (TG)<150 mg/dL, and/or presence of drug treatment); glucose intolerance (fasting plasma glucose (FPG)<110 mg/dL, and/or presence of drug treatment for diabetes mellitus (DM)); hyperuricemia (uric acid>7 mg/dL, and/or presence of drug treatment for hyperuricemia).

Statistical analysis
Statistical analysis was performed using computer software (IBM SPSS Statistics, version 19.0 IBM corporation, New York, USA). Continuous variables were expressed as means ± SD for each subject group. Statis-
tical differences were determined by the two-sided Student’s t-test (for equal variance cases) or Welch’s t-test (for non-equal variance cases). Non-normally distributed variables were compared by the Mann-Whitney U test. Variables given as proportions were compared using the chi-square test. Variables given as proportions were compared using the chi-square test. Relationships between osteoporosis and risk factors were examined by multivariate logistic regression analysis. To analyze relationships between BMD and bone turnover markers, we created scattering profiles by separately plotting BMD data against those for individual bone turnover markers (BAP, DPD, NTX). A p-value <0.05 was taken to be statistically significant.

This study was approved by the Ethics Committee of National Center for Global Health and Medicine (Approval No. NCGM-G-001188-00).

Results
Prevalence of osteoporosis and decreased bone mass
Of the 238 subjects, osteoporosis or decreased bone mass was detected in 35 (14.7%) and 30 (12.6%), respectively. The age- and sex-specific prevalences of osteoporosis and decreased bone mass are listed in Table 1. An increasing prevalence of osteoporosis with age was evident in female subjects (p<0.05), but not in male subjects.

Clinical characteristics and risk factors associated with osteoporosis and decreased bone mass
We first investigated the clinical characteristics and risk factors associated with osteoporosis or decreased bone mass. Table 2 shows there were more females than males with osteoporosis or decreased bone mass. Also, age and total cholesterol and HDL cholesterol levels were significantly higher in these subjects than in normal subjects. In contrast, waist circumference was significantly smaller and BMI and triglyceride, FPG and uric acid levels significantly lower in the former than the latter.

To investigate which risk factors were significantly related to osteoporosis and decreased bone mass, we performed contingency table analysis between the subjects with and without osteoporosis or decreased bone mass using multivariate logistic regression analysis (Table 3). Female gender (OR=4.45, p=0.005) and low BMI (OR=13.58, p<0.0001) and age (OR=1.09, p<0.0001) were statistically significant risk factors for osteoporosis and decreased bone mass.

Next we investigated risk factors specific for females. Table 4 shows the clinical characteristics of subjects

Table 1. Prevalence of Decreased Bone Mass and Osteoporosis

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Decreased bone mass</td>
</tr>
<tr>
<td>Age (&lt;50)</td>
<td>15 83.3%</td>
<td>0 0.0%</td>
</tr>
<tr>
<td>50–59</td>
<td>15 83.3%</td>
<td>3 16.7%</td>
</tr>
<tr>
<td>60–69</td>
<td>26 89.7%</td>
<td>2 6.9%</td>
</tr>
<tr>
<td>70+</td>
<td>24 96.0%</td>
<td>0 0.0%</td>
</tr>
</tbody>
</table>

Table 2. Clinical Characteristics and Laboratory Data of Study Subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Subjects with osteoporosis and decreased bone mass</th>
<th>Subjects without osteoporosis and decreased bone mass</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63.29±10.31(65)</td>
<td>58.01±13.46(173)</td>
<td>0.002</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>(10/55)</td>
<td>(80/93)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>118.80±14.61(65)</td>
<td>120.84±18.23(173)</td>
<td>0.373</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75.22±10.12(65)</td>
<td>76.95±10.92(173)</td>
<td>0.265</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>223.65±45.80(65)</td>
<td>209.90±38.74(173)</td>
<td>0.021</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>130.69±38.65(65)</td>
<td>132.33±110.82(173)</td>
<td>0.907</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>70.88±16.35(65)</td>
<td>61.79±15.24(173)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>107.69±51.90(65)</td>
<td>131.89±88.57(173)</td>
<td>0.01</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>94.08±9.32(65)</td>
<td>102.62±25.20(173)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>4.90±0.98(65)</td>
<td>5.40±1.51(173)</td>
<td>0.004</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>23.83±11.83(65)</td>
<td>23.47±7.99(173)</td>
<td>0.79</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>20.91±9.06(65)</td>
<td>23.14±12.13(173)</td>
<td>0.127</td>
</tr>
<tr>
<td>γ-GTP (U/L)</td>
<td>39.66±109.15(65)</td>
<td>42.64±62.28(173)</td>
<td>0.793</td>
</tr>
<tr>
<td>hsCRP</td>
<td>0.69±0.09(65)</td>
<td>0.12±0.31(173)</td>
<td>0.173</td>
</tr>
<tr>
<td>Body Mass Index (kg/m^2)</td>
<td>21.11±3.05(65)</td>
<td>23.13±3.24(173)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>80.41±9.01(65)</td>
<td>84.56±9.55(173)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Results are shown as mean ± standard deviation (SD).
with and without osteoporosis. Only the proportion of post-menopausal women was significantly higher in subjects with osteoporosis than in those without it.

We then performed another contingency table analysis between subjects with and without osteoporosis using multivariate logistic regression analysis with osteoporosis as a dependent variable and the following 15 explanatory variables: menopause, low BMI, hypertension, high level of total cholesterol, high level of LDL cholesterol, low level of HDL cholesterol, hypertriglyceridemia, glucose intolerance, hyperuricemia, AST >33U/L, ALT >42 U/L in males or ALT >27 U/L in females, hsCRP >0.145, alcohol overuse, tobacco and past history of bone fracture. Menopause (OR=6.89, p=0.016), high level of total cholesterol (OR=5.04, p=0.028) and alcohol overuse (OR=5.04, p=0.041) were statistically significant risk factors for osteoporosis among female subjects (Table 5).

**Relationships between bone mineral density and bone turnover markers**

We assessed relationships between BMD and bone turnover markers (BAP, DPD, NTX) among both male and female subjects. We found that BMD was inversely correlated with NTX (R=-0.44, p<0.0001) and DPD

---

**Table 3. Results of Multivariate Logistic Analysis of Risk Factors for Decreased Bone Mass and Osteoporosis**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Subjects with osteoporosis and decreased bone mass (n=63)</th>
<th>Subjects without osteoporosis and decreased bone mass (n=170)</th>
<th>Adjusted Odds ratio (OR)</th>
<th>95% confidence interval (CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (15.9)</td>
<td>80 (47.1)</td>
<td>0.23</td>
<td>0.08 – 0.63</td>
<td>0.005</td>
</tr>
<tr>
<td>Female</td>
<td>53 (84.1)</td>
<td>90 (52.9)</td>
<td>4.45</td>
<td>1.59 – 12.45</td>
<td>0.005</td>
</tr>
<tr>
<td>Low BMI</td>
<td>13 (20.6)</td>
<td>5 (2.9)</td>
<td>13.58</td>
<td>3.47 – 53.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (31.7)</td>
<td>67 (39.4)</td>
<td>0.85</td>
<td>0.38 – 1.92</td>
<td>0.702</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>36 (57.1)</td>
<td>92 (54.1)</td>
<td>0.78</td>
<td>0.37 – 1.63</td>
<td>0.501</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>4 (6.3)</td>
<td>37 (21.8)</td>
<td>0.30</td>
<td>0.09 – 1.05</td>
<td>0.660</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>2 (3.2)</td>
<td>29 (17.1)</td>
<td>0.19</td>
<td>0.04 – 1.04</td>
<td>0.555</td>
</tr>
<tr>
<td>AST &gt;33U/L</td>
<td>5 (7.9)</td>
<td>14 (8.2)</td>
<td>0.95</td>
<td>0.20 – 4.53</td>
<td>0.945</td>
</tr>
<tr>
<td>ALT &gt;42 U/L in males or ALT &gt;27 U/L in females</td>
<td>8 (12.7)</td>
<td>22 (12.9)</td>
<td>1.11</td>
<td>0.30 – 4.12</td>
<td>0.875</td>
</tr>
<tr>
<td>y-GTP &gt;47 U/L</td>
<td>7 (11.1)</td>
<td>37 (21.8)</td>
<td>0.82</td>
<td>0.23 – 2.93</td>
<td>0.755</td>
</tr>
<tr>
<td>hsCRP &gt;0.145</td>
<td>9 (14.3)</td>
<td>34 (20.0)</td>
<td>0.74</td>
<td>0.27 – 2.06</td>
<td>0.568</td>
</tr>
<tr>
<td>Alcohol overuse</td>
<td>8 (12.7)</td>
<td>40 (23.5)</td>
<td>1.22</td>
<td>0.41 – 3.65</td>
<td>0.727</td>
</tr>
<tr>
<td>Tobacco</td>
<td>16 (25.4)</td>
<td>77 (45.3)</td>
<td>0.66</td>
<td>0.27 – 1.57</td>
<td>0.342</td>
</tr>
<tr>
<td>Past history of bone fracture</td>
<td>8 (12.7)</td>
<td>11 (6.5)</td>
<td>0.76</td>
<td>0.23 – 2.56</td>
<td>0.662</td>
</tr>
</tbody>
</table>

**Table 4. Clinical Characteristics and Laboratory Data of Female Subjects with or without Osteoporosis**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Female subjects with osteoporosis</th>
<th>Female subjects without osteoporosis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.70±11.82 (30)</td>
<td>57.32±12.73 (118)</td>
<td>0.090</td>
</tr>
<tr>
<td>Menopause</td>
<td>(26/29)</td>
<td>(79/114)</td>
<td>0.033</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>117.53±14.73 (30)</td>
<td>115.51±16.48 (118)</td>
<td>0.541</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75.20±10.89 (30)</td>
<td>72.99±8.74 (118)</td>
<td>0.243</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>223.40±39.79 (30)</td>
<td>218.69±45.84 (118)</td>
<td>0.607</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>129.47±42.22 (30)</td>
<td>139.56±132.32 (118)</td>
<td>0.681</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>70.13±14.48 (30)</td>
<td>70.38±14.55 (118)</td>
<td>0.934</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>97.47±47.12 (30)</td>
<td>104.80±49.44 (118)</td>
<td>0.465</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>92.50±10.98 (30)</td>
<td>97.47±23.13 (118)</td>
<td>0.255</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>4.87±1.04 (30)</td>
<td>4.67±1.17 (118)</td>
<td>0.412</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>21.83±5.34 (30)</td>
<td>22.53±7.39 (118)</td>
<td>0.627</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>21.20±9.29 (30)</td>
<td>19.69±9.29 (118)</td>
<td>0.427</td>
</tr>
<tr>
<td>hsCRP</td>
<td>0.07±0.10 (30)</td>
<td>0.11±0.35 (118)</td>
<td>0.565</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>21.62±3.56 (30)</td>
<td>22.05±3.04 (118)</td>
<td>0.510</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>81.76±11.35 (30)</td>
<td>81.55±8.81 (118)</td>
<td>0.913</td>
</tr>
<tr>
<td>Alcohol overuse</td>
<td>(5/30)</td>
<td>(12/118)</td>
<td>0.340</td>
</tr>
<tr>
<td>Tobacco</td>
<td>(6/30)</td>
<td>(30/118)</td>
<td>0.638</td>
</tr>
<tr>
<td>Past history of bone fracture</td>
<td>(4/29)</td>
<td>(12/114)</td>
<td>0.741</td>
</tr>
</tbody>
</table>

Results are shown as mean ± standard deviation (SD).
and negatively correlated with BAP ($R = -0.30, p < 0.0001$) (Fig. 1).

**Discussion**

Osteoporosis is a disease characterized by low mineral density and an altered bone microstructure, which cause bone fragility. It is generally classified as the primary or secondary type\textsuperscript{19}. Risk factors conventionally identified for osteoporosis are advancing age, smoking, alcohol intake, low body weight, physical inactivity, low calcium intake, low vitamin D and estrogen status\textsuperscript{23}.

Osteoporosis most commonly affects postmenopausal women, increasing the risk of bone fractures. According to a study in the United States (U.S.), during the period 2005–2006, 4.5 million women aged >50 years (equal to 10% population of >50 years) had osteoporosis, and another 22.7 million (49%) had osteopenia based on femur neck bone mineral density (BMD) tests. There were 0.8 million men aged >50 years (0.3%) with osteoporosis, and another 11.8 million (30%) had osteopenia\textsuperscript{24}. In Japan, 30% of women in their seventies suffer from osteoporosis.

In the present study, the prevalences of osteoporosis and decreased bone mass also increased with age in female, but not in male subjects (Table 1). Hence, menopause is a risk factor for osteoporosis with a mechanism...
involving a lack of estrogen. However, the exact mechanism of the action of estrogen on bone remains unclear. Estrogen may stimulate synthesis of insulin-like growth factor I (IGF-I) and transforming growth factor-β (TGF-β) in osteoblasts but inhibit production of interleukin 1 (IL-1) and tumor necrosis factor-α (TNF-α) in monocytes. Thus in response to estrogen deficiency there could be great changes in the levels of these cytokines and this might account for the more rapid bone loss in post-menopausal women.

We found that BMI was another risk factor for osteoporosis and decreased bone mass. A low BMI was correlated with osteoporosis and decreased bone mass with a high OR and low p-value (OR=13.58, p<0.0001, Table 3) among male and female subjects. The association between a low body weight and osteoporosis has usually been explained on the basis of small constitutional size in women, i.e. it is assumed that small women have small bones and also less reserve bone mass, which may serve to postpone the onset of osteoporosis. Body weight is considered an important predictor of bone mineral density, and it has been observed that a low body weight raises the relative risk of fracture. Body weight acts as a stimulus for bone formation and helps sustain bone mass.

We also observed that hypercholesterolemia and alcohol overuse were risk factors for osteoporosis in women (Table 5). Osteoporosis has been shown to be strongly correlated with arteriosclerotic vascular diseases, and it has been suggested that hyperlipidemia is a common pathogenic factor for arteriosclerosis. In this regard, in vitro studies have shown that LDL oxidation products had the ability to inhibit osteoblast differentiation and promote adipocyte differentiation, suggesting that these products could be harmful to both the vessel wall and bone structure. In vivo studies have found that hyperlipidemia reduced bone density via increased osteoclastic bone resorption in mice. However, little is known about a relationship between osteoporosis and hyperlipidemia from clinical studies. Some researchers have reported that hyperlipidemia reduced bone mineral density, while others found no relationship between serum lipid levels and bone mineral density.

Alcohol has definite direct effects on bone and mineral metabolism by suppressing osteoblast function, leading to diminished bone formation and defective mineralization. Heavy drinkers may have poor nutrition with respect to calcium, vitamin D (due to liver dysfunction), or protein, causing bone loss. In contrast, the effects of moderate alcohol intake are not deleterious to skeletal health. There is a threshold effect: no increase in osteoporotic or hip fracture risk was found in individuals who took 2 units (16 g of ethanol) or less per day of alcohol, whereas a significant risk was noted if people exceeded this threshold. In the present study, subjects with alcohol overuse were at high risk for osteoporosis (Table 5).

Urinary NTX levels are useful for determining whether individuals have normal or low bone density at the hip and we observed a statistically significant relationship between bone mineral density and bone turnover markers. (NTX: R = -0.44, p<0.0001, DPD: R = -0.42, p<0.0001). Thus bone turnover markers would be useful for estimating bone loss and determining the necessity of osteoporosis treatment. Yoshimura et al. also reported that bone resorption markers, especially DPD, were useful in predicting the risk of osteoporosis and vertebral fractures.

Summing up, risk factors for osteoporosis were age, gender (female) and low BMI, and specifically in female subjects menopause, high serum level of total cholesterol and alcohol overuse. Bone turnover markers were strongly associated with BMD and would therefore be useful for estimating bone loss and selecting the optimal medication for osteoporosis.

The authors state that they have no conflict of interest.

References

(Received June 11, 2013 ; Accepted August 9, 2013)
Effect of Perceived Economic Status on Knowledge about Cancer Prevention, Healthy Behaviors, and Cancer Check-up Rate in Japan

Junko Umihara¹, Mariko Nishikitani²

Abstract

Objective: The economic inequality gap in Japan has rapidly widened in recent years, and financial disparity has been reported to affect health status. The present study investigated a relationship between economic status and cancer knowledge, healthy behavior, and cancer check-up rates.

Methods: This cross-sectional study involved 6,004 residents of Yokohama City and Oyama City, Japan, randomly selected from the gender and age strata. Subjects aged between 35 and 65 were divided into 2 groups according to whether they perceived their economic status as affluent or not.

Results: Nearly 35% of the subjects answered that they did not consider themselves to be affluent. The subjects in this group had lower education levels and less regular employment, and fewer were married, compared with the affluent group. They also tended to have less knowledge about a healthy lifestyle, eat fewer vegetables, smoke, have an unhealthy body weight, and receive fewer cancer check-ups. We found strong correlations between relative economic satisfaction and cancer prevention knowledge, healthy lifestyle, and behaviors. People who did not perceive themselves as affluent tended to know less about cancer risks, have unhealthy diets and smoking habits, and receive fewer cancer check-ups.

Conclusion: A significant positive correlation exists between economic satisfaction and cancer prevention behaviors in Japan. Because economic dissatisfaction derives from a comparison with others, a reduction in social disparity may be necessary to increase cancer check-up rates and promote healthy lifestyles.

Keywords economic inequality, perception of affluence, cancer check-up, cancer knowledge

The rapidly widening social and economic disparity gap in Japan is one of the most significant issues facing the country this century. Economic inequality has been reported to affect people's health status, and the British Whitehall Study found a significant correlation between level of employment and mortality rates among civil servants.

Recently, it has been noted that the influence of social class differences on health status goes beyond absolute standards such as educational background and financial status to relative income distribution and social capital. Relative income distribution has been studied in a unique empirical randomized housing mobility experiment and the findings demonstrated that moving from a high-poverty to a low-poverty neighborhood increased subjective well-being despite the absence of objective change in economic self-sufficiency or in income. Relative income, also known as social comparison, has been shown to influence subjective well-being among members of a community. Kawachi et al. investigated the effect of economic disparity on Americans' health status and found that self-rated health was more varied in states that had larger income disparities.

The results of similar studies conducted in Northern Europe, Canada, and Japan were not as dramatic as that found in the United States but research based on the National Livelihood Survey in Japan established a connection between the income gap and health status.

After World War II, Japan became one of the world's most egalitarian countries in terms of education and
Later studies have confirmed the relationship between income disparity and health status. Several studies focusing on income inequality and health status have been conducted recently. Shibuya et al. used the Gini coefficient to assess income inequality at the prefecture level in data collected in 1995, finding that the Gini coefficient was comparable to that in other industrialized countries in 1995. Later studies have confirmed the relationship between income disparity and health status.

The present study investigated a relationship between subjective economic status and cancer prevention variables such as cancer check-ups, level of cancer knowledge, smoking habit, vegetable consumption, exercise, and body weight management, at a time when social and income disparities continue to increase in Japan.

We hypothesized that subjective economic status would influence cancer check-up rates and cancer-prevention behavior and conducted a cross-sectional study to evaluate this hypothesis.

**Methods**

**Data Collection and Study Population**

The present study was conducted in the Kanto region of Japan, in the Asahi and Sakae wards of Yokohama City in Kanagawa Prefecture and Oyama City in Tochigi Prefecture, between September 1 and November 30, 2009. The 2 wards in Yokohama City were chosen as the target sample because their age distributions were comparable with the national average distribution in 2009. The study was approved as no ethical problem by the Institutional Review Board of Hakuoh University prior to distribution of the survey questionnaire.

The study population consisted of 6,004 people, approximately 3,000 residents from each city, aged between 20 and 80 years. The samples reflected the sex and age distributions for each city. However, population demographics differed between them: Yokohama City had a larger percentage of older residents than Oyama (23% vs. 19%, respectively) and fewer young people (13% vs. 14%, respectively). Furthermore, there were fewer males in Yokohama City than Oyama (0.97 vs. 1.02, with females having a reference value of 1), though both had higher rates than the national average (0.95). A comparison of the average taxed income across the 364 municipalities of the Kanto region, in Ibaraki, Tochigi, Gunma, Saitama, Chiba, Tokyo, and Kanagawa Prefectures, indicated that Oyama City (3.09 million yen per year) was around the Kanto regional median (3.07 million yen per year), whereas the taxed income in Yokohama City (3.88 million yen per year) was in the 90–95th percentile. To adjust for the demographic differences between the two cities, we used dummy variables for each city in the correlation analyses. We distributed questionnaires to the candidate subjects in the selected sample areas and received responses from 1,947 persons (response rate 32.4%). Among them, we analyzed data for 1,085 persons between the ages of 35 and 65 because this age group is eligible for government-subsidized cancer screening.

**Questionnaire**

All questionnaires were distributed together with the informed consent by mail, and when respondents agree to join in the study, they returned them anonymously. The sociodemographic information collected included age, level of formal education, employment status, occupation, number of days worked per week, household income, marriage status, whether there were any children in the household, and the number of family members in the household. Subjective economic status was assessed using the question, “Considering your income status, do you feel...?” Candidates were instructed to choose from among the following responses: very affluent, reasonably affluent, affluent, not affluent, and not affluent at all.

The questionnaire measured subjects’ knowledge of a healthy lifestyle concerning 3 factors: cancer causes, effects of smoking, and appropriate sodium intake. Correct answers for causes of cancer included smoking, viruses, and consumption of fatty food. Incorrect answers included external blows such as to the chest. Questions about the negative effects of smoking concerned the addictive nature of smoking, understanding the meaning of “light cigarette”, research establishing a link between smoking and cancer, and secondhand smoke.

Finally, healthy lifestyle behaviors were assessed. Subjects were asked whether they exercised regularly, i.e., 3 or more days per week (‘regular exercise’), and ate more than 300 g of fruit and vegetables on 3 or more days per week (‘sufficient fruit and vegetable intake’). The questionnaire also asked them about current smoking status and hand-washing habit and whether their body weight was within the desirable range.

Cancer check-up status was assessed by asking subjects whether they underwent regular cancer screening and which types (e.g., uterus, breast, stomach, colon, lung).

**Statistical Methods**

To determine the effect of relative financial satisfaction on healthy lifestyle, we divided the subjects into 2 groups according to perceived affluence, assigning those who answered ‘not affluent’ or ‘not affluent at all’ to a no perceived affluence group (non-affluent group) and those who answered ‘very affluent,’ ‘reasonably affluent,’ or ‘affluent’ to a perceived affluence group (affluent group).

The chi-square test was used to compare socio-
omographic characteristics, healthy lifestyle knowledge, and lifestyle behaviors in the groups according to gender. Logistic regression analysis was then conducted to determine whether there was an association between perception of affluence and healthy lifestyle knowledge and behaviors. Finally, multiple logistic regression analysis was conducted to estimate odds ratios (OR) and 95% confidence intervals (CI) after adjusting for confounding factors such as age (as a continuous valuable), education, employment status, occupation, marriage status, household income, whether there were children in the household, number of family members in the household, and city of residence (as a dummy variable). When correlation coefficients were determined for socioeconomic variables in the logistic regression model, no significant multicollinearity ($r < 0.5$) was found.

Data analyses were conducted using Stata statistical software version 11.0 (Stata Corp, College Station, TX, USA). All tests were two-sided, and a $p$-value of 0.05 was considered statistically significant.

**Results**

The subjects were 455 males and 630 females between 35 and 65 years of age. The sociodemographic characteristics of those in the affluent and non-affluent groups according to gender are shown in Table 1.

About 35% (36% of males, 34% of females) of the subjects responded that they did not feel affluent. Male and female subjects in the non-affluent group reported lower education levels and less regular employment than subjects in the affluent group. Although more subjects in the non-affluent group were single, there were more children in this group than in the affluent group.

A comparison of healthy lifestyle knowledge revealed that subjects in the non-affluent group were less knowledgeable about the causes of cancer than those in the affluent group (Table 2). Compared with the affluent group, more males in the non-affluent group believed (incorrectly) that an external blow was a cause of cancer, and more females believed (incorrectly) that smoking was not a cause of cancer. Female respondents in the non-affluent group tended to be unaware that a large body of research has shown that smoking is linked to cancer, and fewer males in the affluent group knew what a "light cigarette" was compared with males in the non-affluent group.

Regarding lifestyle behaviors (Table 3), non-affluent males and females had a lower consumption of fruit and vegetables, smoked more, and underwent fewer regular cancer check-ups than those in the affluent group.

---

**Table 1. Sociodemographic Characteristics of Subjects with and without a Feeling of Affluence According to Gender (number and percentage of total in each category)**

<table>
<thead>
<tr>
<th></th>
<th>Perceived affluence</th>
<th>No perceived affluence</th>
<th>$p$-value</th>
<th>Perceived affluence</th>
<th>No perceived affluence</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>291</td>
<td>164</td>
<td></td>
<td>418</td>
<td>212</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35–44 years old</td>
<td>68 (23)</td>
<td>46 (28)</td>
<td>0.359</td>
<td>102 (24)</td>
<td>81 (38)</td>
<td>0.001</td>
</tr>
<tr>
<td>45–54</td>
<td>85 (29)</td>
<td>51 (31)</td>
<td></td>
<td>130 (31)</td>
<td>63 (30)</td>
<td></td>
</tr>
<tr>
<td>55–65</td>
<td>136 (47)</td>
<td>67 (41)</td>
<td></td>
<td>186 (45)</td>
<td>68 (32)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undergraduate/graduate school</td>
<td>136 (47)</td>
<td>46 (28)</td>
<td>0.001</td>
<td>80 (19)</td>
<td>20 (9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Job</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Yes)</td>
<td>261 (90)</td>
<td>141 (86)</td>
<td>0.236</td>
<td>270 (65)</td>
<td>154 (77)</td>
<td>0.042</td>
</tr>
<tr>
<td>Household income</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Income (multiple)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject</td>
<td>274 (94)</td>
<td>146 (90)</td>
<td>0.054</td>
<td>180 (43)</td>
<td>124 (59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spouse</td>
<td>97 (33)</td>
<td>49 (30)</td>
<td>0.459</td>
<td>361 (86)</td>
<td>136 (65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parents or children</td>
<td>51 (18)</td>
<td>28 (17)</td>
<td>0.912</td>
<td>69 (17)</td>
<td>49 (23)</td>
<td>0.039</td>
</tr>
<tr>
<td>Working days/week</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 days</td>
<td>24 (9)</td>
<td>13 (9)</td>
<td>0.013</td>
<td>4 (34)</td>
<td>43 (28)</td>
<td>0.208</td>
</tr>
<tr>
<td>5 days</td>
<td>181 (69)</td>
<td>79 (56)</td>
<td></td>
<td>136 (50)</td>
<td>80 (52)</td>
<td></td>
</tr>
<tr>
<td>6 days</td>
<td>56 (21)</td>
<td>49 (35)</td>
<td></td>
<td>40 (15)</td>
<td>31 (20)</td>
<td></td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not regular</td>
<td>53 (20)</td>
<td>44 (31)</td>
<td>0.015</td>
<td>183 (68)</td>
<td>123 (80)</td>
<td>0.008</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professional/managerial</td>
<td>158 (61)</td>
<td>60 (43)</td>
<td>0.006</td>
<td>84 (31)</td>
<td>38 (25)</td>
<td>0.061</td>
</tr>
<tr>
<td>Clerical</td>
<td>20 (8)</td>
<td>13 (9)</td>
<td></td>
<td>68 (25)</td>
<td>28 (18)</td>
<td></td>
</tr>
<tr>
<td>Sales and service</td>
<td>34 (13)</td>
<td>28 (20)</td>
<td></td>
<td>77 (29)</td>
<td>60 (39)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>49 (19)</td>
<td>40 (28)</td>
<td></td>
<td>41 (15)</td>
<td>28 (18)</td>
<td></td>
</tr>
<tr>
<td>Marriage status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not married</td>
<td>30 (10)</td>
<td>31 (19)</td>
<td>0.002</td>
<td>26 (6)</td>
<td>16 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Married</td>
<td>247 (86)</td>
<td>119 (73)</td>
<td></td>
<td>369 (89)</td>
<td>155 (74)</td>
<td></td>
</tr>
<tr>
<td>Divorced/widowed</td>
<td>11 (4)</td>
<td>14 (9)</td>
<td></td>
<td>20 (5)</td>
<td>38 (18)</td>
<td></td>
</tr>
<tr>
<td>Children living in household</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Yes)</td>
<td>88 (30)</td>
<td>50 (30)</td>
<td>0.013</td>
<td>280 (67)</td>
<td>163 (77)</td>
<td>0.010</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban area (Yokohama)</td>
<td>123 (42)</td>
<td>60 (37)</td>
<td>0.235</td>
<td>209 (50)</td>
<td>99 (47)</td>
<td>0.433</td>
</tr>
<tr>
<td>Urban neighborhood (Oyama)</td>
<td>168 (58)</td>
<td>104 (63)</td>
<td></td>
<td>209 (50)</td>
<td>113 (53)</td>
<td></td>
</tr>
<tr>
<td>Family members living in household</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (alone)</td>
<td>13 (4)</td>
<td>17 (10)</td>
<td>0.051</td>
<td>19 (5)</td>
<td>14 (7)</td>
<td>0.538</td>
</tr>
<tr>
<td>2</td>
<td>73 (25)</td>
<td>40 (24)</td>
<td></td>
<td>116 (28)</td>
<td>56 (26)</td>
<td></td>
</tr>
<tr>
<td>3 &gt;</td>
<td>205 (70)</td>
<td>107 (65)</td>
<td></td>
<td>283 (68)</td>
<td>142 (67)</td>
<td></td>
</tr>
</tbody>
</table>

About 35% (36% of males, 34% of females) of the subjects did not have a feeling of affluence concerning their lifestyle. In these subjects, for both genders, there was a lower level of education and more of them were in non-regular employment. Although more subjects without a feeling of affluence were single, there were more children in this group than were in the affluent group.

---

group. Furthermore, the results suggested that the female subjects in the non-affluent group were less concerned about their body weight or the value of a desirable body weight than females in the affluent group.

We used multiple logistic regression analysis to control for confounding variables such as age and socioeconomic status. Most of the odds ratios obtained were similar to those for the simple comparisons (Table 4 and Table 5). The likelihood that females in the non-affluent group were unaware that smoking and fatty food could cause cancer was significantly greater than that in the affluent group (adjusted ORs and 95% CI: smoking; 2.39, 1.06–5.40 and fatty food; 2.24, 1.07–4.68; Table 4). Males in the non-affluent group were more likely to understand what “light cigarette” meant than affluent males (0.36, 0.17–0.79).

The risks of unhealthy lifestyle behaviors according to gender are shown in Table 5. The risk of lower consumption of fruit and vegetables was not significant; however, the odds ratios for current smoking status and lack of regular cancer check-ups were significant in both genders: males and females in the non-affluent group had higher rates of smoking (adjusted ORs, 1.93 and 2.54, respectively) and lower rates for regular cancer check-ups (adjusted ORs, 1.67 and 1.60, respectively) than subjects in the affluent group. Moreover, more females in the non-affluent group reported a weight outside the desirable range and were less knowledgeable about desirable weight than females in the affluent group (adjusted OR, 1.56, 95%; CI, 1.06–2.31).

Discussion

In discussions concerning a connection between sociodemographic inequities and cancer awareness and
mortality rates, social capital has been recognized as a possible factor among many that also include gaps in education due to socioeconomic disparity. The present study examined a relationship between subjective economic status and knowledge concerning cancer, cancer check-ups, and healthy lifestyle behaviors. The results, after adjusting for confounding factors including educational background, age, marital status, and household income, show that presence or absence of economic comfort influenced the frequency of cancer check-ups and overall lifestyle. Furthermore, the effect of relative financial stability on this differed between males and females. With regard to knowledge about cancer, females who did not perceive themselves to be affluent were half as likely to know about the negative effects of smoking and 2.5 times more likely to smoke than females who perceived themselves to be affluent. Although men with no perceived sense of affluence had sufficient knowledge about the negative effects of smoking, their smoking rate was higher than that of males in the affluent group.

The level of knowledge regarding the correlation between a high-fat diet and cancer was lower in females in the non-affluent group compared with those in the affluent group, and the risk of an unhealthy body weight was higher in non-affluent females. The regular cancer check-up rate was lower in males and females in the non-affluent than in the affluent group. Compared with the affluent group, more females in the non-affluent group had never undergone screening for uterine or gastric cancer, and more males had never received screening for gastric cancer.

In Japan, all local governments offer people age 35 or older free screening for uterine and gastric cancer, yet our study revealed that respondents who perceived themselves as not affluent tended not to undergo such screening.

Table 4. Risk of Insufficient Knowledge of Healthy Lifestyle Factors in Participants with No Perception of Affluence According to Gender (odds ratio and 95% confidence intervals)

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking effect</td>
<td>1.13 (0.57–2.22)</td>
<td>2.33 (1.16–4.67)</td>
</tr>
<tr>
<td>Virus effect</td>
<td>0.79 (0.53–1.17)</td>
<td>1.32 (0.95–1.86)</td>
</tr>
<tr>
<td>Fatty food effect</td>
<td>1.04 (0.55–1.95)</td>
<td>1.56 (0.81–3.01)</td>
</tr>
<tr>
<td>No effect of external blow</td>
<td>1.56 (1.02–2.37)</td>
<td>0.99 (0.70–1.41)</td>
</tr>
</tbody>
</table>

Table 5. Risk of Unhealthy Behaviors in Subjects with No Perception of Affluence According to Gender (odds ratio and 95% confidence intervals)

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>No regular exercise (3 days (times) / week &lt;)</td>
<td>1.06 (0.63–1.80)</td>
<td>1.14 (0.72–1.78)</td>
</tr>
<tr>
<td>Lower consumption of fruit and vegetables (less than 300 grams/day)</td>
<td>1.54 (1.05–2.27)</td>
<td>1.55 (1.09–2.21)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>2.22 (1.48–3.33)</td>
<td>2.75 (1.67–4.54)</td>
</tr>
<tr>
<td>Over desirable weight, or not knowing its value</td>
<td>1.09 (0.74–1.60)</td>
<td>1.59 (1.13–2.25)</td>
</tr>
<tr>
<td>No hand-washing habit</td>
<td>1.41 (0.90–2.20)</td>
<td>1.28 (0.85–1.93)</td>
</tr>
<tr>
<td>No regular cancer check-ups</td>
<td>1.82 (1.17–2.84)</td>
<td>1.90 (1.32–2.74)</td>
</tr>
<tr>
<td>Types of cancer screening never received (multiple choice) Uterine</td>
<td>2.07 (1.41–3.02)</td>
<td>1.82 (1.18–2.80)</td>
</tr>
<tr>
<td>Breast</td>
<td>1.74 (1.24–2.44)</td>
<td>1.36 (0.93–1.99)</td>
</tr>
<tr>
<td>Stomach</td>
<td>2.03 (1.36–3.01)</td>
<td>2.17 (1.53–3.07)</td>
</tr>
<tr>
<td>Colon</td>
<td>1.76 (1.17–2.65)</td>
<td>1.43 (1.00–2.04)</td>
</tr>
<tr>
<td>Lung</td>
<td>1.60 (1.08–2.37)</td>
<td>1.77 (1.25–2.49)</td>
</tr>
<tr>
<td>Other</td>
<td>0.70 (0.34–1.45)</td>
<td>0.88 (0.36–2.13)</td>
</tr>
</tbody>
</table>

There were significantly higher odds ratios for current smoking status and lack of regular cancer check-ups in both genders.

* Adjusted by age (as continuous variable), education, employment status, occupation, marriage status, household income, children in household, number of family members in household, and residence city (as dummy variables). p < 0.05, indicated in bold.


Ningen Dock International Vol.1 No.1 2014 51 (51)
screening. This finding suggests that people who do not feel affluent are less motivated to keep in good health than those who feel affluent. In short, lack of perceived affluence appears to decrease motivation to stay healthy by having regular check-ups, and maintaining a desirable weight. Our findings also suggest that non-affluent respondents found it difficult to stop smoking despite their knowledge of the risk.

Our observation that the perception of not being affluent is associated with an unhealthy lifestyle is consistent with that of previous research by Hasegawa showing that there was a significant correlation between income inequality and obesity\(^\text{16}\). Also, Sugimori reported that a lower rate of cancer check-ups was associated with lower health literacy\(^\text{17}\). Since a feeling of being less affluent is attributable to a lower education level and/or socioeconomic status in such aspects as household income, employment status, occupation, and marriage status, it could be expected to relate to lower health literacy. Therefore, increasing health literacy could raise the rate of cancer check-ups\(^\text{18}\).

Our findings suggest that education and cancer screening campaigns are not sufficient for increasing screening rates and promoting a healthy lifestyle because people may not take action to prevent cancer, even when they know the risks. They further suggest that motivation to maintain health through regular check-ups is closely related to a sense of economic satisfaction. Subjective economic statuses are thought to reflect relative income disparities and differences in social capital rather than actual differences in income levels\(^\text{19}\), suggesting that an increase in income disparity and a decrease in relative sense of economic satisfaction may threaten maintenance of health overall. In the future, not only medical policies but also social and economic strategies will be needed to balance social capital and fundamental economic hierarchies in order to safeguard the health of the population overall.

The present study has several limitations. First, the demographics of the 2 sample populations differed in age, gender, and income status. We therefore substituted dummy variables for the cities to control for sampling bias in the demographics. Second, the age distribution of the study population was weighted toward older individuals, with 47% of the respondents aged between 55 and 65 years. **Fig.1** shows the age distribution of the sample populations according to city and gender. The sample populations included more subjects over 50 than under 40 years of age. The relatively low response rate (32.4%) may be accounted for by the low response rate for younger subjects and is a source of information bias. The bias in age distribution may also indicate that people become more aware of their health and health care as they age. However, age did not significantly affect the perception of economic affluence. Subjective economic status is the result of a comparison with others in a similar age group and social position, and elderly people have been reported to have high levels of income satisfaction with no reasonable cause\(^\text{20}\). As the subjects of our study were more than 35 years old and therefore possibly more satisfied with their incomes, a greater number might have been included in the affluent group. Finally, due to its cross-sectional design, this study seems to suggest an association between subjective economic status and knowledge of cancer and behaviors relating to it but did not prove causality between them. A future well-designed longitudinal cohort study should clarify this. In any case, this observation in no way detracts from the findings of this study.

To prevent cancer, people must understand the risk factors and engage in healthy behaviors such as not smoking, maintaining a healthy body weight, and having cancer check-ups regularly. Although conventional cancer prevention campaigns have focused on the dissemination of information and encouraging people to have check-ups, our study suggests that perception of affluence may also play an important role in cancer prevention. The findings of our questionnaire survey indi-

**Fig.1. Age Distributions of Sample Populations and Study Subjects According to Surveyed Cities and Gender**

Both the actual study subjects had less people below 40 and more people above 50 than populations sampled.
cate that certain categories of women, such as part-time workers and single mothers, do not perceive themselves to be affluent. This suggests that the economic inequality present in Japanese society today may cause disparities in health status similar to those in the United States in the future. Therefore, we recommend that overall cancer prevention policies include socioeconomic measures to decrease the financial gap among people in Japan.

Conflict of Interest
The present research was funded by a Grant-in-Aid for Scientific Research provided by the Ministry of Education, Culture, Sports, Science, and Technology (Kiban C 2259064). There was no other conflict of interest in this study.

Acknowledgments
We thank Yokohama City and the Health Promotion Department of Oyama City for collecting random samples. In addition, we would like to express our deepest appreciation to Dr. K. Viswanath, Associate Professor of Harvard School of Public Health, for providing the inspiration to conduct this research. Finally, we benefited greatly from the linguistic expertise of Ms. Tomoko Yokoshima in this project.

This paper was presented during the 53rd Congress of the Japan Society of Ningen Dock held in September 2012.

References

(Received January 31, 2013; Accepted November 11, 2013)
Relationships of High-density Lipoprotein 2 and 3 Cholesterols with Lifestyle Habit Factors in Japanese Adults

Kengo Moriyama, Eiko Takahashi

Abstract

Objective: The aim of this study was to clarify relationships of high-density lipoprotein 2 cholesterol (HDL$_2$-C) and high-density lipoprotein 3 cholesterol (HDL$_3$-C) with lifestyle habit factors in Japanese adults.

Methods: A total of 1,461 qualified subjects who underwent annual health examination were analyzed. Relationships between HDL$_2$-C and HDL$_3$-C, and clinical parameters including obesity, smoking, exercise, and alcohol consumption were studied.

Results: Stepwise multiple linear regression analysis revealed that all independent variables excluding ex-smoker were selected for HDL$_2$-C level. However, only alcohol consumption was selected for HDL$_3$-C level. Both HDL$_2$-C and HDL$_3$-C levels increased together with higher alcohol consumption. HDL$_2$-C levels were decreased by obesity and current smoking and increased by exercise. HDL$_2$-C levels were higher in women than in men.

Conclusion: HDL$_2$-C levels were associated with alcohol consumption, waist circumference (WC), smoking and exercise, and a gender difference was observed. However, HDL$_3$-C levels were only associated with alcohol consumption. Our data provided a better understanding of HDL-C subclasses and lifestyle habit factors.

Keywords: high-density lipoprotein 2 cholesterol, high-density lipoprotein 3 cholesterol, lifestyle habit factors

Although high-density lipoprotein cholesterol (HDL-C) reference values are not uniform across different populations and vary by gender, ethnicity, etc., a low HDL-C level is generally considered a risk factor for cardiovascular disease. For example, a low HDL-C level has been defined as <40 mg/dL for both men and women in the 2005 Japanese criteria, <35 mg/dL for men and <39 mg/dL for women in the 1998 World Health Organization (WHO) criteria and <40 mg/dL for men and <50 mg/dL for women in other criteria. The incidence of coronary artery disease, including angina pectoris and myocardial infarction, is lower in subjects with high HDL-C levels and HDL-C is therefore called "good cholesterol". The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP III) defines a high HDL-C level, a negative risk factor for coronary artery disease, as ≥ 60 mg/dL. In Japan, according to the primary hyperlipidemia research working group of the Ministry of Health, Labor and Welfare, an HDL-C level of ≥100 mg/dL is defined as a high HDL-C level or familial hyper-HDL cholesterolemia when a family history is evident. Causes of high HDL-C levels include cholesterol ester transfer protein (CETP) deficiency and excessive alcohol consumption. However, when high HDL-C levels result from CETP deficiency, no clear consensus exists on whether they are protective against arteriosclerosis. Therefore, it is also important to pay attention to lifestyle habit factors in CETP-deficient patients.

High-density lipoprotein 2 cholesterol (HDL$_2$-C) is one of the 2 major subclasses of HDL-C. Its major role is to act as a final receptor in the reverse cholesterol-transport process. This process involves the movement of cholesterol by HDL from the peripheral tissues and then back to the liver where it is degraded and excreted as bile. HDL$_2$-C appears to provide greater protection against coronary heart disease (CHD) than the other subclass, high-density lipoprotein 3 cholesterol (HDL$_3$-C). It has been reported that compared with control individuals, myocardial infarction (MI) patients...
had significantly lower HDL-C levels. The most striking difference was that HDL₂-C levels were 30% lower; suggesting that HDL₂-C deficiency may be a primary alteration in MI patients. However, both HDL₂-C and HDL₃-C have been seen to be inversely associated with the risk of CHD. Therefore, it is still unclear whether HDL₂-C and/or HDL₃-C are protective against CHD, so it is important to understand factors that influence HDL subclass as well as HDL-C levels.

The results of our previous study on a relationship between HDL-C and insulin resistance in male subjects undergoing annual health examination revealed that there was an inverse association between HDL-C and homeostasis model assessment of insulin resistance (HOMA-IR) in non-metabolic syndrome (MetS) subjects. However, in MetS subjects, the HOMA-IR increased when the HDL-C level was ≥ 90 mg/dL. Since our findings could be explained as being largely due to heavy drinking, it is important to monitor alcohol consumption in persons with high HDL-C levels. We also studied a relationship between HDL-C and insulin resistance in female subjects undergoing annual health examination. Subjects who were not obese, did not smoke, and consumed < 75 g alcohol/day had elevated HDL-C levels, which were associated with improved insulin sensitivity. Although many studies have been conducted on subjects medicated for CHD with HDL₂-C and HDL₃-C atherogenicity, little is known about a relationship between lifestyle factors and HDL-C subclasses. Therefore, it is important to investigate the factors that affect HDL₂-C and HDL₃-C levels in subjects receiving annual health examination.

The aim of this study was to clarify the significance of HDL₂-C and HDL₃-C levels in Japanese adults undergoing annual health examination. It focused on a relationship between lifestyle habit factors and HDL-C subclasses.

Subjects and Methods

Subjects

Our subjects were 1,461 persons (877 men and 584 women) who underwent annual health examination including measurement of HDL subclass at the Health Evaluation and Promotion Center of Tokai University Hachioji Hospital between April 2011 and March 2013. Since our focus was on a relationship between lifestyle habit factors and HDL-C subclasses, and apparent effects of disease treatments on HDL-C levels and lifestyle habit factors were not known, subjects under medication were not excluded in this study.

Measurements

Waist circumference (WC) was measured at the level of the umbilicus while standing and during slight expiration. Blood pressure was measured using an automatic blood pressure monitor (TM-2655P; A&D, Tokyo, Japan) positioned on the upper right arm with the subject in a sitting position. Blood samples were collected early in the morning after overnight fasting. Insulin was measured by fluorescence enzyme immunoassay (FEIA); (ST AIA-PACK IRI; Toxo, Tokyo, Japan). HOMA-IR was calculated as (fasting plasma glucose × fasting insulin)/405. Low-density lipoprotein cholesterol (LDL-C), HDL-C, and triglyceride (TG) levels were measured by visible spectrophotometry (Determiner L LDL-C, Determiner L HDL-C, Determiner L TG II, respectively; Kyowa Medex, Tokyo, Japan). HDL subfractions were isolated by ultracentrifugation and HDL₂-C and HDL₃-C levels were determined enzymatically (L type Wako CHO•H; Wako, Osaka, Japan). Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (γ-GT) levels were measured following the standardized procedure outlined by the Japan Society of Clinical Chemistry (JSCC). Verbal consent for the use of anonymized health records for analysis was obtained from subjects. The study protocol was approved by the institutional ethics committee of Tokai University School of Medicine.

Statistical analysis

Means between 2 groups were compared using the t-test or two-way analysis of variance (ANOVA). Data are presented as mean ± standard deviation (SD) to check distribution and as mean ± 95% confidence interval for comparison of means between groups. We created a dummy-variable multiple regression model having a series of binary (i.e., dummy) variables that identified whether or not an observation belonged to a specific category. The binary variables were coded as 1 or 0. Subjects were asked to express their alcohol consumption as the number of units of sake consumed per day, where 1 unit (180 mL) of sake was taken to be equivalent to 25 g of alcohol. Alcohol consumption was classified into 3 categories: < 25 g/day, 25 to < 50 g/day, ≥ 50 g/day. WC was classified into 6 categories: < 75 cm, 75 to < 80 cm, 80 to < 85 cm, 85 to < 90 cm, 90 to < 95 cm, ≥ 95 cm. Regarding smoking, subjects were divided into 4 groups: non-smoker, ex-smoker, current smoker < 11 cigarettes, current smoker ≥ 11 cigarettes. Exercise habit was evaluated according to 2 groups: < 2 times/week or ≥ 2 times/week, for ≥ 30 min at a time. In case of 5 categories, 4 dummy variables were created. The lowest category was used as a reference for WC and exercise. Non-drinker or non-smoker were used as a reference for alcohol consumption and smoking, respectively. Women were used as a reference for men. Multiple linear regression analysis was performed to find significant determinants of HDL-C subclasses, including alcohol consumption, WC, smoking, exercise and sex. Variables were selected in a stepwise procedure.
(p < 0.1). SAS Software version 9.3 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses. All p values were two-tailed, and p < 0.05 was considered significant.

Results

Table 1 shows the characteristics of the study subjects. The mean age was 57.8 years for both men and women. Age and HDL<sub>1</sub>-C level were not different between men and women. HDL-C, HDL<sub>2</sub>-C, TC, and LDL-C levels were higher in women than in men. The remaining parameters were higher in men than in women.

Fig. 1 shows the relationships between HDL-C, TG and HDL-C subclasses. Analysis was performed after transforming TG levels to naturalized logarithms. For both men and women, there was a strong positive correlation between HDL-C and HDL<sub>2</sub>-C. There was a moderately positive correlation between HDL-C and HDL<sub>1</sub>-C (r = 0.467) in men, and a weakly positive correlation (r = 0.297) in women. In both men and women, there was a moderately negative correlation between HDL<sub>2</sub>-C and TG. There was a weakly negative correlation between HDL<sub>1</sub>-C and TG in men. However, no correlation between HDL<sub>1</sub>-C and TG was observed in women.

Table 2 shows the effect of an interaction between lifestyle habit factors and sex on HDL-C levels by two-way ANOVA. Shaded boxes indicate cases of p < 0.05. There were significant differences in HDL-C and HDL<sub>2</sub>-C levels for WC, alcohol consumption, smoking and exercise, and a gender difference was observed. No interaction between lifestyle habit factors and gender
Table 2. Effect of Interaction between Lifestyle Habit Factors and Sex on HDL Cholesterol by ANOVA

<table>
<thead>
<tr>
<th>Lifestyle Independent variables</th>
<th>HDL-C</th>
<th>HDL₂-C</th>
<th>HDL₃-C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>P</td>
<td>F</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WC</td>
<td>37.220</td>
<td>&lt;.001</td>
<td>41.995</td>
</tr>
<tr>
<td>Sex</td>
<td>161.923</td>
<td>&lt;.001</td>
<td>178.745</td>
</tr>
<tr>
<td>Interaction</td>
<td>0.906</td>
<td>0.476</td>
<td>1.480</td>
</tr>
<tr>
<td>Drinking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drinking</td>
<td>5.400</td>
<td>&lt;.001</td>
<td>4.955</td>
</tr>
<tr>
<td>Sex</td>
<td>87.606</td>
<td>&lt;.001</td>
<td>97.716</td>
</tr>
<tr>
<td>Interaction</td>
<td>0.814</td>
<td>0.486</td>
<td>0.982</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drinking</td>
<td>4.262</td>
<td>&lt;.001</td>
<td>4.845</td>
</tr>
<tr>
<td>Sex</td>
<td>89.356</td>
<td>&lt;.001</td>
<td>102.897</td>
</tr>
<tr>
<td>Interaction</td>
<td>0.512</td>
<td>0.674</td>
<td>0.508</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>14.767</td>
<td>&lt;.001</td>
<td>12.521</td>
</tr>
<tr>
<td>Sex</td>
<td>272.013</td>
<td>&lt;.001</td>
<td>307.919</td>
</tr>
<tr>
<td>Interaction</td>
<td>0.402</td>
<td>0.526</td>
<td>0.042</td>
</tr>
</tbody>
</table>

p < 0.05

Fig. 2. Relationship between WC and HDL-C subclasses

- Men, ○: Women, □: Men and women. **p < 0.01, *p < 0.05 (ANOVA). Error bar represents mean ± 95% confidence interval. HDL₂-C, high-density lipoprotein 2 cholesterol; HDL₃-C, high-density lipoprotein 3 cholesterol.

Fig. 3. Relationship between Smoking and HDL-C Subclasses

- Men, ○: Women, □: Men and women. **p < 0.01, *p < 0.05 (ANOVA). Error bar represents mean ± 95% confidence interval. HDL₂-C, high-density lipoprotein 2 cholesterol; HDL₃-C, high-density lipoprotein 3 cholesterol.
was noted. HDL₁-C levels were significantly different for alcohol consumption. As they were not significantly different for sex, we analyzed the rest of the data without considering its effect on HDL₁-C levels.

**Fig. 2** shows the relationship between WC and HDL-C subclasses. HDL-C and HDL₂-C levels were significantly different for WC. HDL-C and HDL₂-C levels were significantly higher in women than in men. In contrast, HDL₁-C was not related with WC.

**Fig. 3** shows the relationship between smoking and HDL-C subclasses. Since there were few subjects who smoked more than 20 cigarettes a day, subjects were divided into four groups: non-smoker (never smoked), ex-smoker (subjects who used to smoke but had quit), current smoker < 11 cigarettes a day and current smoker ≥ 11 cigarettes a day. HDL-C and HDL₂-C levels were lower in smokers than in non-smokers. HDL-C and HDL₂-C levels were significantly higher in women than in men. In contrast, there was no relationship between HDL₁-C and smoking.

**Fig. 4** shows the relationship between exercise habit and HDL-C subclasses. HDL-C and HDL₂-C levels were higher in subjects who exercised ≥ 30 min a time and ≥ 2 times/week than in subjects who exercised < 2 times/week. HDL-C and HDL₂-C levels were significantly higher in women than in men. In contrast, no significant difference was observed in HDL₁-C levels with respect to exercise.

**Fig. 5** shows the relationship between the alcohol consumption and HDL-C subclasses. HDL-C, HDL₂-C and HDL₃-C, high-density lipoprotein 2 cholesterol; HDL₃-C, high-density lipoprotein 3 cholesterol

---

**Fig. 4. Relationship between Exercise Habit and HDL-C Subclasses**

- Men, ○: Women □: Men and women. **p < 0.01, *p < 0.05 (ANOVA). Error bar represents mean ± 95% confidence interval.

**Fig. 5. Relationship between Alcohol Consumption and HDL-C Subclasses**

- Men, ○: Women □: Men and women. **p < 0.01, *p < 0.05 (ANOVA). Error bar represents mean ± 95% confidence interval.
and HDL₃-C levels were significantly higher in drinkers than in non-drinkers. HDL-C and HDL₂-C levels were significantly higher in women than in men.

Table 3 shows the results of multivariate analyses with alcohol consumption, WC, smoking, exercise and sex as independent variables. Stepwise multiple linear regression analysis was performed to find significant determinants for HDL-C subclasses. Although all independent variables excluding ex-smoker were selected for HDL-C and HDL₂-C, alcohol consumption only was selected for HDL₃-C level. Regression coefficients for each variable are shown; with non-drinker; WC < 75 cm; non-smoker; exercise < 2 times/week, and women used as references. HDL-C, HDL₂-C and HDL₃-C were positively correlated with alcohol consumption. HDL-C and HDL₃-C levels decreased as WC and number of cigarettes increased. HDL-C and HDL₂-C levels were increased by exercise and decreased by male sex.

### Discussion

In this study, we showed that HDL-C and HDL₃-C levels were significantly higher in women than in men. However, there was no gender difference for HDL₂-C levels. Both HDL-C and HDL₂-C were decreased by an increased WC and smoking. HDL₃-C levels were increased by alcohol consumption.

It is widely accepted that HDL-C levels are significantly higher in women than in men and in Caucasians (men, 32.9 mg/dL versus women, 36.4 mg/dL, and men, 27.9 mg/dL versus women, 22.3 mg/dL). Although the reason for such differences is unclear from this study, it is possible that HDL subclass predomination is affected by genetic factors and Western lifestyle.

Obesity is frequently associated with a low concentration, adverse distribution pattern, and abnormal metabolism of HDL particles. It has been also shown to adversely affect the levels of HDL subclasses principally associated with cardioprotection: HDL₂, apolipoprotein (apo) A-I, and pre-β₁. Reduced HDL₂ levels in obese subjects may be caused by 2 factors: an overall elevation in very-low-density triglycerides and a slight increase in glycemia, reflecting insulin resistance, which may have contributed to decreased lipolysis and a defective transfer of surface elements to HDL₁, in the subjects used in the research producing these findings. Pascot et al. reported that HDL₂-C was negatively correlated with body fat indices (i.e., BMI and WC), while HDL₃-C had no correlations with them. Increased HDL clearance is thought to be more responsible for an HDL decrease in obese individuals. It is possible that TG-rich larger HDL is prone to hydrolysis to cholesterol depleted HDL, leading to a decrease in HDL₂, but no change in HDL₃. Although the mechanisms by which obesity mainly affects HDL₂ are not known, loss of excess body fat (4–6 kg), either through exercise or reduced dietary calories has been seen to increase HDL-C by 10% but HDL₂-C by 40%. It has been reported that in comparison with mid-thigh fat, intra-abdominal fat was a more critical independent predictor for low HDL₂ levels in obese premenopausal women. In agreement with these previous studies, we observed an inverse relationship between WC and HDL₂-C in the present study.

### Table 3. Results of Multivariate Regression Analyses

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>SE</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drinking non-drinker</td>
<td>2.42</td>
<td>0.88</td>
<td>7.54</td>
</tr>
<tr>
<td>&lt;25g/day</td>
<td>2.39</td>
<td>0.86</td>
<td>6.64</td>
</tr>
<tr>
<td>25 ≤ &lt;50g/day</td>
<td>6.47</td>
<td>1.25</td>
<td>26.82</td>
</tr>
<tr>
<td>≥50g/day</td>
<td>12.70</td>
<td>1.41</td>
<td>80.92</td>
</tr>
<tr>
<td>WC</td>
<td>&lt;75 cm</td>
<td>7.36</td>
<td>1.23</td>
</tr>
<tr>
<td>75 ≤ &lt;80 cm</td>
<td>12.13</td>
<td>1.20</td>
<td>102.02</td>
</tr>
<tr>
<td>80 ≤ &lt;85 cm</td>
<td>14.25</td>
<td>1.25</td>
<td>130.17</td>
</tr>
<tr>
<td>90 ≤ &lt;95 cm</td>
<td>16.68</td>
<td>1.47</td>
<td>131.89</td>
</tr>
<tr>
<td>≥95 cm</td>
<td>16.88</td>
<td>1.47</td>
<td>131.89</td>
</tr>
<tr>
<td>Smoking non-smoker</td>
<td>-4.08</td>
<td>1.84</td>
<td>4.93</td>
</tr>
<tr>
<td>&lt;11 cigarettes</td>
<td>-4.41</td>
<td>1.67</td>
<td>6.97</td>
</tr>
<tr>
<td>≥11 cigarettes</td>
<td>-5.58</td>
<td>1.10</td>
<td>25.61</td>
</tr>
<tr>
<td>Exercise &lt;2 times/week</td>
<td>2.43</td>
<td>0.81</td>
<td>8.99</td>
</tr>
<tr>
<td>≥2 times/week</td>
<td>1.88</td>
<td>0.74</td>
<td>6.55</td>
</tr>
<tr>
<td>Sex women</td>
<td>-13.02</td>
<td>0.86</td>
<td>229.78</td>
</tr>
<tr>
<td>Constant</td>
<td>80.01</td>
<td>1.00</td>
<td>6461.94</td>
</tr>
</tbody>
</table>
Smoking decreases the HDL-C level, a likely consequence of the oxidative stress due to tobacco smoke, which leads to HDL dysfunction. In a prospective study on Finnish males, current smokers had significantly lower HDL\(_2\)-C levels than non-smokers, but no difference was observed in HDL\(_3\)-C levels. It has also been reported that HDL\(_1\)-C levels were not significantly affected by smoking status in young Japanese women. While the precise mechanisms by which smoking decreases HDL\(_2\)-C but not HDL\(_1\)-C in both men and women are not known, this could be due to the combination of 1) a decrease in lecithin: cholesterol acyltransferase (LCAT) activity and 2) an increase in hepatic lipase (HL) activity. LCAT plays a central role in the maturation of HDL particles by esterification of free cholesterol on immature HDL and a decrease in its activity would result in a reduction in larger HDL. On the other side, HL converts large, TG-rich HDL\(_2\) back into small TG and cholesteryl ester–poor HDL\(_3\). In the present study, male and female non-smokers had higher HDL-C and HDL\(_2\)-C levels than male and female smokers.

Through a variety of mechanisms, regular aerobic exercise increases HDL-C levels by approximately 5% within 2 months of initiation. Also, more than 30 min of aerobic exercise per session, and a total of at least 120 min per week, is recommended for increasing HDL-C levels. Furthermore, a previous study utilizing a meta-analytic approach showed that aerobic exercise increased HDL\(_2\)-C levels in adults. However, the reason why exercise should mainly affect HDL\(_2\)-C level is uncertain. It has been reported that endurance exercise affects the activities of many enzymes related to lipid metabolism; LCAT and lipoprotein lipase activities are increased and CETP and hepatic triacylglycerol lipase activities are decreased. It has been suggested that such changes in lipid metabolism due to exercise play a central role in catabolism of TG-rich lipoproteins (i.e., very low-density lipoprotein cholesterol and LDL) as well as the conversion of HDL\(_2\) to HDL\(_3\). We therefore speculate that such changes lead to accumulation of HDL\(_2\). In the present study, HDL-C levels in subjects who exercised ≥30 min/day more than twice a week were significantly higher than in non-exercisers. Although HDL\(_2\)-C levels in subjects who exercised was higher than that in non-exercisers (21.6 mg/dL versus 21.3 mg/dL), the difference was not significant. Therefore other factors in addition to exercise habit should be considered when drawing a conclusion.

Moderate ethanol intake (generally up to 30 g/day or about two drinks a day) consistently raised HDL-C, by about 4 mg/dL, in over 40 short-term trials included in a meta-analysis. A prospective alcohol-consumption study revealed that alcohol-induced increases in HDL-C levels appeared to be primarily in HDL\(_2\). Other studies have indicated that there is often an increase in both HDL subclasses, but the one in HDL\(_2\) is greater, whereas a few studies have observed comparable increases in HDL\(_1\) and HDL\(_2\). The reason for the discrepancy in HDL subclass level changes could be due to variability in the ethanol dose. However, precise mechanisms to explain the reason why ethanol intake mainly affects HDL\(_1\) remain unknown.

In addition to raising HDL-C levels, ethanol intake has also been associated with higher TG levels. The moderate negative correlation between HDL\(_2\)-C and TG levels and a weak negative or no correlation between HDL\(_1\)-C and TG in this study suggest that the raising of HDL-C levels by ethanol may not be associated with its effect on TG levels.

A relationship between increased HDL-C levels due to alcohol consumption and insulin resistance has been reported. We previously reported that an increase in the alcohol consumption was associated with a progressive increase in the HDL-C level, but there was a progressive reduction in HOMA-IR in Japanese women. An association between an increase in alcohol consumption and a progressive increase in HDL-C level was also observed in Japanese men without MetS, but again there was a progressive reduction in HOMA-IR. Furthermore in male MetS subjects with HDL-C levels <90 mg/dL, HDL-C was inversely correlated with HOMA-IR, while HOMA-IR increased in subjects with HDL-C ≥90 mg/dL, and this was more prominent in subjects who drank ≥75 g/day. These findings suggest that a considerable number of subjects with high HDL-C levels and alcohol consumption of ≥75 g/day are prone to developing MetS.

In the present study, we observed that HDL\(_2\)-C levels were associated with alcohol consumption, WC, smoking and exercise, whereas only alcohol consumption was associated with HDL\(_1\)-C levels. We recently observed a correlation of HDL\(_1\)-C with HOMA-IR as well as high molecular weight adiponectin (HMW-Ad) (data not shown). Also, HDL-C and HDL\(_2\)-C levels were negatively correlated with HOMA-IR, but positively correlated with HMW-Ad. On the other hand, HDL\(_1\)-C levels were not correlated with either HOMA-IR or HMW-Ad. Further studies will be needed to investigate whether high HDL-C levels due to alcohol consumption are associated with anti-arteriosclerotic effects, including evaluation of the HDL-C subclasses.

Since the present study was cross-sectional, a cause-and-effect relationship could not be ascertained. This study included subjects who were well-controlled through medication and the possibility that medication affected their HDL-C levels cannot be ruled out. Future studies should pursue this issue to determine if there is...
such a relationship, which will further benefit the evaluation of HDL-C subclasses.

Conclusion
Analysis of the relationships between HDL-C subclasses and lifestyle habits revealed that HDL2-C was associated with WC, smoking and exercise. HDL2-C level was higher in women than those in men. In contrast, HDL3-C was associated with alcohol consumption and no gender difference was observed. Our data provided the better understanding on the levels of HDL-C subclasses and lifestyle habits.

Acknowledgement
There are no conflicts of interest for both authors.

References


(Received August 5, 2013 ; Accepted November 15, 2013)
Comparison Among Body Mass Index, Waist Circumference, Waist-to-height Ratio, and Percent Body Fat as Predictors of Incident Diabetes in a Japanese Health Screening Population

Eiji Oda

Abstract

Objective: The aim of this study was to compare the ability of body mass index (BMI), waist circumference (WC), waist-to-height ratio (WHtR) and percent body fat (PBF) to predict incident diabetes.

Methods: Areas under receiver operating characteristic curves (AUCs) for these parameters were calculated for a Japanese population consisting of 1,704 men and 1,016 women to determine incident diabetes and hazard ratios (HRs) for each one SD increase in these parameters, and also when they were dichotomously defined.

Results: During 4 years of follow-up (mean 3.4 years), 54 men (3.2%) and 19 women (1.9%), of whom 69 (94.5%) were prediabetes at baseline, developed diabetes. The AUCs [95% confidence intervals (CIs)] for BMI, WC, WHtR and PBF were 0.69 (0.61–0.76), 0.68 (0.61–0.76), 0.70 (0.63–0.78) and 0.65 (0.59–0.71), respectively, in men and 0.74 (0.61–0.86), 0.75 (0.61–0.88), 0.76 (0.64–0.88) and 0.77 (0.65–0.88), respectively, in women. After adjusting for fasting glucose, hemoglobin A1c and other confounders, only BMI in men was significant [HR (95% CI): 1.49 (1.07–2.07), p=0.018] among continuous parameters, while only WC and PBF in women were significant [HRs (95% CIs): 5.22 (1.24–21.91), p=0.024 and 5.67 (1.33–24.20), p=0.019, respectively] among dichotomous parameters.

Conclusion: The abilities of these anthropometric parameters to predict incident diabetes were almost and limited when both fasting glucose and hemoglobin A1c were measured.

Keywords incident diabetes, anthropometry
Subjects and Methods

Subjects

Between April 2008 and March 2009, 2,435 men and 1,437 women visited our Medical Check-up Center for general health screening and gave written informed consent to take part. They were required to fill out a questionnaire which included questions about their history of cardiovascular disease (CVD), smoking and drinking status, level of physical activity and use of antihypertensive, antidiabetic and antihyperlipidemic medications. Excluding subjects with diabetes or a history of CVD at baseline, left 2,142 men and 1,373 women as candidates for this follow-up study. Among them, 1,704 men and 1,016 women revisited our Medical Check-up Center between April 2009 and March 2013 and were enrolled in the present study. The study was approved by the ethics committee of Tachikawa Medical Center. Diabetes was defined as fasting plasma glucose ≥ 126 mg/dL and/or hemoglobin A1c (HbA1c) ≥ 6.5% and/or use of antidiabetic medications. Prediabetes was defined as 125 mg/dL ≥ fasting glucose ≥ 100 mg/dL and/or 6.4% ≥ HbA1c ≥ 5.7%. HbA1c was expressed in NGSP%.

Measurements

Blood samples were obtained after an overnight fast to measure blood levels of routine medical check-up parameters including fasting plasma glucose, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and HbA1c. Measurements were performed at BML Nagaoka (Nagaoka, Japan). LDL cholesterol was measured by a direct surfactant method using Cholestest-LDL (Sekisui Medical Inc, Tokyo, Japan) and HbA1c by latex aggregation immunooassay using Determiner HbA1 c (Kyowa Medex, Tokyo, Japan). Average systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated from 2 measurements in the sitting position after a 5-minute rest. Body weight was measured with the subject wearing light clothes provided by our center and the weight of the clothes was subtracted from the measured body weight. BMI was calculated as weight in kilograms divided by the square of height in meters. WC was measured at the level of the umbilicus in the standing position. PBF was measured by bioelectrical impedance analysis using TBF-210 (TANITA, Tokyo, Japan). The reproducibility of the PBF measurement was ±0.1%.

Statistical analysis

Baseline data for all candidate subjects and those actually followed up were compared to evaluate bias resulting from drop-outs (those who did not revisit). Baseline data for subjects who developed diabetes and those who did not were also compared.

The following statistical analyses were performed separately for each gender. Areas under receiver operating characteristic curves (AUCs) for BMI, WC, WHtR and PBF were calculated to discriminate incident diabetes and optimal cutoff points were estimated as the maximal points of the sum of the sensitivity and specificity.

Associations between anthropometric parameters and incident diabetes were examined using Cox regression analysis. Hazard ratios (HRs) of incident diabetes for each one SD increase in BMI, WC, WHtR and PBF and dichotomously defined parameters for them were calculated and adjusted for age, SBP, triglycerides, HDL cholesterol, LDL cholesterol, current smoking, everyday drinking, physical activity, and use of antihypertensive and antihyperlipidemic drugs (Model 1), adjusted for covariates in Model 1 plus fasting glucose (Model 2) and further adjusted for covariates in Model 2 plus HbA1c (Model 3). DBP was not included in the adjustment covariates because SBP and DBP were strongly correlated. Physical activity was defined as walking for one hour or longer per day or exercising for 30 minutes or longer twice or more per week.

Means and percentages for baseline data were compared using t-tests and chi-squared tests, respectively. All calculations were performed using Dr-SPSS-2 software (IBM Japan, Tokyo, Japan). p-values less than 0.05 were considered to be statistically significant.

Results

Baseline data for potential candidates and actually followed-up subjects are shown in Table 1. There were no significant differences in the baseline data between the potential candidates and the actually followed-up subjects (Table 1).

During 4 years of follow-up (mean 3.4 years), 54 men (3.2%) and 19 women (1.9%) developed diabetes. Among the 73 subjects who developed diabetes, 20 were diagnosed by fasting glucose and HbA1c, 18 were diagnosed by fasting glucose alone, 30 were diagnosed by HbA1c alone, 5 were diagnosed by use of medication, and 69 (94.5%) were prediabetes at baseline.

Baseline data stratified by development of diabetes are shown in Table 2. Male sex and use of antihypertensive and antihyperlipidemic drugs were more frequent and age, BMI, WC, WHtR, PBF, SBP, DBP, fasting glucose, HbA1c, triglycerides and LDL cholesterol were higher, while HDL cholesterol was lower, in subjects who developed diabetes than those who did not.

AUCs with 95% confidence intervals (CI) and optimal cutoff points (OCPs) based on their sensitivities/specificities for BMI, WC, WHtR and PBF for discriminating incident diabetes are presented in Table 3. The AUCs (95% CIs) for BMI, WC, WHtR and PBF were 0.69 (0.61–0.76), 0.68 (0.61–0.76), 0.70 (0.63–
The HRs for BMI, WC, WHtR and PBF were all significant both in men and women in Model 1 (1.69–1.81 in men and 1.62–1.84 in women). In Model 2, BMI, WC and WHtR in men and PBF in women were significantly associated with incident diabetes, while only BMI in men was significant in Model 3. HRs (95% CIs) of diabetes for dichotomously defined BMI, WC, WHtR and PBF are shown in Table 5. The HRs for BMI, WC, WHtR and PBF were all significant in men while that for WHtR was not significant in women in Model 1 (2.28–2.85 in men and 2.79–4.57 in women). In

### Table 1. Baseline Data for Potential Candidates and Actually Followed-up Subjects

<table>
<thead>
<tr>
<th></th>
<th>Candidates</th>
<th>Followed-up</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>3515</td>
<td>2720</td>
<td></td>
</tr>
<tr>
<td>male sex (%)</td>
<td>60.9</td>
<td>62.6</td>
<td>0.169</td>
</tr>
<tr>
<td>age (years)</td>
<td>51.1 (9.5)</td>
<td>51.3 (9.2)</td>
<td>0.356</td>
</tr>
<tr>
<td>body mass index (kg/m²)</td>
<td>22.6 (3.0)</td>
<td>22.6 (3.0)</td>
<td>0.803</td>
</tr>
<tr>
<td>waist circumference (cm)</td>
<td>82.0 (8.6)</td>
<td>82.1 (8.4)</td>
<td>0.759</td>
</tr>
<tr>
<td>waist-to-height ratio</td>
<td>0.50 (0.05)</td>
<td>0.50 (0.05)</td>
<td>0.897</td>
</tr>
<tr>
<td>percent body fat (%)</td>
<td>23.9 (5.9)</td>
<td>23.9 (5.8)</td>
<td>0.569</td>
</tr>
<tr>
<td>systolic blood pressure (mmHg)</td>
<td>118.2 (17.9)</td>
<td>118.3 (17.7)</td>
<td>0.852</td>
</tr>
<tr>
<td>diastolic blood pressure (mmHg)</td>
<td>74.6 (11.2)</td>
<td>74.7 (11.1)</td>
<td>0.622</td>
</tr>
<tr>
<td>fasting glucose (mg/dL)</td>
<td>91.6 (8.7)</td>
<td>91.7 (8.7)</td>
<td>0.747</td>
</tr>
<tr>
<td>hemoglobin A1c (%)</td>
<td>5.39 (0.30)</td>
<td>5.39 (0.30)</td>
<td>0.808</td>
</tr>
<tr>
<td>triglycerides (mg/dL)</td>
<td>106.6 (68.1)</td>
<td>105.5 (63.7)</td>
<td>0.498</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>61.5 (15.2)</td>
<td>61.5 (15.2)</td>
<td>0.931</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>121.5 (29.5)</td>
<td>121.5 (28.9)</td>
<td>0.989</td>
</tr>
<tr>
<td>antihypertensive drugs (%)</td>
<td>12.9</td>
<td>13.6</td>
<td>0.427</td>
</tr>
<tr>
<td>antihyperlipidemic drugs (%)</td>
<td>7.7</td>
<td>8.1</td>
<td>0.519</td>
</tr>
<tr>
<td>current smoking (%)</td>
<td>23.8</td>
<td>24.3</td>
<td>0.635</td>
</tr>
<tr>
<td>everyday drinking (%)</td>
<td>37.8</td>
<td>38.1</td>
<td>0.822</td>
</tr>
<tr>
<td>physical activity (%)</td>
<td>35.3</td>
<td>35.2</td>
<td>0.926</td>
</tr>
</tbody>
</table>

mean (SD) or %, * defined as walking for one hour or longer per day or exercising for 30 minutes or longer twice or more per week

### Table 2. Baseline Data Stratified by Development of Diabetes

<table>
<thead>
<tr>
<th></th>
<th>developers</th>
<th>non-developers</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>73</td>
<td>2647</td>
<td></td>
</tr>
<tr>
<td>male sex (%)</td>
<td>74.0</td>
<td>62.3</td>
<td>0.043</td>
</tr>
<tr>
<td>age (years)</td>
<td>54.8 (7.8)</td>
<td>51.2 (9.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>body mass index (kg/m²)</td>
<td>25.4 (4.4)</td>
<td>22.5 (2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>waist circumference (cm)</td>
<td>89.1 (9.9)</td>
<td>81.9 (8.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>waist-to-height ratio</td>
<td>0.54 (0.06)</td>
<td>0.50 (0.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>percent body fat (%)</td>
<td>27.6 (7.4)</td>
<td>23.8 (5.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>systolic blood pressure (mmHg)</td>
<td>127.2 (18.3)</td>
<td>118.1 (17.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>diastolic blood pressure (mmHg)</td>
<td>80.5 (10.9)</td>
<td>74.6 (11.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>fasting glucose (mg/dL)</td>
<td>107.0 (10.1)</td>
<td>91.2 (8.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hemoglobin A1c (%)</td>
<td>5.99 (0.30)</td>
<td>5.38 (0.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>triglycerides (mg/dL)</td>
<td>139.5 (85.6)</td>
<td>104.6 (62.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>53.9 (12.7)</td>
<td>61.7 (15.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>128.5 (29.0)</td>
<td>121.3 (28.9)</td>
<td>0.035</td>
</tr>
<tr>
<td>antihypertensive drugs (%)</td>
<td>37.0</td>
<td>13.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>antihyperlipidemic drugs (%)</td>
<td>16.4</td>
<td>7.9</td>
<td>0.008</td>
</tr>
<tr>
<td>current smoking (%)</td>
<td>32.9</td>
<td>24.1</td>
<td>0.083</td>
</tr>
<tr>
<td>everyday drinking (%)</td>
<td>45.2</td>
<td>37.9</td>
<td>0.204</td>
</tr>
<tr>
<td>physical activity (%)</td>
<td>42.5</td>
<td>35.0</td>
<td>0.189</td>
</tr>
</tbody>
</table>

mean (SD) or %, * defined as walking for one hour or longer per day or exercising for 30 minutes or longer twice or more per week

0.78) and 0.65 (0.59–0.71), respectively, in men and 0.74 (0.61–0.86), 0.75 (0.61–0.88), 0.76 (0.64–0.88) and 0.77 (0.65–0.88), respectively, in women. The OCPs (sensitivities/specificities) of BMI, WC, WHtR and PBF were 25 kg/m² (0.47/0.79), 88 cm (0.58/0.72), 0.52 (0.61/0.74) and 25% (0.50/0.75), respectively, in men and 25 kg/m² (0.53/0.87), 88 cm (0.56/0.86), 0.52 (0.79/0.65) and 33% (0.58/0.87), respectively, in women.

HRs (95% CIs) of diabetes for each one SD increase in BMI, WC, WHtR and PBF are shown in Table 4.
Table 3. Areas Under Receiver Operating Characteristic Curves and Optimal Cutoff Points Based on Sensitivities and Specificities for Anthropometric Parameters for Discrimination of Incident Diabetes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Men</th>
<th>p-value</th>
<th>Women</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (kg/m²)</td>
<td>0.69 (0.61–0.76)</td>
<td>&lt;0.001</td>
<td>0.74 (0.61–0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>0.68 (0.61–0.76)</td>
<td>&lt;0.001</td>
<td>0.75 (0.61–0.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist-to-Height ratio (x)</td>
<td>0.70 (0.63–0.78)</td>
<td>&lt;0.001</td>
<td>0.76 (0.64–0.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percent body fat (%)</td>
<td>0.67 (0.60–0.74)</td>
<td>&lt;0.001</td>
<td>0.77 (0.65–0.88)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note: AUC = area under receiver operating characteristic curve; OCP = optimal cutoff point; CI = confidence interval.

Table 4. Hazard Ratios of Diabetes for Each 1 SD Increase in Individual Obesity Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Men</th>
<th>p-value</th>
<th>Women</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (kg/m²)</td>
<td>1.81 (1.39–2.35)</td>
<td>&lt;0.001</td>
<td>1.62 (1.18–2.22)</td>
<td>0.003</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>1.69 (1.26–2.27)</td>
<td>&lt;0.001</td>
<td>1.84 (1.22–2.78)</td>
<td>0.004</td>
</tr>
<tr>
<td>Waist-to-Height ratio (x)</td>
<td>1.77 (1.33–2.37)</td>
<td>&lt;0.001</td>
<td>1.82 (1.19–2.77)</td>
<td>0.006</td>
</tr>
<tr>
<td>Percent body fat (%)</td>
<td>1.73 (1.30–2.31)</td>
<td>&lt;0.001</td>
<td>1.73 (1.13–2.64)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Note: HR = hazard ratio; CI = confidence interval; Model 1: adjusted for age, systolic blood pressure, triglycerides, HDL cholesterol, LDL cholesterol, smoking, drinking, physical activity, and use of antihypertensive and antihyperlipidemic drugs. Model 2: adjusted for covariates in Model 1 and fasting glucose. Model 3: adjusted for covariates in Model 2 and hemoglobin A1c.

Table 5. Hazard Ratios of Diabetes for Dichotomously Defined Obesity Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Men</th>
<th>p-value</th>
<th>Women</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index ≥ 25 kg/m²</td>
<td>2.52 (1.40–4.54)</td>
<td>&lt;0.001</td>
<td>2.95 (1.09–8.00)</td>
<td>0.003</td>
</tr>
<tr>
<td>Waist circumference ≥ 88 cm</td>
<td>2.62 (1.46–4.69)</td>
<td>&lt;0.001</td>
<td>4.57 (1.69–12.38)</td>
<td>0.003</td>
</tr>
<tr>
<td>Waist-to-Height ratio ≥ 0.52</td>
<td>2.85 (1.57–5.17)</td>
<td>&lt;0.001</td>
<td>2.79 (0.86–9.08)</td>
<td>0.880</td>
</tr>
<tr>
<td>Percent body fat ≥ 25%</td>
<td>2.28 (1.29–4.03)</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent body fat ≥ 33%</td>
<td>4.46 (1.62–12.31)</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: HR = hazard ratio; CI = confidence interval; Model 1: adjusted for age, systolic blood pressure, triglycerides, HDL cholesterol, LDL cholesterol, smoking, drinking, physical activity, and use of antihypertensive and antihyperlipidemic drugs. Model 2: adjusted for covariates in Model 1 and fasting glucose. Model 3: adjusted for covariates in Model 2 and hemoglobin A1c.
Model 2, the HRs for BMI, WC and WHtR were significant in men (1.96–2.24) while those for WC and PBF were significant in women (3.89 and 4.13, respectively). In Model 3, only WC (HR: 5.22) and PBF (HR: 5.67) in women were significant predictors of incident diabetes.

**Discussion**

The present study demonstrated that the abilities of BMI, WC, WHtR and PBF to predict incident diabetes were almost equal in a Japanese health screening population. After adjusting for fasting glucose, HbA1c and other confounders, only BMI calculated as a continuous parameter in men and only WC and PBF calculated as dichotomous parameters in women were significant predictors of incident diabetes. These results suggest that the utility of anthropometric parameters is limited in the prediction of incident diabetes in Japanese in whom obesity is not prevalent while impaired insulin secretion has a greater impact on the incidence of diabetes than insulin resistance.

A meta-analysis of 17 prospective and 35 cross-sectional studies with the aim of comparing BMI, WC and waist-to-hip ratio (WHR) regarding their associations with incidence and prevalence of diabetes concluded that all studies showed that BMI, WC or WHR predicted or was associated with diabetes independently, regardless of the controversial findings concerning which of these obesity parameters is better. This meta-analysis indicates that BMI and WC can be used interchangeably since they have similar predicting abilities for future risk of diabetes, while various clinical guidelines primarily favor the use of BMI in screening programs. Another meta-analysis showed that the pooled relative risks (95% CI) of 15 eligible studies with 6,472 diabetes cases were 1.63 (1.49–1.79) for WC, 1.62 (1.48–1.78) for WHtR, 1.55 (1.43–1.69) for BMI and 1.52 (1.40–1.66) for WHR and a systematic review of longitudinal studies assessing a relationship between abdominal obesity and the incidence of diabetes reported that the pooled odds ratio (95% CI) of incident diabetes for abdominal obesity was 2.14 (1.70–2.71). WC is one of the requirements for the diagnosis of metabolic syndrome, although there has been no agreement on specific cutoff points for any ethnic group. Yet another meta-analysis reported that robust statistical evidence from studies involving more than 300,000 adults of several ethnic groups showed the superiority of WHtR over WC and BMI for detecting hypertension, type 2 diabetes, dyslipidaemia, metabolic syndrome and CVD in both sexes.

The heterogeneity of diabetes has been demonstrated and this heterogeneity indicates that different anthropometric indices may be closely associated with the risk of diabetes in different populations. BMI, WC and WHR were approximately equivalent in their ability to predict diabetes in African American and White subjects enrolled in the Atherosclerosis Risk in Communities cohort, although sensitivities and specificities differed among ethnic groups and between genders. Also, BMI was superior to PBF as a predictor of obesity and PBF was minimally predictive of the physiological markers of obesity independent of BMI in subjects from the Third National Health and Nutrition Examination Survey population. Further, both BMI and WC were strongly related to the development of diabetes and there was an additive effect of BMI and WC in a prospective population-based cohort study from the second or third Monitoring Trends and Determinants on Cardiovascular Diseases Augsburg survey. In a study using data from 4 UK cohorts, no strong evidence to support replacing BMI with measures of central adiposity and fat mass for the prediction of coronary heart disease, diabetes, and all-cause mortality was obtained. In a prospective cohort study in Spain, overall and central obesity were independently associated with diabetic risk, and BMI had the strongest association with diabetes in men whereas waist-related indices were stronger independent predictors in women. Also, in an Iranian population, BMI as a dichotomous parameter in both genders and WHtR in men and BMI in women as continuous parameters were the best predictors of incident diabetes. Furthermore, WHtR, and to some degree WC, were the best predictors of diabetes, followed by BMI, then WHR in a Chinese population.

In the present study, as a continuous parameter, BMI was a significant predictor of incident diabetes in men while as dichotomous parameters, WC and PBF were significant predictors in women after adjusting for fasting glucose and HbA1c. These gender differences are hypothetical because the reasons for them are unknown and the numbers of cases were relatively small. However, differences among these anthropometric parameters in ability to predict incident diabetes seem to be too small to mandate the replacement of BMI, of which the cutoff points for overweight and obesity are generally accepted worldwide, with other anthropometric parameters. Compared with insulin resistance, impaired insulin secretion has a greater impact on the incidence of diabetes and metabolic syndrome is a poor predictor of diabetes in Japanese in whom obesity is not prevalent. Thus, the usefulness of anthropometry in predicting incident diabetes may be limited when both fasting glucose and HbA1c are measured at baseline in Japanese.

**Limitations**

The subjects of the present study were not from...
a nationwide general population but from a health screening population and a substantial number of candidate subjects dropped-out. However, there were no significant differences in the baseline data between the potential candidates who dropped out and the actually followed-up subjects. Information about other risk factors of diabetes such as family history and diet was not available. Diabetes was diagnosed using data at one time point and glucose tolerance tests were not performed. WHR was not examined because hip circumference was not measured. Although some antihypertensive drugs and statins influence the development of diabetes, detailed information about drugs was not obtained. Therefore, the present results are hypothetical.

Acknowledgements
The author thanks all subjects who participated in the study, the paramedical staff at our center who assisted with the study and Honorary Prof. Yoshifusa Aizawa for his instructive comments.

Conflict of Interest
The author received no financial support for this study and has no conflict of interest to disclose.

References
2. Garber AJ: Obesity and type 2 diabetes : which patients are at risk? Diabetes Obes Metab 2012; 14: 399–408.
22. Freemantle N, Holmes J, Hockey A, et al: How strong is the association between abdominal obesity and the incidence of...


(Received October 9, 2013; Accepted December 2, 2013)
Lifestyle and Blood Pressure Control in Japanese Adults Receiving Hypertension Treatment: An Analysis of the 2009 Japan Society of Ningen Dock Database

Eiko Takahashi1,2, Kengo Moriyama2, Minoru Yamakado1,3, and the Ningen Dock Database Group

Abstract
Objective: The Japanese Society of Hypertension (JSH) has recommended target levels of blood pressure (BP) control based on guidelines for the management of hypertension. The Japan Society of Ningen Dock created a database of subjects receiving annual health examinations nationwide and using its data, we evaluated the efficacy of current treatment for hypertension patients based on the JSH recommendations as well as an association between adherence to lifestyle habits and BP control.

Methods: This multicenter, retrospective study was conducted using data obtained from 21 institutions across Japan. To assess BP control in the Japanese population, we analyzed previously obtained measurements of conventional BP in 31,754 patients aged 40 to 79 years (mean age: 58.6 ± 8.3 years, 23,868 men and 7,886 women) taking hypertensive medications.

Results: The overall mean systolic BP in these patients was 129.7 ± 15.2 mmHg, and diastolic BP was 79.7 ± 10.5 mmHg. According to the JSH2009 guidelines, the target office BP was achieved in 45.2% of all subjects; 36.2% of patients with diabetes mellitus, chronic kidney disease, or a history of coronary heart disease; 70.4% of elderly patients; 44.7% of nonelderly patients (younger than 65 years); and 76.2% of patients with cerebrovascular disease. When 140/90 mmHg were used as hypertension criteria for conventional BP measurements, the achievement rate was 69.8%. Undesirable lifestyle habits, except smoking, were associated with poor BP control.

Conclusion: Hypertension is considered to be insufficiently managed in more than half of patients and therefore strict management through lifestyle modification is necessary to reduce the complications rate.

Keyword: blood pressure control, guidelines, hypertension, treatment

Hypertension is one of the most important risk factors for stroke and heart disease and the fundamental goal in the treatment of hypertension is to reduce the risk of cardiovascular morbidity and mortality.

The Japanese Society of Hypertension (JSH) first published guidelines for the management of hypertension in 2000 (JSH2000)9, and revisions followed in 2004 (JSH2004)10 and 2009 (JSH2009)9. In the JSH2004 guidelines, the target level of blood pressure (BP) control was <130/80 mmHg in those with diabetes mellitus (DM) or chronic kidney disease (CKD), <130/85 mmHg in young and middle-aged individuals and <140/90 mmHg in elderly people. In the JSH2009 guidelines, the target level of BP control was <130/80 mmHg in high-risk patients (such as those with DM, CKD or those who have experienced myocardial infarction), <130/85 mmHg in young or middle-aged patients and <140/90 mmHg in elderly patients and those who have experienced cerebrovascular disease (CVD).

It has been reported that only a small proportion of patients on antihypertensive medication have well controlled BP11–14, which finding is often attributed to poor compliance with such medication11,14.

Hypertension requires continuous medical care and ongoing patient self-management to reduce the risk of long-term complications and lifestyle interventions play a pivotal role in a therapeutic strategy to maintain good
BP control and prevent complications in patients with hypertension. Recent lifestyle-related studies have indicated that a healthy lifestyle that combines a prudent diet, regular physical activity, maintenance of a healthy weight, moderate alcohol consumption, and smoking cessation decreases the risk for cardiovascular disease, DM, and metabolic syndrome\textsuperscript{15–17}. However, these studies were conducted in the general population and not in patients with hypertension. Furthermore, most of them were conducted in Western populations.

The Japan Society of Ningen Dock collected data from 21 institutions during the years 2008 and 2009 as the preparatory stage for developing a database\textsuperscript{18–20}. Among the 287,342 subjects who underwent health examinations in 2009, 31,754 treated hypertensive patients older than 40 and younger than 80 years of age were analyzed.

As the present status of BP control in Japanese patients with hypertension is an important public health concern, we assessed the effectiveness of hypertension care provided by general practitioners in Japan and investigated an association between adherence to lifestyle habits and BP control.

**Materials and Methods**

**Study design**

This was a cross-sectional, observational study that assessed the percentage of patients in each risk category and achievement rates for target levels of BP control based on the JSH2009 guidelines\textsuperscript{6}.

**Study population**

This multicenter, retrospective study was conducted using data for 287,342 subjects who underwent annual health examinations at 21 Ningen Dock institutes located throughout Japan in 2009\textsuperscript{18}. Data from a total of 238,729 subjects (150,291 men and 88,438 women) aged 40 to 79 years was analyzed in this study.

It was designed in compliance with the ethics regulations outlined in the Declaration of Helsinki. Anonymized health records were used for the analysis, and the privacy of the participants was completely protected. This study was approved by the ethics committee of the Japan Society of Ningen Dock.

**Methods**

Anthropometric measurements and blood samples were obtained after overnight fasting in principle. Patients’ BPs were measured twice consecutively in the sitting position after a rest. Physicians or nurses measured BP by the auscultation method using a mercury or aneroid sphygmomanometer, or the cuflocillometric method using electronic arm-cuff devices that had been validated and approved by the Ministry of Health, Labor, and Welfare of Japan. DM was defined as receiving DM medications or fasting plasma glucose ≥126 mg/dL. Serum creatinine was measured by an enzymatic method and the estimated glomerular filtration rate (eGFR) was obtained using the Japanese equation for eGFR\textsuperscript{21}. In keeping with the universal definition, CKD was defined as reduced renal function (eGFR <60 mL/min/1.73 m\textsuperscript{2}). Serum LDL-cholesterol levels were calculated using the Friedewald formula\textsuperscript{22}.

We divided patients into 4 groups: 1) those with DM, CKD, or a history of coronary heart disease (CHD); 2) those with a history of CVD; 3) elderly patients 65 years and older without DM, CKD, and a history of CHD or CVD; and 4) nonelderly patients younger than 65 years without DM, CKD, and a history of CHD or CVD. Within these groups, office BP control was assessed according to JSH2009\textsuperscript{6}. The target level of BP control was <130/80 mmHg in patients with DM, CKD or a history of CHD, <130/85 mmHg in young and middle-aged patients and <140/90 mmHg in elderly patients and patients with a history of CVD.

Lifestyle recommendations were made on the basis of the questionnaire developed for specific health examination and health guidance\textsuperscript{23}, and comprised 9 health-related behavioral recommendations, including those relating to smoking, physical activity, dietary habits, and alcohol consumption. Multivariate logistic regression analysis was performed to assess the strength of an association between BP control as an objective variable and other parameters as explanatory variables, and odds ratios and 95% confidence intervals (CI) with p-values were calculated. Variable selection was made by a stepwise procedure.

All statistical analyses were carried out using SAS Software version 9.3 (SAS Institute Inc., Cary, NC, USA). Data are presented as the mean ± SD. A p-value <0.05 was considered statistically significant.

**Results**

**Fig. 1** shows the proportions of patients taking medications for hypertension following stratification by sex and age. Among the 238,729 subjects, 31,754 patients (mean age: 58.6 ± 8.3 years, 23,868 men and 7,886 women) were taking hypertension medications. When stratified by age, the treatment rate was higher in men 74 years of age and younger. The proportions of patients receiving hypertension treatments were greater in elderly subjects.

**Table 1** shows the characteristics of the study patients. The mean age was 58.2 years for men and 60.0 years for women. The overall mean systolic BP (SBP) in these patients was 129.7 ± 15.2 mmHg, and diastolic BP (DBP) was 79.7 ± 10.5 mmHg. The clinical parameters in men, with the exception of age, SBP, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, and eGFR, were higher...
than those in women. Since proportions of the subjects with DM, CKD, history of CHD, and history of CVD were higher in men than in women, men had greater cardiovascular risks than women.

Table 1 shows the treatment goals and achievement rates of these goals in each risk category. According to the JSH2009 guidelines, target BPs were achieved in 45.2% of all subjects; 36.2% of patients with DM,
CKD, or a history of CHD; 44.7% of nonelderly patients; 70.4% of elderly patients; and 76.2% of patients with a history of CVD.

Table 3 shows the various treatment goals and achievement rates of these goals in each risk category. White boxes represent treatment goals according to the JSH2009 guidelines and gray ones treatment goals proposed in the JSH2014 guidelines. Proposed treatment goals for subjects with DM or CKD, history of CVD, and 65 to <75 years are the same as in the JSH2009 guidelines. In this study, the achievement rate of the treatment goals according to JSH2009 was 45.2% but increases to 59.3% when the treatment goals in the JSH2014 guidelines are applied. When the target office BP was adjusted to a uniform <140/90 mmHg regardless of the risk level, the achievement rate was 69.8%.

Table 4 shows the relationships between BP control and undesirable lifestyle habits. We performed multivariate logistic regression analysis for poor BP control and found that physical activity <1 h/day, fast eater, supper <2 h before bedtime, skip breakfast, consume alcohol every day, and smoking were significantly associated with poor BP control. The odds ratios for smoking was significantly lower for those with poor BP control than for those with good BP control. The odds ratios for physical activity <1 h/day, fast eater, supper <2 h before bedtime, skip breakfast and consume alcohol every day were significantly higher for those with poor BP control than for those with good BP control. These undesirable lifestyle habits, except smoking, were associated with poor BP control.

**Table 2. Achievement Rates for Blood Pressure Treatment Goals According to JSH2009 Guideline**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>Target goal</th>
<th>Achievement</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM, CKD, History of CHD</td>
<td>11647</td>
<td>60.4 ± 8.2</td>
<td>129.8 ± 15.7</td>
<td>&lt;130/80</td>
<td>4217 (36.2%)</td>
</tr>
<tr>
<td>History of CVD</td>
<td>621</td>
<td>59.7 ± 8.5</td>
<td>127.3 ± 14.6</td>
<td>&lt;130/85</td>
<td>473 (76.2%)</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>15772</td>
<td>54.7 ± 5.8</td>
<td>129.5 ± 14.6</td>
<td>&lt;130/80</td>
<td>7051 (44.7%)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>3714</td>
<td>69.7 ± 3.7</td>
<td>131.2 ± 15.6</td>
<td>&lt;140/90</td>
<td>2613 (70.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>31754</td>
<td>58.6 ± 8.3</td>
<td>129.7 ± 15.2</td>
<td>&lt;150/90</td>
<td>14354 (45.2%)</td>
</tr>
</tbody>
</table>

**Table 3. Achievement Rates for Various Blood Pressure Treatment Goals**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>&lt;130/80</th>
<th>&lt;130/85</th>
<th>&lt;140/90</th>
<th>&lt;150/90</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM or CKD</td>
<td>9985</td>
<td>60.4 ± 8.2</td>
<td>130.3 ± 15.7</td>
<td>3477 (34.8%)</td>
<td>4440 (44.5%)</td>
<td>6869 (68.8%)</td>
<td>7865 (78.8%)</td>
</tr>
<tr>
<td>History of CHD</td>
<td>1662</td>
<td>60.2 ± 8.4</td>
<td>126.5 ± 15.0</td>
<td>840 (44.5%)</td>
<td>921 (55.4%)</td>
<td>1286 (77.4%)</td>
<td>1395 (83.9%)</td>
</tr>
<tr>
<td>History of CVD</td>
<td>621</td>
<td>59.7 ± 8.5</td>
<td>127.3 ± 14.6</td>
<td>244 (39.3%)</td>
<td>320 (51.5%)</td>
<td>473 (76.2%)</td>
<td>533 (85.8%)</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>15772</td>
<td>54.7 ± 5.8</td>
<td>129.5 ± 14.6</td>
<td>5114 (32.4%)</td>
<td>7051 (44.7%)</td>
<td>10910 (69.2%)</td>
<td>12127 (76.9%)</td>
</tr>
<tr>
<td>65 to &lt;75 years</td>
<td>3277</td>
<td>68.7 ± 2.8</td>
<td>131.0 ± 15.5</td>
<td>1317 (40.2%)</td>
<td>1512 (46.1%)</td>
<td>2311 (70.5%)</td>
<td>2719 (83.0%)</td>
</tr>
<tr>
<td>≥75 years</td>
<td>437</td>
<td>76.7 ± 1.4</td>
<td>132.4 ± 15.6</td>
<td>186 (42.1%)</td>
<td>193 (44.2%)</td>
<td>302 (69.1%)</td>
<td>370 (84.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>31754</td>
<td>58.6 ± 8.3</td>
<td>129.7 ± 15.2</td>
<td>11076 (34.9%)</td>
<td>14437 (45.5%)</td>
<td>22151 (69.8%)</td>
<td>25009 (78.8%)</td>
</tr>
</tbody>
</table>

**Table 4. Relationship between Blood Pressure Control and Undesirable Lifestyle Habits**

<table>
<thead>
<tr>
<th>Habit</th>
<th>Good BP control (n=14354)</th>
<th>Poor BP control (n=17400)</th>
<th>OR (95% CI) for poor BP control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>2895 (20%)</td>
<td>3017 (17%)</td>
<td>0.773 (0.729 – 0.820)</td>
</tr>
<tr>
<td>Exercise &lt;2 times/week</td>
<td>9276 (65%)</td>
<td>11538 (66%)</td>
<td>1.135 (1.084 – 1.189)</td>
</tr>
<tr>
<td>Physical activity &lt;1 h/day</td>
<td>8935 (62%)</td>
<td>11338 (65%)</td>
<td>1.120 (1.064 – 1.180)</td>
</tr>
<tr>
<td>Not a fast walker</td>
<td>7021 (49%)</td>
<td>8550 (49%)</td>
<td>1.054 (1.007 – 1.103)</td>
</tr>
<tr>
<td>Fast eater</td>
<td>5871 (41%)</td>
<td>7393 (42%)</td>
<td>1.054 (1.007 – 1.103)</td>
</tr>
<tr>
<td>Supper &lt;2 h before bedtime</td>
<td>3615 (25%)</td>
<td>4865 (28%)</td>
<td>1.120 (1.064 – 1.180)</td>
</tr>
<tr>
<td>Snacks after supper</td>
<td>1708 (12%)</td>
<td>2206 (13%)</td>
<td>1.159 (1.068 – 1.258)</td>
</tr>
<tr>
<td>Skip breakfast</td>
<td>1130 (8%)</td>
<td>1583 (9%)</td>
<td>1.178 (1.123 – 1.236)</td>
</tr>
<tr>
<td>Consume alcohol every day</td>
<td>4642 (32%)</td>
<td>6222 (36%)</td>
<td>1.178 (1.123 – 1.236)</td>
</tr>
</tbody>
</table>

BP, blood pressure; OR, odds ratio; CI, confidence interval
consume alcohol every day) and BP control. As the number of undesirable lifestyle habits increased, the percentage of good BP control decreased ($p<0.01$ by Mantel-extension method).

Table 5 shows the relationship between smoking and age, BMI and undesirable lifestyle habits. The proportions of obesity and undesirable lifestyle habits, except fast eater, were higher in the smoking group.

### Discussion

BP was better controlled in elderly patients and patients with CVD than in nonelderly patients or in high-risk patients, but the mean systolic BPs did not differ among the 4 groups. Although mean systolic and diastolic BPs were less than 130/80 mmHg, the total achievement rate of target office BPs according to each of the 4 categories of the JSH2009 guidelines was only 45.2% (Table 2), and rates among patients with DM, CKD, and a history of CHD, and those younger than 65 years without diseases were relatively poor. We clearly demonstrated that achievement rates were related to target BPs; with the high-risk group, whose target BP was 130/80 mmHg, having the lowest achievement rate of 36.2%. Target BPs were 130/85 mmHg for <65 years subjects and 140/90 mmHg for subjects with history of CVD and ≥65 years subjects. Achievement rates were 44.7% for <65 years subjects, 76.2% for subjects with a history of CVD and 70.4% for ≥65 years subjects.

Several studies have assessed the achievement of treatment goals according to the JSH guidelines in Japan. According to the JSH2000 guidelines, 41.5% of subjects (n=907, median age: 66.7 years, males: 46.4%) achieved the target BP, with a mean SBP of 140 mmHg and a mean DBP of 80 mmHg. According to the JSH2004 guidelines, 45.4% of subjects (n=3,313, median age: 71.0 years, males: 46.1%) achieved the
target BP, with a median SBP of 134 mmHg and a median DBP of 76 mmHg. According to the JSH 2009 guidelines, 53.9% of the subjects (n=675, median age: 70.1 years, males: 44.6%) achieved the target BP, with a mean SBP of 135 mmHg and a mean DBP of 76 mmHg. However, the majority of such studies assessing achievement rates for treatment goals in the JSH guidelines have been small in scale and large-scale investigations, like the present one targeting over 30,000 subjects, are extremely rare. Although they were small in scale, the findings of the above studies suggest that the publication of the JSH guidelines has been effective in improving target BP achievement rates, since they gradually increased (41.5%, 45.4%, and 53.9%) after publication of the JSH guidelines in 2000, 2004, and 2009.

This survey was performed in 2009, just after the JSH 2009 guidelines were published. Analyzing the data obtained from this survey according to each of the categories in JSH 2009, may appear odd but the difference between the JSH2004 guidelines and the JSH2009 guidelines is minor and involves only the classification of patients with a history of MI and CVD.

The ESH/ESC 2013 guidelines were published in June 2013. Although target BPs had been changed in ESH/ESC 2007 according to risk level, the 2013 revision recommends that the target BP is uniformly adjusted to <140/90 mmHg regardless of the risk level.

In the preliminary draft of JSH2014 that was released in August 2013, the target level of BP control has been adjusted to <140/90 mmHg regardless of the risk level.

In the present study, the percentage of smoking was higher in those with poor BP control than in those with good BP control. The percentage of smoking was 31.9% in men and 36.8% in women. It has also been shown that a large proportion of hypertensive patients on antihypertensive medication have inadequate office BP control.

Hypertension is a lifestyle-related disease, and it has been shown that it cannot only be prevented but also managed by lifestyle modifications. Although many patients fail to achieve target BP control through lifestyle modifications alone, they can at least reduce the types and doses of antihypertensive drugs needed. Lifestyle modifications must therefore be maintained even after the initiation of antihypertensive drug therapy. In our study, the percentages of undesirable lifestyle habits except smoking were significantly higher in those with poor BP control than in those with good BP control. Moreover, lifestyle habits were strongly associated with BP control in patients receiving hypertension treatment. In a Korean study, diabetes patients who adhered to ≥5 of 10 lifestyle recommendations had better blood lipid levels and glycemic control than those who did not. Our findings in hypertensive patients support those of previous studies.

In the present study, the percentage of smoking was higher in those with good BP control than in those with poor BP control but the reason for this was uncertain. Since it was cross-sectional, a cause-and-effect relationship between smoking and BP control could not be ascertained. In addition, the proportions of obese subjects and undesirable lifestyle habits, which except for fast eater were associated with poor BP control, were higher in smokers than in non-smokers. Despite recent evidence for the effect of smoking on the development of hypertension, the overall effect of smoking on blood pressure has not been established. However, smoking is a strong risk factor for not only non-cardiovascular diseases, including cancer, but also ischemic heart disease and stroke. Smoking is also reportedly related to metabolic syndrome. Therefore, not only hypertensive patients with cardiovascular risks but also healthy people should quit smoking.

The present study had some limitations. Health-affecting behavior was evaluated based on self-reporting, which could have been inaccurate or biased. However, it was the first to evaluate adherence to lifestyle recommendations in Japanese people with hypertension. In addition, this study targeted people with hypertension from a large nationally representative sample while other studies have often been clinic-based. It therefore has important implications regarding medical care for people with hypertension. Furthermore, our results indicate that adherence to lifestyle recommendations is associated with improved BP control in those with hypertension. Future studies should focus on developing more effective ways to implement lifestyle recommendations in people with hypertension and since the majority of the JSH guidelines will be revised in 2014, we intend to investigate achievement rates of their goals in 2014 and thereafter.
To our knowledge, this is the first study to systematically evaluate adherence to lifestyle recommendations among Japanese patients receiving hypertension treatment. As over half of the patients had poor BP control, they should make efforts to improve control by adopting lifestyle modifications, which should reduce the rate of complications.

The authors state that they have no conflicts of interest.

Acknowledgment

We thank all those at the institutes who kindly provided the data from individuals receiving annual health examinations used in this pilot study.

Members of the Ningen Dock Database Group

Principal investigator: Eiko Takahashi.

Advisory committee: Minoru Yamakado, Chikako Ito.


References


(Received October 10, 2013 ; Accepted December 20, 2013)
Acknowledgments

We are very grateful to the following individuals who served as reviewers for the papers submitted to Ningen Dock International Vol. 1 No.1, March 2014. I sincerely thank their kind cooperation.

Editor-in-Chief

Eiko Takahashi (2)
Hiroki Sugimori (1)
Hiroshi Hayashi (2)
Junichi Kaburaki (3)
Kazuhiko Kamei (1)
Kazuo Murakami (1)
Keiichiro Atarashi (1)
Kiminori Kato (1)
Kiyonobu Sakagami (1)
Minoru Yamakado (1)
Norihide Takaya (1)
Takeki Iwasaki (1)
Toshiki Fukui (1)
Toshimitsu Niwa (1)
Toshiyuki Shibosawa (1)
Yasuji Arase (2)
Yuzo Sato (1)
The Regulations of the International Society of Ningen Dock

Article 1
Name
The name of the association shall be the International Society of Ningen Dock.

Article 2
Office
The Society has its principal office in Japan Society of Ningen Dock.

Article 3
Aims
The Society, an organization of Japan Society of Ningen Dock for international operations, aims to contribute to global health promotion by enhancing the development of ningen dock as a medical check-up system.

Article 4
Tasks
The Society conducts the following tasks to achieve the aims described in the preceding section.
1. Holds congress (World Congress on Ningen Dock), board meetings, lectures, and committee meetings
2. Publishes journals and news magazines
3. Communicates and cooperates with related academic societies both in Japan and overseas
4. Promotes research activities in ningen dock and related fields
5. Does whatever is necessary to achieve the aims of the Society

Article 5
Membership
1. The Society consists of the following members
   1) Regular member
      A regular member shall be a member of the International Society of Ningen Dock who agrees to the aims of the Society, and has expert knowledge, techniques, or experience in the areas associated with the Society.
   2) Supporting member
      A supporting member shall be a person, a corporation, or a group that agrees to the aims of the Society, and supports its programs.
   3) Honorary member
      An honorary member shall be recommended, from those who have significantly contributed to the areas associated with the Society, by the executive board.
2. Those who want to apply for regular or supporting membership of the Society shall submit the prescribed application form with the membership fee.
3. The board meeting will process applications mentioned in the preceding section, and promptly notify the applicants of its decision.
Article 6
Officials
1. The Society shall appoint the following honorary advisors and officials.

Honorary advisor: Number not decided
Congress president: 1
President: 1
Vice president: 3 (from Japan: 2, overseas: 1)
Board members: up to 25 (from Japan: 15 or less, overseas: 10 or less)
Auditor: 2

Article 7
Honorary advisor
1. An honorary advisor shall be appointed by the president from those who have contributed to the development of the Society for a long period, and approved by the executive board.
2. Honorary advisors shall be eligible to attend the board meeting, and to express opinions; honorary advisors will not have voting rights.

Article 8
Congress president
1. The congress president shall be recommended by the executive board and appointed by the president.
2. The congress president shall represent the Society and host the World Congress on Ningen Dock as a scientific meeting.

Article 9
President
1. The president shall be selected by and from among board members and delegated by the president of the Japan Society of Ningen Dock.
2. The president shall preside the Society.

Article 10
Vice president
1. The vice president shall be appointed, from among board members, by the president.
2. The vice president shall assist the president. In the case of accident, one of the vice presidents will be appointed by the president and will temporarily take over the duties.

Article 11
Board members
1. Board members from Japan shall be selected among candidates from regular members at Japan Society of Ningen Dock.
2. Overseas board members shall be selected at the recommendation of the executive board.
3. Board members execute duties for the Society under the orders from the president.
4. Board members, together with the president and the vice president, comprise the executive board.
Article 12
Board meeting
1. The president will call a board meeting on an as-needed basis, and serves as the chairman of the meeting.
2. The board meeting will pass resolutions on important matters of the Society.
3. The board meeting shall have the right to start proceedings if the majority of all the board members (including a letter of proxy) attend the meeting.
4. The board meeting shall pass resolutions with the majority votes of attendances.

Article 13
Auditor
Auditors shall audit accounts of the Society, and report to the board meeting.

Article 14
Commissioner
For the aims of successful programs of the Society, the president will set up committees and divisions through the resolutions of the executive board, and delegate the commissioners to regular members or other members of the Society.

Article 15
Accounting
1. The fiscal year for the Society starts on April 1 every year and ends on March 31 the following year.
2. Expenses required for the Society shall be covered by the following revenues.
   1) Membership fees
   2) Grants
   3) Donations
   4) Others

Article 16
Modification of rules
The rules of the Society can be amended by the resolution of the executive board.

Article 17
Miscellaneous provisions
Detailed regulations necessary for the enforcement of the rules of the Society are defined elsewhere by the president with the approval of the executive board.

Article 18
Additional clause
The Regulations of the International Society of Ningen Dock will come into effect on September 15, 2006.
Detailed Regulations of the International Society of Ningen Dock

Detailed regulations of the International Society of Ningen Dock are defined as follows:

(Detailed regulations on members)

Article 1
1. Members shall pay the following annual membership fee; honorary members will be exempt from membership fee.
   1) Regular member: 2,000 yen
   2) Supporting member: from one unit (unit: 20,000 yen)
2. Annual membership fee paid shall not be refunded for any reason.
3. Members with foreign citizenship shall pay a 3-year membership fee of 50 dollars.

Article 2
Members will be given priority in the following events:
1) Participation in scientific meetings hosted by the Society;
2) Contributions of articles to and receipt of the journal of the Society.

Article 3
Members shall lose their memberships in the event of the following:
1) Withdrawal from membership;
2) Adjudication of incompetence or quasi-incompetence;
3) Death or adjudication of disappearance, or dissolution of the group in the case of a member of a supporting group;
4) Delinquency in payment of membership fee for over three years.

Article 4
Those intending to withdraw from the Society must submit the notice of withdrawal in the prescribed form to be approved by the executive board.

Article 5
The Society can expel a member to whom either of the following would apply, with a resolution of the executive board:
1) Those who violate their duty as members of the Society;
2) Those who damage the honor of members of the Society or act against the aims of the Society.

Article 6
Those who satisfy Sections 1 and 2 of Article 5 of the Regulations of the International Society of Ningen Dock will be accepted as members of the Society.

(Detailed regulations on officials)

Article 7
1. The president will be selected from the board members of Japan Society of Ningen Dock.
2. In principle, the majority of board members from Japan will be selected from among the board members of Japan Society of Ningen Dock.
3. Overseas board members will essentially be selected from Asia, Pacific Rim, North America, or Europe.

**Article 8**
1. The term of the congress president will be from the end of the congress of which he/she is in charge to the next congress.
2. The term of board members will be six years (two terms of three years).

**(Detailed regulations on congress and board meeting)**
**Article 9**
Congress and board meeting will be held as follows:
1) The title of the congress will be World Congress on Ningen Dock.
2) In principle, the congress and the board meeting will be held once every three years; with the resolution of the executive board, however, the congress and the board meeting will be held as needed.
3) The congress and the board meeting will be held at the same time.
4) The name of the congress president and the location of the next congress will be announced.

**Article 10**
1. Those who want to take part in the congress shall pay the participation fee, which is defined separately.
2. Participation fee for the congress will be defined accordingly by the congress president.
3. Only regular members shall be allowed to present the results of their studies, except those who have been approved by the congress president.

**(Enforcement of the detailed regulations)**
**Article 11**
1. The detailed regulations will come into effect on September 15, 2006.
INSTRUCTIONS TO AUTHORS
Ningen Dock International
Official Journal of Japan Society of Ningen Dock

Ningen Dock is the official journal of Japan Society of Ningen Dock, in which original articles, case reports, and review articles in both Japanese and English are published. Ningen Dock accepts only manuscripts that are original work in the field of ningen dock and related areas not previously published or being considered for publication elsewhere, except as abstracts. The manuscripts published in Ningen Dock will appear on the website of our society.

If the manuscript concerns a clinical study, it must be in accordance with the Declaration of Helsinki of 1964 (subsequent revisions included). Therefore, for a manuscript whose content is epidemiological or clinical research, the approval of the facility's Institutional Review Board (IRB) or the Ethics Committee of Japanese Society of Ningen Dock must have been obtained for the study described. Also, in the text, it should be indicated that informed consent has been obtained from subjects. Additionally, for case reports, it should be stated that adequate care has been taken to ensure the privacy of the subject concerned.

Online submission system
Ningen Dock uses an online submission system called ScholarOne Manuscripts. Please access http://mc.manuscriptcentral.com/ningendock
This site is only in Japanese at this time.

Preparation of manuscript
All manuscripts must be written in English with MS-Word, Excel, PowerPoint and/or a common graphic format. Authors who are not fluent in English must seek the assistance of a colleague who is a native English speaker and is familiar with the field of the manuscript.

The title, abstract, text, acknowledgments, references, tables, and figure legends should begin on separate sheets, with pages numbered, and be typed double-spaced using the 12-point font size in MS-Word. Files for submission should be prepared in English in a Microsoft Word or other file format that may be uploaded to the online system.

Available formats for files to be uploaded: doc (docx), xls (xlsx) ppt (pptx), jpg, tiff, gif, ai, eps, psd File names must consist of alphanumeric characters and an extension.

Example file names: Manuscript.doc, Fig1.jpg, Table1.xls, etc.

Please indicate the version of Microsoft Office used in a cover letter accompanying the uploaded files.

All measurements should be expressed in SI units. Less common abbreviations should be spelled out at first usage and the abbreviated form used thereafter.

Title page
Titles should be concise and informative. Include the full names of authors, names and addresses of affiliations, and name and address of a corresponding author to whom proofs are to be sent, including a fax number, telephone number and e-mail address.
Abstract
The abstract should not exceed 250 words, and should be arranged under the following subheadings: Objective, Methods, Results, Conclusions, and have up to 4 keywords.

Types of articles
Original articles: An original article should not exceed 3,000 words, and should be arranged as follows: Abstract, Objective, Methods, Results, Discussion, (Conclusion), (Acknowledgments), and References.
Case reports: A case report should not exceed 2,000 words, and be arranged as follows: Abstract (which should be a brief summary of the content without headings), Introduction, Case report, Discussion, and References.
Review articles: Review articles should not exceed 4,000 words. Review articles are usually by invitation. However, articles submitted without an invitation may also be considered by the Editorial Board.

References
References should be numbered consecutively in order of appearance in the text and cited in the text using superscript numbers. For example, according to the study by Sasamori1. For journals, the names and initials of the first three authors, followed by “et al” if there are other coauthors, the complete title, abbreviated journal name according to Index Medicus, volume, beginning and end pages, and year should be included. For books, the names and initials of the first three authors, followed by “et al” if there are other coauthors, the complete title, book name, edition number, beginning and end pages, name and city of publisher, and year should be included. Examples of references are given below.

Tables
Tables should be cited in the text, and numbered sequentially with Arabic numerals. Each table should be given a number and a brief informative title, and should appear on a separate page. Explain in footnotes all abbreviations used.

Figures
Figures should be cited in the text, and numbered sequentially with Arabic numerals. A brief descriptive legend should be provided for each figure. Legends are part of the text, and should be appended to it on a separate page. Color figures can be reproduces if necessary, but the authors will be expected to contribute towards the cost of publication.

Conflict of Interest (COI)
All authors are required to disclose any conflict of interest (COI) on the form designated by the Japan Society of Ningen Dock.

If no author has any COI, this should be indicated in the manuscript.
Page proofs
The corresponding author will receive PDF proofs, the author should correct only typesetting errors. After correcting, page proofs must be returned promptly.

Reprints
Thirty reprints of each paper are free, and additional reprints are available at charge in lots of 10, but for a minimum order of 50. Reprints should be ordered on submission of the manuscript as follows: For example, "I order 100 reprints: 30 (free) + 70."

The Editorial Board considers only manuscripts prepared according to the Instructions to Authors, and makes decisions regarding the acceptance of manuscripts as well as the order of printing them. All published manuscripts become the permanent property of Japan Society of Ningen Dock, and may not be published elsewhere without written permission from the Society.
Check list for submission of papers to Ningen Dock
Official Journal of Japan Society of Ningen Dock

Categories of manuscript:

☐ Original article (not more than 3,000 words)
☐ Case report (not more than 2,000 words)
☐ Review article (not more than 4,000 words)

Typing:

☐ Manuscript on A4 paper with wide margins
☐ Type double space using 12-point

Title page:

☐ Title of paper
☐ Full names of authors and affiliations without title of MD, PhD, etc
☐ Full name and address of a corresponding author including fax number, telephone number and e-mail address.
☐ Running title not more than 50 characters.

Abstract:

☐ Not more than 250 words.
☐ Arranged in the order of Background, Methods, Results, and Conclusion.
☐ Up to four key words.

Text of paper:

☐ Manuscript is arranged in the order of Objective, Methods, Results, Discussion, (Conclusion), (Acknowledgments), and References.
☐ Measurements are expressed in SI units.
☐ Abbreviations are spelled out at first usage.

References:

☐ References are numbered consecutively in order of appearance in the text and cited in the text using superscript numbers.
☐ Format is consistent with examples in Instructions for Authors.
Tables:
☐ Each table is given a number and a brief informative title, and appears on separate page.
☐ All abbreviations used are explained in footnotes.

Figures:
☐ Figure legends are appended to the text on a separate page.
☐ The top of the figure, the first author’s name, and the figure number are indicated lightly in soft pencil on the back of the four figures.

Submission:
☐ Check list, agreement, cover letter, manuscript (title page, abstract, text, acknowledgments, and references), figure legends, tables, figures and/or photos prepared in due form.
☐ One set of the original manuscript and three sets of the copies (with original photos, if any) are submitted.
☐ All pages are numbered.

Date: ________________________________

Name (print) ______________________ Signature ____________________________
Official Journal of Japan Society of Ningen Dock’s Agreement

1. The authors undersigned hereby affirm that the manuscript entitled:

________________________________________________________________________

is original and does not infringe any copyright, and that it has not been published in whole or in part and is not being submitted or considered for publication in whole or in part elsewhere except in the form of an abstract.

2. Assignment of Copyright. The authors hereby transfer, assign or otherwise convey all copyright ownership to Japan Society of Ningen Dock in the event this work is published by Japan Society of Ningen Dock in any format.

3. Signature of all authors:

Name (print)________________________Signature________________________Date__________

(A                         )

Name (print)________________________Signature________________________Date__________

(A                         )

Name (print)________________________Signature________________________Date__________

(A                         )

Name (print)________________________Signature________________________Date__________

(A                         )

Name (print)________________________Signature________________________Date__________

(A                         )

Name (print)________________________Signature________________________Date__________

(A                         )

Name (print)________________________Signature________________________Date__________

(A                         )

Name (print)________________________Signature________________________Date__________

(A                         )

Name (print)________________________Signature________________________Date__________

(A                         )
### Abbreviations

<table>
<thead>
<tr>
<th>No.</th>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,5-AG</td>
<td>1,5-anhydroglucitol</td>
</tr>
<tr>
<td>2</td>
<td>17-OHCS</td>
<td>17α-hydroxyprogesterone</td>
</tr>
<tr>
<td>3</td>
<td>95% CI</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>4</td>
<td>α-Gl</td>
<td>α-glucosidase inhibitor</td>
</tr>
<tr>
<td>5</td>
<td>β₂-MG</td>
<td>β₂-microglobulin</td>
</tr>
<tr>
<td>6</td>
<td>γ-GTP</td>
<td>γ-glutamyl transpeptidase</td>
</tr>
<tr>
<td>7</td>
<td>A/G ratio</td>
<td>Albumin-globulin ratio</td>
</tr>
<tr>
<td>8</td>
<td>ABI</td>
<td>ankle-brachial index</td>
</tr>
<tr>
<td>9</td>
<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
</tr>
<tr>
<td>10</td>
<td>ADL</td>
<td>activities of daily living</td>
</tr>
<tr>
<td>11</td>
<td>AFP</td>
<td>α-fetoprotein</td>
</tr>
<tr>
<td>12</td>
<td>ALP</td>
<td>alkaline phosphatase</td>
</tr>
<tr>
<td>13</td>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>14</td>
<td>Apo(a)</td>
<td>apolipoprotein (a)</td>
</tr>
<tr>
<td>15</td>
<td>APTT</td>
<td>activated partial thromboplastin time</td>
</tr>
<tr>
<td>16</td>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>17</td>
<td>BMI</td>
<td>body-mass index</td>
</tr>
<tr>
<td>18</td>
<td>CA 12S</td>
<td>carbohydrate antigen 125</td>
</tr>
<tr>
<td>19</td>
<td>CA 19-9</td>
<td>carbohydrate antigen 19-9</td>
</tr>
<tr>
<td>20</td>
<td>cAMP</td>
<td>cyclic adenosine 3', 5'-monophosphate</td>
</tr>
<tr>
<td>21</td>
<td>CAPD</td>
<td>continuous ambulatory peritoneal dialysis</td>
</tr>
<tr>
<td>22</td>
<td>CBC</td>
<td>complete blood count</td>
</tr>
<tr>
<td>23</td>
<td>Ccr</td>
<td>creatinine clearance</td>
</tr>
<tr>
<td>24</td>
<td>cDNA</td>
<td>complementary deoxyribonucleic acid</td>
</tr>
<tr>
<td>25</td>
<td>CEA</td>
<td>carcinoembryonic antigen</td>
</tr>
<tr>
<td>26</td>
<td>cGM</td>
<td>cyclic guanosine 3', 5'-monophosphate</td>
</tr>
<tr>
<td>27</td>
<td>ChE</td>
<td>cholinesterase</td>
</tr>
<tr>
<td>28</td>
<td>CKD</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>29</td>
<td>COI</td>
<td>conflict of interest</td>
</tr>
<tr>
<td>30</td>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>31</td>
<td>CK</td>
<td>creatine kinase</td>
</tr>
<tr>
<td>32</td>
<td>CRP</td>
<td>c-reactive protein</td>
</tr>
<tr>
<td>33</td>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>34</td>
<td>CVA</td>
<td>cerebrovascular accident</td>
</tr>
<tr>
<td>35</td>
<td>D-Bil</td>
<td>direct bilirubin</td>
</tr>
<tr>
<td>36</td>
<td>DBP</td>
<td>diastolic blood pressure</td>
</tr>
<tr>
<td>37</td>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>38</td>
<td>DRG</td>
<td>diagnosis-related group</td>
</tr>
<tr>
<td>39</td>
<td>dsDNA</td>
<td>double stranded deoxyribonucleic acid</td>
</tr>
<tr>
<td>40</td>
<td>EBM</td>
<td>evidence-based medicine</td>
</tr>
<tr>
<td>41</td>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>42</td>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
</tr>
<tr>
<td>43</td>
<td>EIA</td>
<td>enzyme immunoassay</td>
</tr>
<tr>
<td>44</td>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>45</td>
<td>EPO</td>
<td>erthropoietin</td>
</tr>
<tr>
<td>46</td>
<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>47</td>
<td>FBG</td>
<td>fasting blood glucose</td>
</tr>
<tr>
<td>48</td>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>49</td>
<td>FEV</td>
<td>forced expiratory volume</td>
</tr>
<tr>
<td>50</td>
<td>FEV₁</td>
<td>forced expiratory volume in one second</td>
</tr>
<tr>
<td>51</td>
<td>FEV₁%</td>
<td>forced expiratory volume % in one second</td>
</tr>
<tr>
<td>52</td>
<td>FPG</td>
<td>fasting plasma glucose</td>
</tr>
<tr>
<td>53</td>
<td>FSF</td>
<td>follicle stimulating hormone</td>
</tr>
<tr>
<td>54</td>
<td>FT3</td>
<td>free triiodothyronine</td>
</tr>
<tr>
<td>55</td>
<td>FT4</td>
<td>free thyroxine</td>
</tr>
<tr>
<td>56</td>
<td>FVC</td>
<td>forced vital capacity</td>
</tr>
<tr>
<td>57</td>
<td>GFR</td>
<td>glomerular filtration rate</td>
</tr>
<tr>
<td>58</td>
<td>GH</td>
<td>growth hormone</td>
</tr>
<tr>
<td>59</td>
<td>Hb</td>
<td>hemoglobin</td>
</tr>
<tr>
<td>60</td>
<td>HbA1c</td>
<td>hemoglobin A1c</td>
</tr>
</tbody>
</table>

**Note:** The table includes abbreviations that may not be fully explained in the text due to the limitations of the provided information. The full explanation of each abbreviation can be found in the context of the document. Additionally, some abbreviations may have multiple meanings depending on the field of study. For a comprehensive understanding, consult a medical dictionary or relevant scientific literature.
Notice about photocopying

In order to photocopy any work from this publication, you or your organization must obtain permission from the following organization which has been delegated for copyright clearance by the copyright owner of this publication.

Except in the USA
Japan Academic Association for Copyright Clearance, Inc. (JAACC)
6-41 Akasaka 9-chome, Minato-ku, Tokyo 107-0052 Japan
Phone : +81-3-3475-5618  Fax: +81-3-3475-5619
E-mail: info@jaacc.jp

In the USA
Copyright Clearance Center, Inc.
222 Rosewood Drive,
Denvers, MA 01923, U SA
Phone: +1-978-750-8400  Fax: +1-978-646-8600

Masaharu Nara
President
Japan Society of Ningen Dock