Table 1
Baseline characteristics of the study subjects.

	CAD (n=112)	p^*	Normolipidemic CAD (n=37)	p^*	Controls (n=30)
Age (years)	65.8±9.1	n.s.	65.5±9.0	n.s.	66.3±8.3
BMI (kg/m^2)	24.0±2.7	n.s.	24.1±3.4	n.s.	23.3±2.9
SBP (mmHg)	127±18.8	n.s.	123±19.7	<0.05	134±14.2
DBP (mmHg)	74.1±11.7	n.s.	71.7±12.5	<0.05	77.9±9.7
HbA1c (%)	7.3±1.4	<0.05	7.1±1.4	n.s.	6.4±1.2
T-Cho (mg/dL)	203±41.4	n.s.	181±22.9	n.s.	193±20.3
TG (mg/dL)	142±77.9	<0.001	92.2±25.4	n.s.	85.3±29.3
LDL-C (mg/dL)	131±34.7	0.051	110±21.7	n.s.	115±16.1
HDL-C (mg/dL)	43.9±9.4	<0.0001	49.8±8.6	<0.05	55.2±11.2
ApoA-I (mg/dL)	115±18.5	<0.0001	123±16.6	<0.01	137±21.0
ApoB (mg/dL)	108±27.3	<0.01	90.0±16.1	n.s.	93.4±12.3
Creatinine (mg/dL)	0.93±0.32	<0.01	0.93±0.34	<0.01	0.73±0.18
BUN (mg/dL)	17.7±7.3	n.s.	16.8±4.0	n.s.	15.4±4.0
AST (IU/L)	37±19.5	n.s.	38.1±16.3	n.s.	32.0±11.0
ALT (IU/L)	27.4±20.2	<0.05	29.1±22.8	<0.05	19.0±9.0
ChE (U/L)	325±77.6	n.s.	308±77.9	n.s.	316±67.2
Medications, n (%)					
Aspirin	90(80.4%)	<0.0001	28(75.7%)	<0.0001	2(6.7%)
Nitrates	87(77.7%)	<0.0001	24(64.9%)	<0.0001	1(3.3%)
Calcium channel blockers	51(45.5%)	n.s.	17(45.9%)	n.s.	13(43.3)
Beta blockers	37(33.0%)	n.s.	10(27.0%)	n.s.	5(16.7%)
ACE inhibitors	26(23.2%)	n.s.	8(21.6%)	n.s.	3(10.0%)
Diuretics	10(8.9%)	n.s.	3(8.1%)	n.s.	1(3.3%)
Digoxin	6(5.4%)	n.s.	0(0.0%)	n.s.	1(3.3%)
ARBs	2(1.8%)	n.s.	1(2.7%)	n.s.	1(3.3%)
Antiplatelet	27(24.1%)	<0.01	9(24.3%)	<0.01	0(0.0%)
Antidiabetics	45(40.2%)	n.s.	13(35.1%)	n.s.	9(30.0%)
Lipid-lowering agents	3(2.7%)	n.s.	1(2.7%)	n.s.	0(0.0%)

Data are shown as mean±S.D. or number. ARBs: angiotensin II receptor blockers.
* Significance vs. controls.

the preβ1-HDL level and lipid metabolism by examining for correlations between the preβ1-HDL level and the concentrations or activities of various lipid metabolic markers.

2. Methods

2.1. Study subjects

One hundred and twelve coronary artery disease patients were recruited from inpatients and outpatients of Chiba Cardiovascular Center (Chiba, Japan). The diagnosis of CAD was based on a history of myocardial infarction, clinical symptoms including prolonged chest pain, and the presence of angiographically demonstrated stenosis (≥75% obstructive lesions). The CAD group was divided into 36 patients with uAP and 76 patients with sCAD based on the clinical symptoms. uAP was diagnosed in accordance with the American Heart Association (AHA) classification (1975): the presence of chest pain which began during the previous 3 weeks and most recently occurred within the previous 1 week; and the absence of both ST segment elevation on the electrocardiogram and serum biochemical markers of cardiac necrosis. All patients with uAP belonged to class I or II in severity and class B or C in the clinical circumstances according to Braunwald's classification (1989). The sCAD subgroup was composed of 32 patients with stable effort angina pectoris and 44 patients with old myocardial infarction. We also enrolled 30 age- and BMI-matched subjects as the control group. The control subjects were recruited from outpatients of Chiba Cardiovascular Center and included type 2 diabetics and/or hypertension patients without dyslipidemia and no history of CAD. The control subjects were all confirmed to have no cardiac disorders on the exercise-loaded electrocardiogram. Normolipidemic subjects in the CAD group and the control group were determined on the basis of the concentrations of four serum lipid markers, i.e., total cholesterol (T-Cho) <220 mg/dL, LDL-cholesterol (LDL-C) <140 mg/dL, triglyceride (TG) <150 mg/dL, and HDL-cholesterol (HDL-C) ≥40 mg/dL. Patients with renal and/or liver dysfunction were excluded from this study.

We obtained informed consent from all participants at entry. This study was conducted in accordance with the Declaration of Helsinki of the World Medical Association.

2.2. Blood collection

Venous blood samples for plasma and serum were drawn from the subjects after fasting for one night. The blood samples for plasma were drawn into plastic tubes containing EDTA-2Na, immediately chilled in ice water and centrifuged at 2 °C. The plasma was diluted with 20 volumes of 50% sucrose solution for stabilization and then stored at −80 °C until preβ1-HDL was assayed. The blood samples for serum were separated and stored at −80 °C until assay for serum lipids, apolipoproteins, LCAT activity and other markers of liver or renal function.

2.3. Measurement of preβ1-HDL and biochemical parameters

Preβ1-HDL levels were measured by a sandwich enzyme immunoassay using Mab55201 [15,18]. The preβ1-HDL level was expressed as both an absolute value and a relative value. The absolute value indicates the preβ1-HDL concentration (mg/L) in the plasma, and the relative value indicates the percentage of preβ1-HDL in the total apolipoprotein A-I in the plasma.

The T-Cho, TG, LDL-C, HDL-C, creatinine, blood urea nitrogen (BUN), aspartate transaminase (AST), alanine transaminase (ALT) and cholinesterase (ChE) concentrations were determined enzymatically using an automated analyzer. Apolipoprotein concentrations were determined by immunoturbitometry with commercial reagents from Daiichi Pure Chemicals (Tokyo, Japan), using an automated analyzer. Hemoglobin A1c (HbA1c) was determined by an automated liquid-chromatographic system. LCAT

Table 2
Comparisons of preβ1-HDL levels between CAD and control groups and between uAP and sCAD subgroups.

	n	Preβ1-HDL (mg/L)	p	Preβ1-HDL/apoA-I (%)	p
CAD	112	34.8 ± 12.9	<0.001*	3.05 ± 1.04	<0.0001*
Normolipidemic CAD	37	36.2 ± 12.8	<0.001*	2.94 ± 0.95	<0.0001*
CAD (HDL-C ≥ 40 mg/dL)	74	36.9 ± 13.1	<0.0001*	2.98 ± 0.97	<0.0001*
CAD (high LCAT**)	28	36.5 ± 12.3	<0.001*	3.15 ± 0.93	<0.0001*
Controls	30	26.6 ± 6.9	–	1.97 ± 0.51	–
uAP	36	43.1 ± 11.5	<0.0001	3.66 ± 0.95	<0.0001
sCAD	76	30.9 ± 11.7		2.76 ± 0.95	
Normolipidemic					
uAP	16	43.1 ± 9.1	<0.01	3.42 ± 0.76	<0.01
sCAD	21	30.9 ± 12.8		2.58 ± 0.94	
HDL-C ≥ 40 mg/dL					
uAP	26	44.9 ± 11.6	<0.0001	3.54 ± 0.87	<0.001
sCAD	48	32.6 ± 11.9		2.68 ± 0.89	
HDL-C < 40 mg/dL					
uAP	10	38.3 ± 10.3	<0.05	4.00 ± 1.10	<0.01
sCAD	28	28.1 ± 11.0		2.90 ± 1.05	

Data are shown as mean ± S.D.
* Significance vs. controls.
** LCAT activity ≥80 nmol/mL/h/37 °C.

activities were determined only in 58 randomly selected CAD (9 uAP and 49 sCAD) patients, by the method of Nagasaki and Akanuma using an endogenous substrate [19].

2.4. Statistics

Statistical analyses were performed using Stat Flex for Windows ver. 5.0 (Artech Inc., Osaka, Japan). The difference between two groups was assessed using Student's paired *t*-test. Categorical variables were compared using the χ^2-test. The relationship between two parameters was examined using Pearson's Correlation Coefficient. Receiver-operating characteristic (ROC) curves were plotted, and the area under the curve (AUC) was analyzed to compare the predictive powers of preβ1-HDL, HDL-C and LDL-C for uAP using the sCAD and the control group as reference groups. The AUC indicates the diagnostic accuracy of tests [20]. For all analyses, $p < 0.05$ was considered statistically significant.

Table 3
Comparisons of baseline characteristics between sCAD and uAP subgroups.

	uAP (*n* = 36)	sCAD (*n* = 76)	p
Age (years)	67.0 ± 8.8	65.3 ± 9.2	n.s.
BMI (kg/m²)	24.6 ± 3.4	23.8 ± 2.4	n.s.
SBP (mmHg)	129 ± 22.3	126 ± 16.9	n.s.
DBP (mmHg)	76.8 ± 13.5	72.9 ± 10.7	n.s.
HbA1c (%)	7.5 ± 1.3	7.3 ± 1.4	n.s.
T-Cho (mg/dL)	191 ± 41.8	209 ± 40.2	<0.05
TG (mg/dL)	129 ± 67.4	147 ± 82.1	n.s.
LDL-C (mg/dL)	118 ± 35.6	132 ± 33.5	<0.05
HDL-C (mg/dL)	44.4 ± 9.8	43.6 ± 9.2	n.s.
ApoA-I (mg/dL)	119 ± 20.3	112 ± 17.3	n.s.
ApoB (mg/dL)	100 ± 26.3	112 ± 27.0	<0.05
Creatinine (mg/dL)	0.96 ± 0.29	0.91 ± 0.34	n.s.
BUN (mg/dL)	17.7 ± 4.8	17.8 ± 8.2	n.s.
AST (IU/L)	39.8 ± 21.2	35.7 ± 18.7	n.s.
ALT (IU/L)	28.6 ± 20.6	26.9 ± 20.1	n.s.
ChE (U/L)	30.5 ± 89.8	335 ± 69.6	n.s.
LCAT activity (nmol/mL/h/37 °C)*	72.9 ± 21.0	72.9 ± 12.4	n.s.
Medications, *n* (%)			
Aspirin	28 (77.8%)	62 (81.6%)	n.s.
Nitrates	27 (75.0%)	60 (78.9%)	n.s.
Calcium channel blockers	16 (44.4%)	35 (46.1%)	n.s.
Beta blockers	12 (33.3%)	25 (32.9%)	n.s.
ACE inhibitors	10 (27.8%)	16 (21.1%)	n.s.
Diuretics	4 (11.1%)	6 (7.9%)	n.s.
Digoxin	1 (2.8%)	5 (6.6%)	n.s.
ARBs	0 (0.0%)	2 (2.6%)	n.s.
Antiplatelet	11 (30.6%)	16 (21.1%)	n.s.
Antidiabetics	9 (25.0%)	36 (47.4%)	<0.05
Lipid-lowering agents	1 (2.8%)	2 (2.6%)	n.s.

Data are shown as mean ± S.D. or number (%). ARBs: angiotensin II receptor blockers.
* Determined in 9 uAP and 49 sCAD patients.

3. Results

3.1. Comparison between CAD patients and controls

Table 1 shows the baseline characteristics of the study subjects. Age, BMI and blood pressure were comparable between the CAD and control groups. The concentrations of HbA1c, TG and apoB were significantly higher, and the concentrations of HDL-C and apoA-I were significantly lower, in the CAD group than in the control group. In the normolipidemic subjects, the only differences were that the concentrations of HDL-C and apoA-I were slightly higher in the control group. Medications were comparable between the CAD and control groups except for aspirin, nitrates and antiplatelet drugs. The absolute and relative values for the preβ1-HDL level were markedly higher in the CAD group than in the control group. These differences were also seen even in the normolipidemic subjects only (Table 2). We then compared the preβ1-HDL levels between the CAD subgroups with high HDL-C (≥40 mg/dL) or high LCAT activity (≥80 nmol/mL/h/37 °C) and the control group. The preβ1-HDL levels were markedly higher in both the CAD subgroups than in the control group (Table 2).

3.2. Comparison between uAP and sCAD subgroups

We divided the CAD group into a uAP subgroup and an sCAD subgroup and compared the preβ1-HDL levels between them. The absolute and relative values for the preβ1-HDL level were markedly higher in the uAP subgroup than in the sCAD subgroup. Moreover, even in the comparisons using only the normolipidemic subjects, only the high HDL-C (≥40 mg/dL) subjects and only the low HDL-C (<40 mg/dL) subjects, the differences remained significant between the two subgroups (Table 2). On the other hand, the concentrations of lipid markers, age, BMI, blood pressure, renal and hepatic function markers and medications did not differ between the uAP and

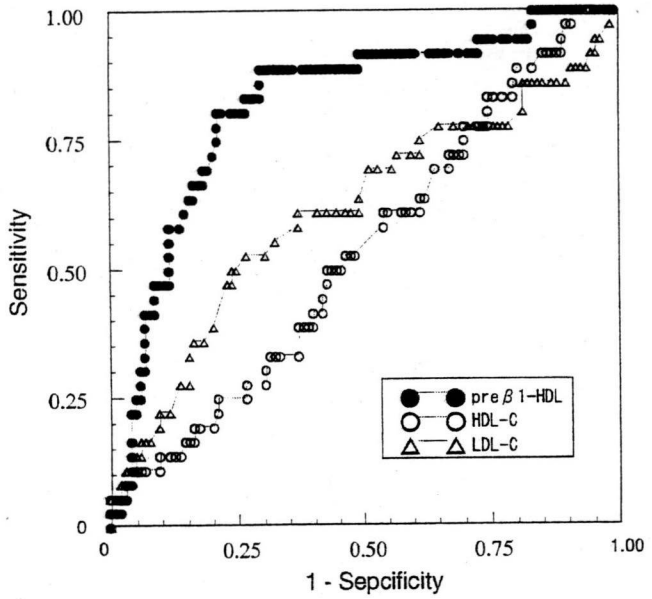

Fig. 1. ROC curves of preβ1-HDL, HDL-C, LDL-C for diagnosis of uAP. The true-positive rate (sensitivity as *y* axis) was plotted vs. the false-positive rate (1-specificity as *x* axis) by changing the cutoff values for the test. The areas under the curves were 0.821 (95% CI, 0.780–0.863) for preβ1-HDL, 0.536 (95% CI, 0.482–0.591) for HDL-C and 0.616 (95% CI, 0.557–0.675).

sCAD subgroups, except that the concentrations of T-Cho, LDL-C and apoB were slightly lower and that the patients taking antidiabetics were slightly fewer in number in the uAP subgroup (Table 3).

3.3. Preβ1-HDL as a diagnostic marker of uAP

ROC analyses were performed to evaluate preβ1-HDL as a diagnostic marker of uAP. The AUC of preβ1-HDL was significantly greater than that of either HDL-C or LDL-C (vs. HDL-C, $p < 0.0001$; vs. LDL-C, $p < 0.01$) (Fig. 1).

3.4. Correlations between preβ1-HDL level and clinical factors

We examined for correlations between the absolute preβ1-HDL concentration and various clinical factors in the CAD patients and in the control subjects. In the CAD patients, the preβ1-HDL concentration showed a strong, significant positive correlation with apoA-I and a significant positive correlation with HDL-C. On the other hand, no correlation was found with the LDL-C, T-Cho or LCAT activity. TG showed a slightly positive correlation with preβ1-HDL. The only other marker correlating significantly with preβ1-HDL was ALT, which correlated slightly. In the control subjects, none of the factors showed a significant correlation with preβ1-HDL (Table 4).

Table 4
Correlations between preβ1-HDL and clinical factors.

	CAD group ($n = 112$)		Control group ($n = 30$)	
	r	p	r	p
Age	0.163	n.s.	−0.122	n.s.
BMI	0.134	n.s.	−0.026	n.s.
SBP	−0.037	n.s.	0.117	n.s.
DBP	0.003	n.s.	0.115	n.s.
HbA1c	0.127	n.s.	−0.039	n.s.
T-Cho	0.146	n.s.	−0.013	n.s.
TG	0.200	<0.05	−0.157	n.s.
LDL-C	0.025	n.s.	−0.054	n.s.
HDL-C	0.247	<0.01	0.194	n.s.
ApoA-I	0.400	<0.0001	0.189	n.s.
ApoB	0.070	n.s.	−0.157	n.s.
Creatinine	0.172	n.s.	−0.012	n.s.
BUN	0.183	n.s.	0.181	n.s.
AST	0.182	n.s.	0.035	n.s.
ALT	0.207	<0.05	−0.195	n.s.
ChE	0.068	n.s.	−0.033	n.s.
LCAT activity*	0.204	n.s.	–	–

* Determined in 58 CAD patients.

We then examined for correlations between the preβ1-HDL and the HDL-C, apoA-I or LCAT activity in the uAP and sCAD subgroups separately. HDL-C showed a significant positive correlation with preβ1-HDL in the sCAD subgroup, but not in the uAP subgroup (Fig. 2A). ApoA-I showed a significant positive correlation with preβ1-HDL in both the uAP and sCAD subgroups (Fig. 2B), whereas LCAT activity did not (Fig. 2C).

4. Discussion

The present study clearly showed that the plasma preβ1-HDL level was high in the CAD group even when excluding dyslipidemic patients (Table 2). Earlier studies reported the plasma preβ1-HDL concentration to be elevated in patients with CAD, dyslipidemia and obesity, and also in hemodialysis patients [15–17,21,22]. The present study excluded patients with renal disorders, including hemodialysis patients, and BMI-matched control subjects were

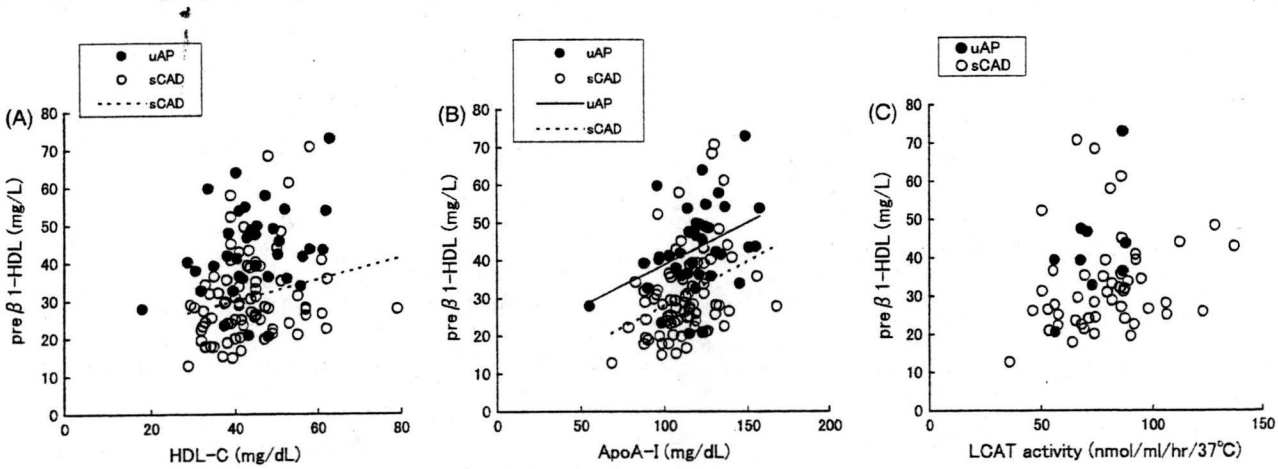

Fig. 2. Correlations (Pearson's Coefficients) between preβ1-HDL levels and HDL-C levels (A), apoA-I levels (B) and LCAT activities (C) in uAP and sCAD subgroups. A: uAP ($n = 36$), $r = 0.313$, $p = 0.063$; sCAD ($n = 76$), $r = 0.227$, $p < 0.05$. B: uAP ($n = 36$), $r = 0.394$, $p < 0.05$; sCAD ($n = 76$), $r = 0.350$, $p < 0.01$. C: uAP ($n = 9$), $r = 0.538$, $p = 0.135$; sCAD ($n = 49$), $r = 0.215$, $p = 0.139$.

used to exclude any effect of obesity. When the CAD group was divided into uAP and sCAD subgroups, the preβ1-HDL level was markedly higher in the uAP subgroup than in the sCAD subgroup. Moreover, the difference remained significant even when dyslipidemic patients were excluded from the two subgroups (Table 2). The age, BMI, blood pressure and concentrations of HbA1c, hepatic function markers, renal function markers, HDL-C and apoA-I did not differ significantly between the two subgroups, although T-Cho, LDL-C and apoB were somewhat lower in the uAP subgroup than in the sCAD subgroup (Table 3). ROC analyses were performed to investigate the potential of preβ1-HDL as a predictive marker for uAP. Preβ1-HDL showed better diagnostic accuracy than other lipid markers, suggesting that preβ1-HDL may be useful for identifying patients with uAP (Fig. 1).

Two earlier studies reported elevation of the preβ1-HDL levels in CAD patients [16,17]. However, the mechanism responsible for that elevation has not been elucidated. Miida et al. reported that delayed catabolism of preβ1-HDL, specifically, delayed LCAT-dependent conversion of preβ1-HDL into α-migrating HDL, causes elevation of the preβ1-HDL level in CAD patients. However, they also described that some CAD patients had a high preβ1-HDL level despite the high LCAT activity, suggesting that some other mechanism may be responsible for preβ1-HDL elevation [16]. Asztalos et al. reported that CAD patients with low HDL-C levels (≤35 mg/dL) have high preβ1-HDL levels and suggested that delayed catabolism of preβ1-HDL is responsible for the elevated preβ1-HDL [17]. In our study, the normolipidemic CAD patients, excluding those with low HDL-C levels (<40 mg/dL), also showed elevated preβ1-HDL levels (Table 2). We speculate that the many uAP patients included in the present study may have been the cause of the elevated preβ1-HDL level in CAD patients without dyslipidemia. If, as has been suggested [17], delayed catabolism of preβ1-HDL is responsible for preβ1-HDL elevation, the HDL-C concentration and LCAT activity should be lower in the uAP subgroup than in the sCAD subgroup and should correlate negatively with the preβ1-HDL concentration. However, we could not find any difference in either the HDL-C concentration or the LCAT activity between the uAP and sCAD subgroups (Table 3), and there was no negative correlation between the preβ1-HDL concentration and either the HDL-C concentration or the LCAT activity in the CAD patients. In fact, the preβ1-HDL concentration conversely showed a significant and positive correlation with the HDL-C concentration in the CAD patients (Table 4 and Fig. 2A). In addition, the CAD patients with either a high HDL-C level or high LCAT activity also showed an elevated preβ1-HDL level (Table 2). These results suggest that some other mechanism must be responsible for preβ1-HDL elevation.

Perhaps that mechanism is enhancement of preβ1-HDL formation. The following three formation pathways are known: synthesis in the liver [9,10], new formation through interaction of apoA-I and peripheral cells [6–8] and dissociation through remodeling of α-HDL [11]. In the case of CAD, the last two of these preβ1-HDL formation pathways seem most likely and are discussed below.

Preβ1-HDL formation is increased in atherosclerotic CAD due to accelerated interaction of apoA-I and peripheral cells. It was reported that foam cell formation enhanced expression of ATP-binding cassette transporter A1 and apoA-I-mediated cholesterol efflux from cells in *in vitro* experiments [23,24]. Since preβ1-HDL is formed by the cellular cholesterol efflux of lipid-free apoA-I or lipid-poor apoA-I mediated by ABCA1 [3,4,6–8], the formation of preβ1-HDL in atherosclerotic CAD caused by accumulation of excess cholesterol might be accelerated by enhancement of that efflux in the peripheral cells.

The other most likely pathway of preβ1-HDL formation in uAP is that preβ1-HDL generation is enhanced by α-HDL remodeling caused by an increase in acute-phase proteins during inflammation. Serum amyloid A (SAA), group IIa secretory phospholipase A2 (sPLA2-IIa) and phospholipid transfer protein (PLTP), whose blood concentrations or activities are elevated in the acute-phase, are known to be factors that facilitate α-HDL remodeling [25–28]. For example, it was reported that the amount of SAA in HDL particles increases markedly during the acute inflammatory phase [28] and that it dissociates preβ1-HDL from α-HDL when it binds to α-HDL [29]. The blood concentration of SAA increases in uAP [30], and SAA is highly expressed in atherosclerotic lesions [31]. van der Westhuyzen et al. suggested a model for the acute-phase response in CAD in which SAA and sPLA2-IIa, present at sites of inflammation and tissue damage, play protective roles by enhancing cellular cholesterol efflux, thereby promoting the removal of excess cholesterol from macrophages [25]. Thus, acute-phase proteins, including SAA, seem to be factors promoting preβ1-HDL elevation in uAP, although the results of the present study are not sufficient to prove this hypothesis.

In summary, we demonstrated that the preβ1-HDL level is elevated in CAD patients, especially in uAP patients, even when excluding dyslipidemic subjects. These results suggest that elevation of the plasma preβ1-HDL level is associated with the atherosclerotic phase of CAD. Elevation of plasma preβ1-HDL may be useful for the identification of patients with uAP. Moreover, that elevation may be caused by a different mechanism from the previously proposed delayed catabolism of preβ1-HDL due to low LCAT activity.

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Review

Establishment of a concept of visceral fat syndrome and discovery of adiponectin

By Yuji MATSUZAWA[*1,*2,†]

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Abstract: Although obesity is a major background of life style-related diseases such as diabetes mellitus, lipid disorder, hypertension and cardiovascular disease, the extent of whole body fat accumulation does not necessarily the determinant for the occurrence of these diseases. We developed the method for body fat analysis using CT scan and established the concept of visceral fat obesity, in other word metabolic syndrome in which intra-abdominal visceral fat accumulation has an important role in the development of diabetes, lipid disorder, hypertension and atherosclerosis. In order to clarify the mechanism that visceral fat accumulation causes metabolic and cardiovascular diseases, we have analyzed gene expression profile in subcutaneous adipose tissue and visceral adipose tissue. From the analysis, we found that adipose tissue, especially visceral adipose tissue expressed abundantly the genes encoding bioactive substances such as cytokines, growth factors and complements. In addition to known bioactive substances, we found a novel collagen-like protein which we named adiponectin. Adiponectin is present in plasma at a very high concentration and is inversely associated with visceral fat accumulation. Adiponectin has anti-diabetic, anti-hypertensive and anti-atherogenic properties and recent studies revealed that this protein has an anti-inflammatory and anti-oncogenic function. Therefore hypoadiponectinemia induced by visceral fat accumulation should become a strong risk factor for metabolic and cardiovascular diseases and also some kinds of cancers.

In this review article, I would like to discuss the mechanism of life style-related diseases by focusing on the dysregulation of adiponectin related to obesity, especially visceral obesity.

Keywords: visceral fat, metabolic syndrome, adiponectin, hypoadiponectinemia

Fat distribution and morbidity of obesity

Contemporary civilized countries provide an increasing number of opportunities for overeating and decreased muscular exercise, where common health problems are closely correlated to this over-nutritional state and its typical consequence, obesity. However, previous studies on the morbidity of obesity have indicated that the severity of obesity-related diseases such as diabetes mellitus, lipid disorders and cardiovascular disease does not necessarily correlate to the extent of body fat accumulation, but it closely related to body fat distribution. Several classifications of obesity concerning body fat distribution have been proposed in order to distinguish the possible mechanisms of obesity-related diseases. An ancient Japanese artist showed great insight into the morbidity of obesity 800 years ago when he painted a picture of an obese woman with the title "A very obese woman who can hardly walk" (Fig. 1) in the old Japanese picture scroll "Yamai Zoshi" which means an illustrated scroll for various diseases. Comparing the body figure of an obese girl painted by famous Renoir, she has marked adiposity in her abdomen.

In the end of 1940s, Prof. Vague noted that "Fat excess is dangerous because of its metabolic complications and a woman normally has twice a man's fat mass, i.e. the mass of an obese man. Though she is as often obese a man or is fatter, she dies later and less often from metabolic complica-

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Fig. 1. High risk obesity (left) and low risk obesity (right) in classical paintings.

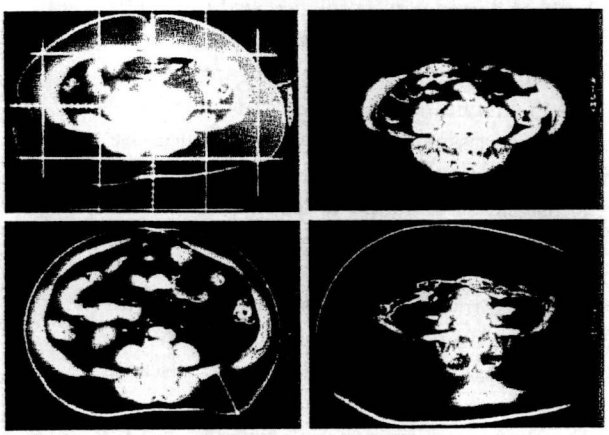

Fig. 2. Marked variation of fat distribution between intra-abdominal cavity and subcutane.[4]

tions of obesity." Then he proposed a classification of obesity into android type and gynoid type in 1947.[1] His classification was based on the brachio-femoral adipomuscular ratio (BFAMR) and the subjects with higher BFAM were designated to be android type in whom metabolic complications were more prevalent. Although his classification is not exactly the same as current one, he is no doubt a pioneer of recognition for high risk obesity based on fat distribution.

In early 1980s, Prof. Björntorp proposed a classification between central obesity and peripheral obesity and Prof. Kissebah proposed a classification between upper body segment obesity and lower body segment obesity based on waist/hip ratio.[2),3)] Our group developed the method for fat analysis using CT scan which enabled us to analyze adipose tissues in body cavity in 1983 and we noticed that there is marked variation in fat distribution between subcutaneous fat and intra-abdominal visceral fat. (Fig. 2)[4)]

Visceral fat accumulation and metabolic or cardiovascular diseases

Using CT scan method for fat analysis, we demonstrated the contribution of visceral fat accumulation to the development of metabolic disorders, including glucose intolerance and hyperlipidemia. For example, visceral fat area determined by CT correlates significantly with glucose area after oral glucose tolerance test, and with cholesterol and triglyceride levels.[5),6)] Visceral fat accumulation is associated not only with quantitative changes in serum lipids and lipoproteins and but also with qualitative changes in lipoproteins, such as small dense LDL. Studies on muscle glucose uptake reported by Kissebah *et al.*[7)] and the steady-state plasma glucose method by our group,[8)] clearly show that visceral fat obesity has greater insulin resistance than subcutaneous fat obesity.

In addition to these metabolic disorders, we have demonstrated that in premenopausal women visceral fat accumulation correlates closely with systolic blood pressure.[9)] In hypertensive people, we reported a close correlation between the extent of visceral fat reduction, not subcutaneous fat reduction, and a lowering of blood pressure after weight reduction.

Visceral fat accumulation relates to the development of cardiovascular risks mentioned above and might relate directly to the development of cardiovascular disease. Several studies, including ours, have shown that visceral adiposity determined by CT scanning is related to coronary artery disease even in mildly obese individuals.[10)] Visceral fat accumulation is also related to the development of cardiac dysfunction and sleep apnea syndrome.[11),12)] From these evidences, we can conclude that visceral fat accumulation is a major risk of cardiovascular disease as well as metabolic diseases.(Fig. 3)

Visceral fat syndrome and metabolic syndrome

In the end of 1980s, the concept of multiple risk factor clustering syndrome has been proposed as a

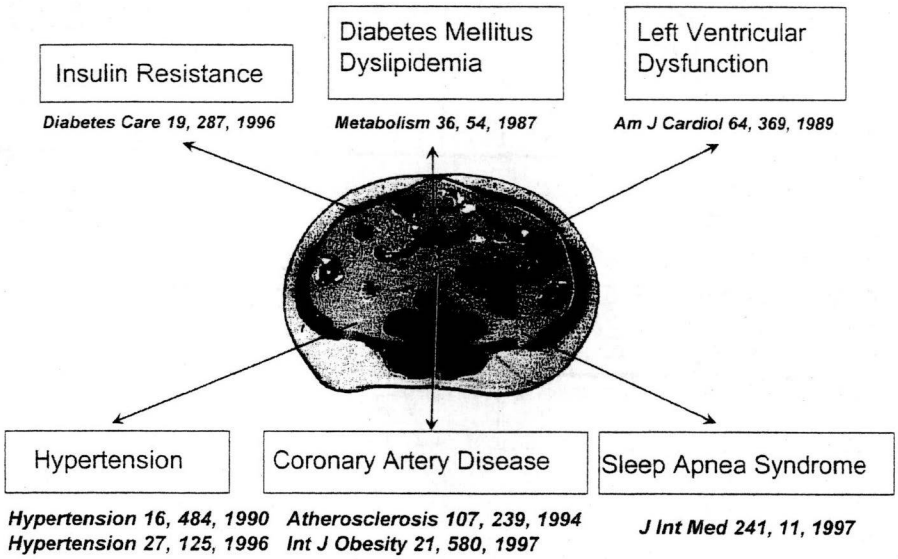

Fig. 3. Visceral fat accumulation is related a variety of diseases.

highly atherogenic state independent from hypercholesterolemia.[13),14)] A variety of common disorders, such as hyperglycemia, hyperlipidemia and hypertension, are seen in individuals with this syndrome, and cardiovascular disease is very prevalent and this syndrome has been called to be the metabolic syndrome. The disorders such as diabetes, dyslipidemia and hypertension are not clustered coincidently, and there is thought to be a key to the simultaneous development within certain individuals along with the associated development of cardiovascular disease. As I showed above, visceral fat accumulation might be present in the upstream of a variety of disorders including cardiovascular disease. Therefore we have proposed the concept of a visceral fat syndrome on the basis of our clinical researches shown above as the same concept of metabolic syndrome.[15)] An important question is, then, why does visceral fat accumulation causes common disorders; more importantly, why is this syndrome so atherogenic? In order to answer these questions, we have investigated the functions of adipose-tissue, which has been traditionally regarded as a tissue passively storing excess energy in the form of triglycerides.

The concept of adipocytokines

To elucidate the molecular mechanism of visceral fat-related diseases, particularly those in the metabolic syndrome, we have investigated the biological characteristics of visceral adipose tissue and subcutaneous adipose tissue by analysis of the gene-expression profile compared with that of other mesenchymal cells. We systematically analyzed active genes by constructing a 3′-directed complementary DNA library in which the messenger RNA population was faithfully reflected. We found an unexpectedly high frequency of the genes encoding secretary proteins in adipose tissue, most of which are important bioactive substances. Of the gene group classified by functions and subcellular localization, approximately 20% of all genes in subcutaneous adipose tissue encode secretory proteins. This frequency rises to about 30% in visceral adipose tissue. (Fig. 4) We classified these adipose-tissue-derived bioactive substances as adipocytokines. (Fig. 5)

Adipocytokines and diseases

We found that the genes encoding plasminogen activator inhibitor type 1 (PAI-1) and heparin binding epidermal growth factor-like growth factor are highly expressed in adipose tissue.[16),17)] PAI-1 messenger RNA concentrations increased up to 10-fold in visceral adipose tissue during development of fat accumulation in ventromedial hypothalamic-lesioned rats, which is an experimental animal model of obesity. In subcutaneous adipose tissue, concentrations remained unchanged. In addition to the animal model, we demonstrated that plasma levels of PAI-1 were significantly correlated with visceral adiposity, assessed by CT scanning, in humans. (Fig. 6) Circu-

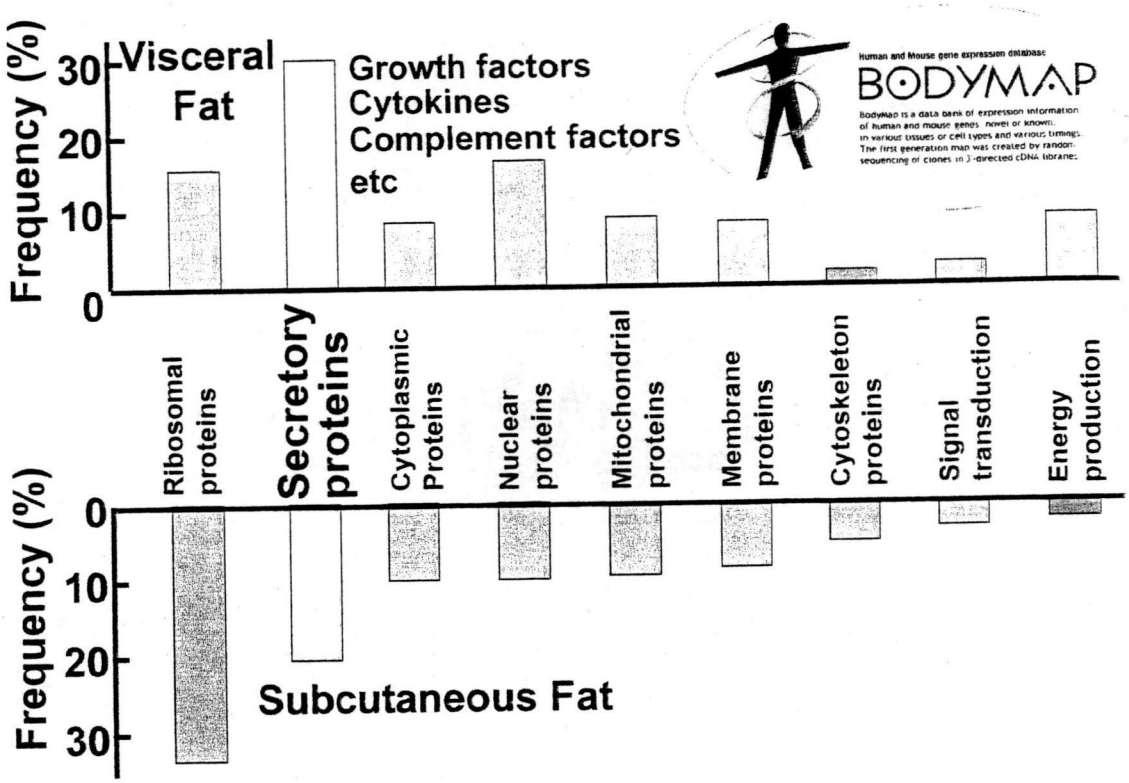

Fig. 4. Distribution profile of gene groups expressed in visceral fat and subcutaneous fat.[44]

lating PAI-1 is deemed as a strong risk factor for thrombotic diseases, including acute myocardial infarction, in metabolic syndrome.[18] Heparin binding epidermal growth factor-like growth factor, a potent factor for smooth-muscle-cell proliferation, secreted from accumulated adipose tissue could also have some significance for vascular remodeling in obesity. Tumor necrosis factor-α was also reported to be secreted from adipose tissue and to induce insulin resistance by Dr. Hotamisligil.[19]

Discovery of adiponectin and its clinical significance

When we started the comprehensive genetic analysis of human adipose tissue, 40% of the expressed genes were previously unknown genes. The gene expressed most abundantly in adipose tissue, which we named adipose most abundant gene transcript-1, apM-1, was a novel gene.[20] The molecule encoded by apM-1 possesses a signal peptide, collagen-like motif and globular domain, and has notable homology with collagen X, VIII and complement factor C1q. This protein is present in plasma in a unique multimer form, which is more active than low molecule weight form. (Fig. 7) We termed this collagen-like protein adiponectin. The mouse homolog of adiponectin has been cloned as ACRP30.[21] We established the method for the measurement of plasma adiponectin levels using enzyme-linked immunosorbent assay. The average levels of adiponectin in human plasma are extremely high-up to 5–10 μg/ml.[22] Plasma concentrations are negatively correlated with visceral adiposity, whereas PAI-1 increases with visceral fat accumulation as mentioned previously. (Fig. 6)

The mechanism by which plasma levels are reduced in individuals with visceral fat accumulation is not yet clarified. Co-culture with visceral fat inhibits adiponectin secretion from subcutaneous adipocytes. This finding suggests that some inhibiting factors for adiponectin synthesis or secretion are secreted from visceral adipose tissue.[23] Tumor necrosis factor-α was reported to be a strong inhibitor of adiponectin promoter activity.[24] The negative correlation between visceral adiposity and adiponectin levels might be explained by the increased secretion

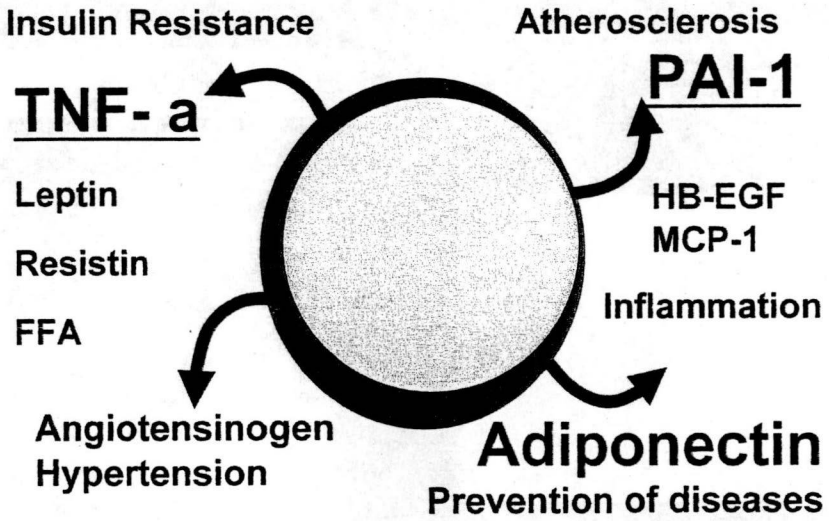

Fig. 5. Concept of adipocytokines.

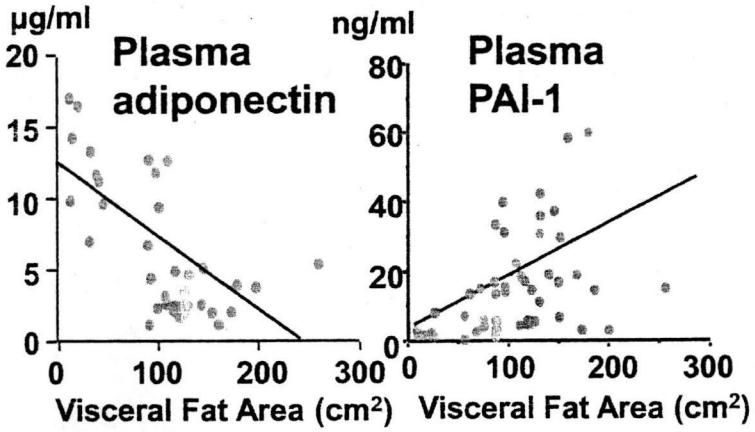

Fig. 6. Correlation between visceral adiposity and plasma levels of adiponectin and PAI-1.[44]

of this cytokine from accumulated visceral fat as at least one mechanism.

Plasma adiponectin concentrations are lower in people who have type 2 diabetes mellitus than in BMI-matched controls.[25] The plasma concentrations have been shown to correlate strongly with insulin sensitivity, which suggests that low plasma concentrations are related to insulin resistance.[26] In a study of Pima Indians, individuals with high levels of adiponectin were less likely than those with low concentrations to develop type 2 diabetes. High adiponectin concentration was, therefore, a notable protective factor against development of type 2 diabetes.[27]

Studies on adiponectin knockout mice support observations in humans. The KO mice showed no specific phenotype when they were fed a normal diet but a high-sucrose and high-fat diet induced a marked elevation of plasma glucose and insulin levels. Notable insulin resistance, estimated by insulin tolerance test during the high-sucrose with high-fat diet, also developed in the knockout mice. The supplementation of adiponectin by adenovirus transfection clearly improved this insulin resistance.[28] Adiponectin has been shown to exert its actions on muscle fatty acid oxidation and insulin sensitivity by activation of AMP-activated protein kinase.[29]

Plasma levels of adiponectin are also decreased in hypertensive humans, irrespective of the presence of insulin resistance.[30] Endothelium-dependent vasoreactivity is impaired in people with hypoadiponecti-

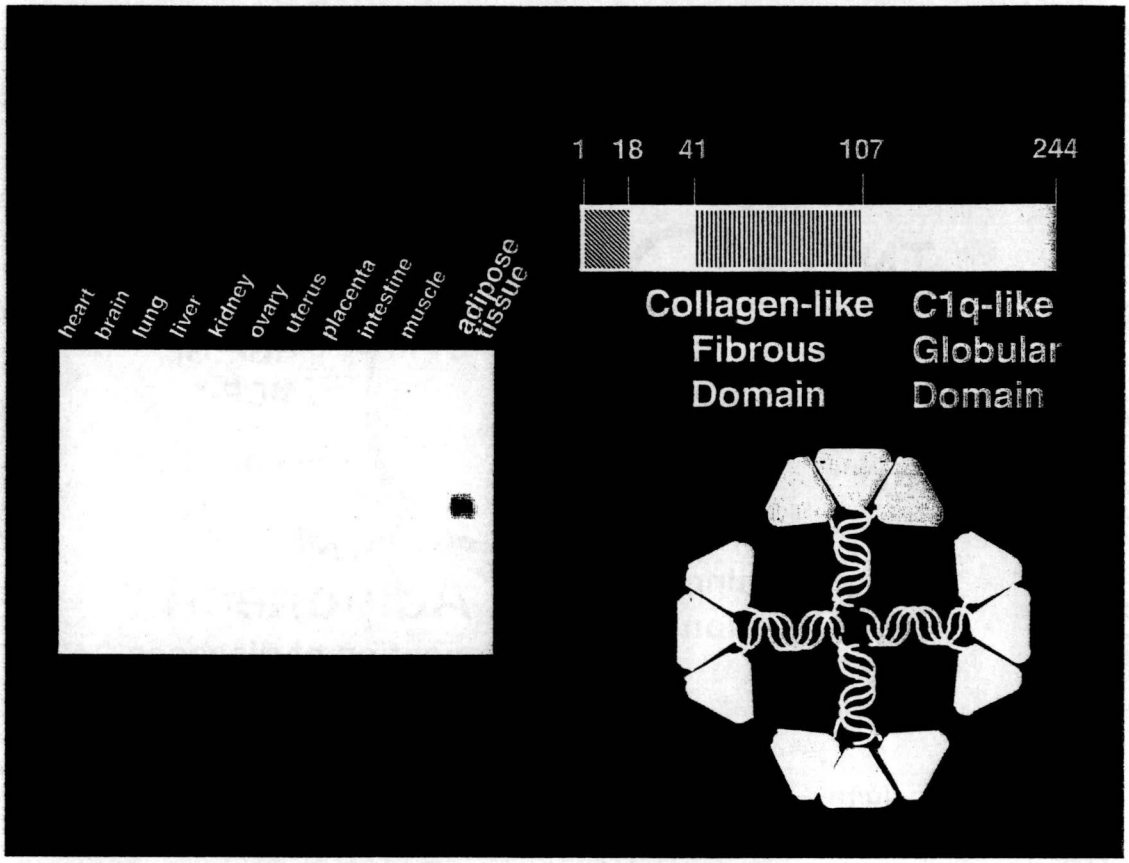

Fig. 7. Adipose-specific collagen-like protein, adiponectin.

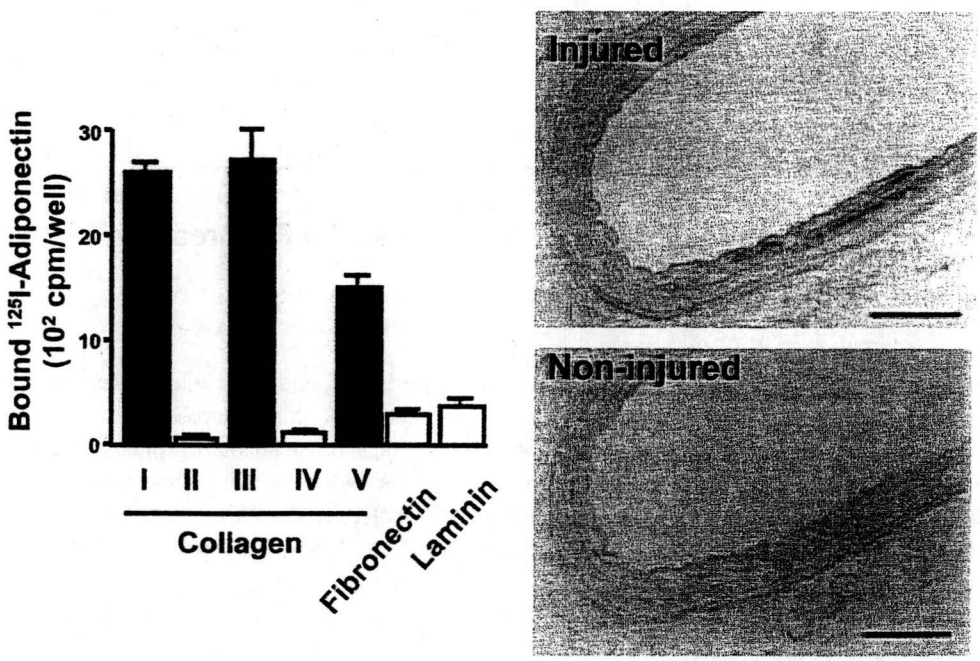

Fig. 8. Adiponectin accumulate injured vascular walls by binding subendothelial collagens.[38]

nemia, which might be at least one mechanism of hypertension in visceral obesity.[31]

Most importantly, plasma concentrations of adiponectin are lower in people with coronary heart disease than in controls even when BMI and age are matched.[32] A case-control study performed in Japan demonstrated that the group with hypoadiponectinemia with the plasma levels less than 4μg/ml has been shown to have increased risk of CAD and multiple metabolic risk factors, which indicates that hypoadiponectinemia is a key factor in the metabolic syndrome.[33] A prospective study by Pischon *et al.*[34] confirmed that high adiponectin concentrations are associated with reduced risk of acute myocardial infarction in men. In addition to hypoadiponectinemia accompanied with visceral fat accumulation, genetic hypoadiponectinemia caused by a missense mutation has been reported, which also exhibit the clinical phenotype of metabolic syndrome.[35]

These clinical evidences show that hypoadiponectinemia is a strong risk factor for cardiovascular disease.

Cell biological functions of adiponectin

Antiatherogenicity of adiponectin is also demonstrated in animal experiments. Adiponectin knockout mice developed more-severe intimal thickening by endothelial injury than did wild-type mice.[36] In addition, overexpression of human adiponectin by adenovirus transfection attenuated plaque formation in apolipoprotein E-KO mice.[37]

A large amount of adiponectin flows with the blood stream and, therefore, comes into contact with the vascular walls all over the body. The ways in which adiponectin interacts with vascular cells would be important to know. Immunohistochemical examination with antibodies to adiponectin showed no adiponectin protein in the untreated normal vascular walls in rabbits. Markedly positive immunohistochemical staining was detected, however, in balloon-injured vascular walls. Since adiponectin has the ability to bind subendothelial collagens such as collagen I, III, and V, endothelial injury may induce the adiponectin from entering into the subendothelial space through binding to these collagens. (Fig. 8)[38]

Cell biological studies have demonstrated that adiponectin has multiple, potent antiatherogenic functions. When the endothelial barrier is injured by attacking factors such as oxidized LDL, chemical substances and mechanical stress, adiponectin accumulates in the subendothelial space of vascular walls by binding to subendothelial collagen, at which point antiatherogenic properties of adiponectin become apparent.[38] The protein suppresses monocyte attachment to vascular endothelial cells by inhibiting the expression of adhesion molecules, such as vascular cell adhesion molecule 1, intracellular-adhesion molecule 1 and E-selectin via the inhibition of NF-κB activation.[39] Adiponectin also attenuates growth-factor-induced proliferation of vascular smooth-muscle cells by the inhibition of mitogen-activated protein kinase.[40] Adiponectin suppresses foam-cell formation by the inhibition of expression of scavenger receptor class A. (Fig. 9)[41]

Acute coronary syndromes are considered to determine the prognosis of cardiovascular disease in which vulnerability of plaque is the important determinant of plaque rupture. In this process, matrix metalloproteinase secreted from macrophages is thought to play an important part in plaque vulnerability. Tissue inhibitor of metalloproteinase is thought to act as a protector of plaque rapture by inhibition of matrix metalloproteinase. Adiponectin increases the expression of messenger RNA and protein production of tissue inhibitor of metalloproteinase in macrophages via the induction of interleukin-10 synthesis. This finding suggests that adiponectin protects plaque rapture by the inhibition of matrix metalloproteinase function, through the induction of interleukin-10-dependent production of tissue inhibitor of metalloproteinase.[42] Shibata *et al.* have demonstrated that adiponectin-deficient mice shows enhanced concentric hypertrophy and increased mortality under pressure overload. These phenomena were associated with increased extracellular signal-regulated kinase and diminished AMP-activated protein kinase signaling in the myocardium.

Adenovirus-mediated supplementation of adiponectin attenuated cardiac hypertrophy in response to pressure overload.[43]

Molecular mechanism of adiponectin functions has not been fully clarified and is considered to be very complicated. Not like other bioactive substances such as cytokines and hormones, adiponectin is present abundantly in plasma. In addition, bioactivities of adiponectin are displayed more potently in multimerized high molecule form than monomer or trimer type. With respect to the studies on adiponectin receptor, two kinds of concept have been proposed

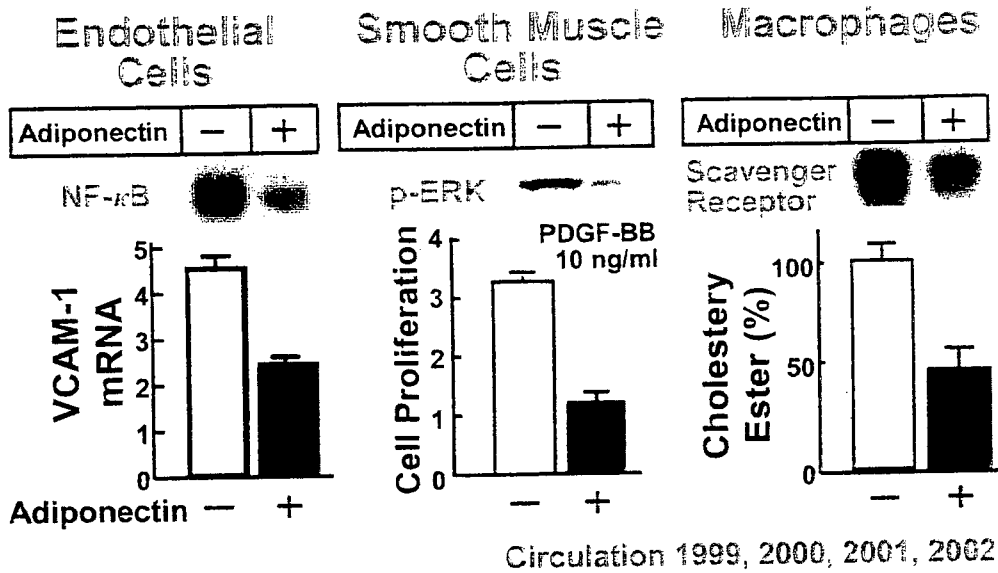

Fig. 9. Cell biological mechanism of anti-atherogenicity of adiponectin.

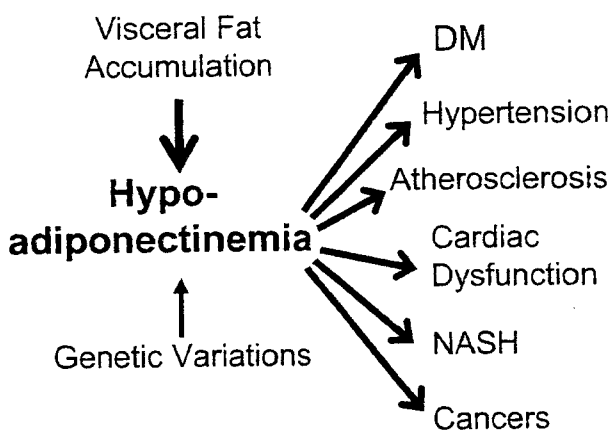

Fig. 10. A disease entity of hypoadiponectinemia

adiponectin receptors, AdipoR1 and AdipoR2 were identified by Kadowaki *et al.*[44] They showed that both receptors have roles in activation of AMP activated kinase, AMPK and PPARγ. Lodish *et al.* suggested that T-cadherin may act as a coreceptor for an-yet-unidentified signaling receptor through which adiponectin transmits metabolic signals.[45] As I mentioned above, the mode of action adiponectin may be dierent from that of other bioactive substances. It accumulates in injured tissue primarily by binding with extracellular collagens and may bind to some adhesion molecule such as T-cadherin or some signaling receptors such as AdipoRs which are expressed in target cells Further studies for molecular mechanism of adiponectin action are necessary to know physiological role of this unique protein.

Establishment of a disease entity-hypoadiponectinemia

As shown above, it is no doubt that adiponectin is the most important adipocytokine which prevent cardiovascular disease as well as metabolic diseases including type 2 diabetes. In other words, hypoadiponectinemia has been demonstrated to be related to a variety of major diseases such as cardiovascular disease and metabolic disease, namely metabolic syndrome which may threaten life.[46] In addition to the metabolic syndrome, recently hypoadiponectinemia has been reported to be related to non-alcoholic steatohepatitis and some kinds of cancer such as breast cancer and endometrial cancer. (Fig. 10) Therefore I would like to propose a disease entity named hypoadiponectinemia. Hypoadiponectinemia may be classified into two types; one is primary hypoadiponectinemia which may be caused by genetic disorders and the other is secondary hypoadiponectinemia which is caused by visceral fat accumulation. The later is corresponding to metabolic syndrome and much more frequent than primary one. Then I expect the development of therapeutic strategy which can elevate plasma levels of adiponectin, as statin was developed for hypercholesterolemia.

Conclusion

Adipocytes secrete various adipocytokines to control the functions of other organs and cells. Production and secretion of adipocytokines are considered to be dynamically regulated mainly by the nutritional condition. Lifestyle factors, such as overeating and physical inactivity, induce visceral fat accumulation, which results in the dysfunction of adipocytes. Oversecretion of oensive adipocytokines, such as PAI-1, tumor necrosis factor-α and hyposecretion of defensive adipocytokines, such as adiponectin, might be major mechanisms of lifestyle-related diseases, including diabetes mellitus, hyperlipidemia, hypertension and atherosclerosis, comprising the so-called metabolic syndrome. The reduction of visceral fat might be, therefore, an essential preventive measure for metabolic syndrome and its consequence, cardiovascular disease. The regulation of key adipocytokines such as adiponectin might be considered as an efficient therapeutic procedure.[46]

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Profile

Yuji Matsuzawa was born in 1941 in Tanabe City, Wakayama Prefecture. He graduated Osaka University Medical School in 1966 and received PhD in 1977. He became Professor of the Second Department of Internal Medicine in 1993 and had been Director of Osaka University Hospital from 2000 to 2002. Since 2003, he is Director of Sumitomo Hospital. He has been working on lifestyle-related diseases such as obesity, hyperlipidemia and atherosclerosis. He established a concept of visceral fat syndrome which is corresponding to so-called metabolic syndrome and discovered adiponectin, a key molecule of lifestyle-related diseases. By these achievements, he received the medical award of Japan Medical Association in 2000, Takeda Award in 2004 and Willendorf's Award from International Association for the Study of Obesity in 2006. He is now President of Asian Pacific Atherosclerosis Federation and also the President of Asia Oceania Association for the Study of Obesity.

Review

Food safety and food labeling from the viewpoint of the consumers

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Distrust of food safety has grown among the Japanese people after the occurrence of bovine spongiform encephalitis (BSE) in 2001. The Food Safety Commission was formed under the Cabinet Office and made a network among the ministries. The newly-established Consumer Agency may strengthen the quick response to emergencies. *Shoku-iku* (food and dietary education) Law is being implemented by the Cabinet Office with cooperation from relevant ministries and NGOs. Food Sanitation Law and Health Promotion Law are briefly explained, and the necessity of functional nutriology for non-nutrient biologically active substances is described. With regard to public health nutrition, a new food label showing energy balance and antioxidant unit (AOU) as a surrogate marker of fruit and vegetables has been developed for tailor-made nutrition which makes it easy to for individuals to control energy intake.

Key Words: food safety, food for specified use (FOSHU), functional nutriology, functional food factor (FFF), food labelling

FOOD SAFETY COMMISSION: NETWORK BETWEEN THE MINISTRY OF HEALTH, LABOUR AND WELFARE, MINISTRY OF AGRICULTURE, FORESTRY AND FISHERY, AND CABINET OFFICE

Distrust of food safety has grown among the Japanese people, triggered by various problems beginning with the occurrence of bovine spongiform encephalitis (BSE) in 2001. In response, Japan enacted the Basic Law on Food Safety, a comprehensive law to ensure food safety for the purpose of protecting the health of the nation. Through the development of related laws, Japan has introduced a risk analysis approach as well as a precautious strategy to the food safety network (Figure 1).[1]

Risk assessments are conducted by the Food Safety Commission established under the Basic Law on Food Safety. The approach aims to scientifically assess risks, expressed as the probability and degree of adverse health effects, and develop necessary measures based on the risk assessment. The Food Safety Commission is an organization that undertakes risk assessment, and is independent from risk management organizations such as the Ministry of Agriculture, Forestry and Fisheries, as well as the Ministry of Health, Labour and Welfare. Risk assessment, risk management, and risk communication are a set of solution oriented strategies conducted by exchanging information between the above Food Safety Commission and Ministries. A newly established Consumer Agency should be able to provide early response to an emergency.

THE FOOD SANITATION LAW

In 1947, The Ministry of Health and Welfare (MHLW) enacted the Food Sanitation Law as the first comprehensive law for food safety and hygiene.[2] All food additives have been regulated by this law, and only additives designated as safe by the MHLW are allowed to be used in foods. At first, only chemically synthesized additives were designated, but currently, all types of additives are included under the positive list system. Currently, 345 additives and 46 substances are designated as approved food additives by the MHLW.

The Food Sanitation Law covers various responsibilities such as: the establishment of standards/specifications for food, additives, apparatus, and food containers/ packages; inspection to assess whether these established standards are met; hygiene management of the manufacture process and sale of food; and business licensing. The Abattoir Law and the Poultry Slaughtering Business Control and Poultry Inspection Law cover the regulation of livestock and poultry, including inspection systems for meat. Imported foods are inspected by 31 quarantine stations placed across Japan under the central government.

Local governments and health centres also play an important role. The local governments share responsibilities to conduct inspection of and give advice to food-related businesses.

In recent years the global food trade has been increasing, and imported foods occupy nearly 60 percent of the

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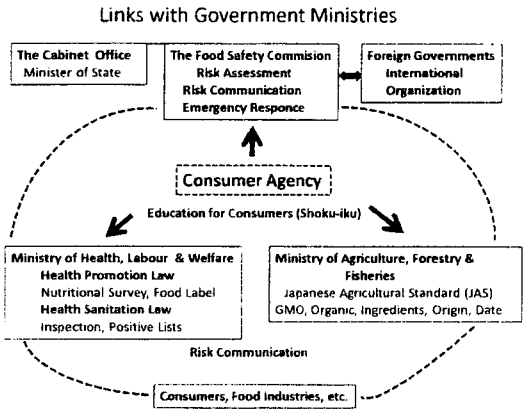

Figure 1. Safety Network of Food Safety Commission. Links between Government Ministries

Japanese market. Also, there is a growing possibility that imported foods contain food additives that are unauthorized in Japan. Safety assessments, conducted by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) will facilitate international harmonization of substances that are internationally proven safe and widely used in the world.[3-6]

Ingredients which make up only a small portion of a product may be omitted under JAS Law. Allergenic substances, however, require labelling under the Food Sanitation Law. Mandatory labelling is required at the distribution stage, and is mandatory for eggs, milk, wheat, buckwheat and peanuts, and recommended for abalone, squid, salmon roe, shrimp/prawn, oranges, crab, kiwifruit, beef, tree nuts, salmon, mackerel, soybeans, chicken (poultry), pork, mushrooms, peaches, yams, apples and gelatine.

HEALTH PROMOTION LAW OF MHLW

The "Healthy Japan 21" program was implemented at the beginning of 21st century to prevent life-style related diseases, such as cancer, cardiovascular disease, diabetes mellitus, and hypertension.[2] The Health Promotion Law supports this program. Foods with Health Claims refers to foods that comply with the specifications and standards established by the MHLW and are labelled as having certain nutritional or health functions. These foods are categorized into two groups: Foods with Nutrient Function Claims (FNFC) and Foods for Specified Health Uses (FOSHU).

The former includes foods that contain vitamins and minerals as nutritional ingredients, and the latter are foods officially approved to claim physiological effects on the human body.

FOODS FOR SPECIFIED HEALTH USES (FOSHU)

In 1992, MHLW established "FOSHU" that allows health claims on packaging (Figure.2). Japanese researchers refer to these as "Functional foods".[7-9] FOSHU approval requires scientific evidence of the effectiveness proved by clinical studies, additional safety studies to prove no side effects by oral intake, and exact determination of the specific effective components in foods.

Categories, functional factors and Health Claims for FOSHU are as follows:[2,10]

1. GI (Gastro-intestinal) condition: Carbohydrate, such as oligosaccharides, dietary fiber and chitosan; "Helps maintain a good GI condition."
2. Blood pressure: Lacto-tripeptide from fermented milk, dodecapeptide from casein, a group of peptides from sardine and soy protein; "Suitable for people with mild high blood pressure."
3. Serum cholesterol: Soy protein, chitosan, low molecule sodium alginate and phytosterol "Helps decrease serum cholesterol level."
4. Blood glucose: Indigestible dextrin, wheat albumin, L-arabinose etc.; "Helpful for those who are concerned about their blood glucose level."
5. Absorption of minerals: Fructo-oligosaccharides, caseinphospho peptide; "Improves absorption of calcium." Heme iron from hemoglobin; "Suitable for people with mild iron deficiency anemia."
6. Blood neutral fat: Diacylglycerol and globin degradation product, EPA, DHA; "Helps reduce postprandial

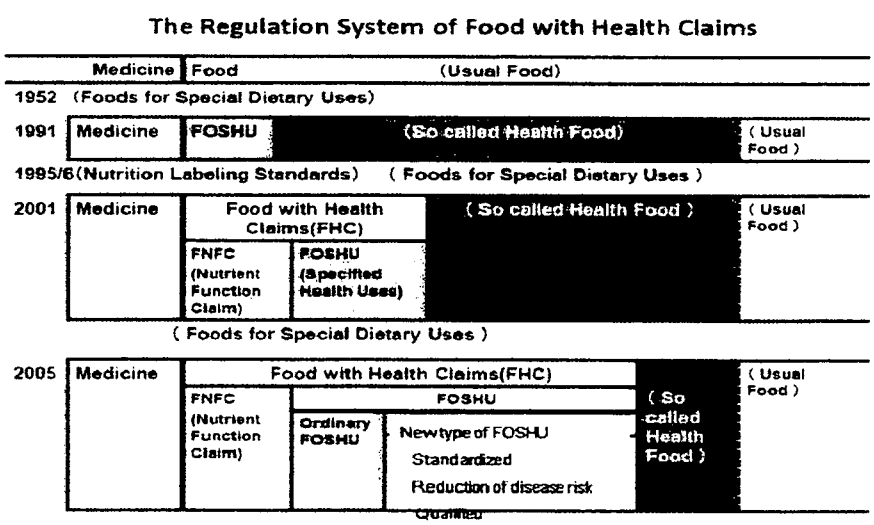

Figure 2. Changes of The Regulation System of Food with Health Claims.

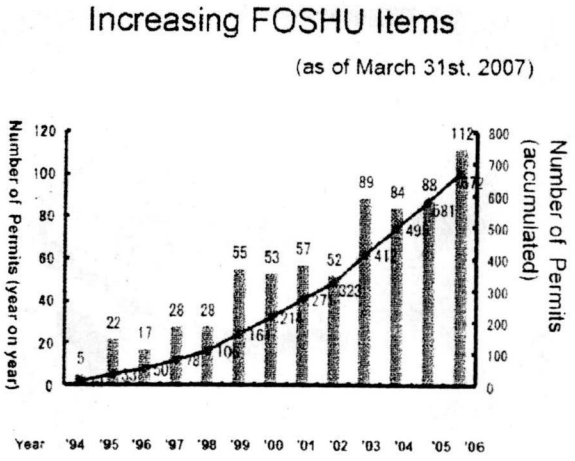

Figure 3. Increasing FOSHU Items as of March 31st, 2007

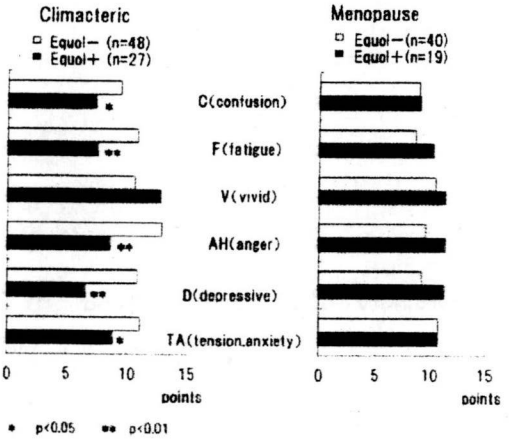

Figure 4. Profile of Mood States (POMS) Feeling Test Scores in Relation to Equol Producibility. Climacteric women, age 40-49.[14]

blood triglyceride levels." "Makes it difficult for fat to cling to the body."

7. Dental health: Some sugar alcohols such as xylitol, maltitol, erythritol, and palatinose (low cariogenic). Green tea polyphenol (non-cariogenic). "This is a low- or non-cariogenic product." "Makes teeth strong and healthy."
8. Bone health: Microorganisms producing high quantities of Vitamin K2, and soy isoflavone. "Promote bone calcification."

Food for Special Dietary Uses (FOSDU) refer to foods that are approved and permitted to display that the food is appropriate for specified dietary use. There are five categories of FOSDU: Formulas for pregnant or lactating women, Infant formulas, Foods for the elderly who have difficulty in masticating or swallowing, Medical foods for the ill.

NECESSITY OF FUNCTIONAL FOOD FACTOR (FFF) DATA-BASE AND FUNCTIONAL NUTRIOLOGY

The market for supplements as well as FOSHU is expanding, and more than 700 supplements are designated as FOSHU at the end of 2007 (Figure 3). Accordingly, reports of adverse effects are increasing. We made a database in NIHN Safety Net containing 1956 cases of adverse effects associated with taking so-called healthy foods, in which 728 were considered to be due to allergic constitution, 456 were due to long-term or excess intake, and 334 were due to interactions with other medicine.[10]

Problems with supplements are differences between in vivo and in vitro effects, differences between product information and those of raw materials, variable quality of natural products due to lack of standards, insufficient data about long term use, and insufficient data about safety for diseased people.

Ingredients in FOSHU and other supplements vary, and functional substances in foods include phytochemicals, certain lipids, amino acids and peptides. Most of these are not ordinary nutrients. It is expected that insufficient intake of macro- and micro-nutrients will result in various physiological manifestations of disease, but nutraceuticals such as FOSHU are expected to have more subtle pharmacological effects. A good example are phytoestrogens, which are believed to be beneficial for maintainingo keep bone density and reducing climacteric symptoms.[11,12]

Antioxidants, however, may prevent cancer and cardiovascular disease,[9] but the necessary doses remain unknown. As with the undesirable interaction between grapefruit and warfarin, unknown interactions between nutraceuticals, drugs and macromolecules inside the body suggest a cautious approach.

Thus, we constructed a database to estimate phytochemical intake from the whole diet; current data allows more than 80 percent this intake to classified and accounted for.[13] Isoflavone intake by the Japanese is very high (Median=15-20 mg) compared to other nations. Recently attention has been called to the isoflavone metabolite equol, because of its stronger estrogenic action. The ability to metabolize daidzein to equol depends on the presence of a certain type of intestinal bacteria. More than half of the older Japanese populationcan convert daidzein to epuol, but this percentage drops to 20-30 percent among the younger generation. Equol producers appear to have differential health profiles (Figure 4). Equol producers showed less severe psychological climacteric symptoms.[14] Caucasians exhibit lower equol producer prevalence rates, so the expected estrogenic effect of isoflavones may differ across populations as well between individuals.

Effective doses of phytochemicals or nutraceuticals can be summarized in a standard table. Large doses of a particular vitamins may cause pharmacological effects, like vitamin C. Such evidence is conceptualized as "Functional Nutriology" in which nutritional or dietary therapy, and use of supplements, effectively makes a bridge to medical treatment (Figure 5). Food industries would benefit by developing supplements, and excluding false or dangerous so-called healthy foods from the market.

TAILOR MADE NUTITION FOR PUBLIC HEALTH

The epidemic increase of obesity in the world mostly results from over-eating of high energy density foods, although several single-nucleotide polymorphisms (SNPs) are considered to influence energy metabolism. Proper

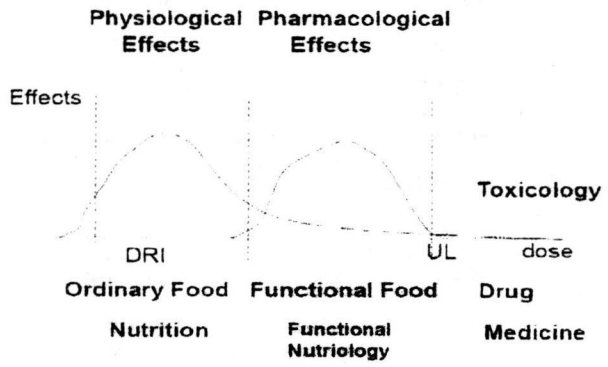

Fig. 5. Concept of Functional Nutrioloty

Fig. 6. Food icon on the menu, showing Energy and com-position of C, P, F and antioxidant unit (AOU) as a surrogate marker of fruit and vegetables. C; carbohydrate, P; protein, L; lipid, AOU; antioxidant unit.

energy intake and physical activity are the most important factors controlling obesity. If energy intake is successfully controlled, other nutrient recommendations can be easily followed. In Japan, a portion size of 80 kcal is a unit widely used for diabetic patients. We have defined a new energy unit (E-unit), as the energy required to melt 1 Kg of ice. Coincidentally it corresponds with a portion size of 80 kcal.

A healthy adult with average activity level requires [body weight (kg) x 0.4] E-units and an active person needs [body weight x 0.5] E-units. For example, a 60 kg man needs 24 E-units, so 8 E-units should be consumed at breakfast, lunch and dinner. In children and adolescents, the body weight multiplier is 1.0 for 10-19 kg body weight, 0.9 for 20-29 kg, 0.8 for 30-39 kg, 0.7 for 40-49 kg, 0.6 for 50-59 kg, and 0.5 for 60-69 kg. The calculated values fit well with those of the dietary reference intake 2010.[15] Desired body weight can be used for the calculation if an individual is overweight or underweight.

If E-units are shown on food labels and restaurant menus, and become popular, this would facilitate control

Table 1. Recommended Energy Intake by DRI2010 in Japan and Calculated Energy Intake by E-Unit System

	Age range	Recommended Energy Intake by PA			kg*1	Energy Intake by E-unit System		
		PAI	PAII	PAIII		Factor	b.w.*0.4	b.w.*0.5
Male	0-5M		550					
	6-8M		650					
	9-11M		700					
	1-2Y		1000		11.7	1.0	936	
	3-5Y		1330		16.2	1.0	1296	
	6-7Y	1350	1550	1700	22.0	0.9	1584	
	8-9Y	1600	1800	2050	27.5	0.9	1980	
	10-11Y	1950	2250	2500	35.5	0.8	2272	
	12-14Y	2200	2500	2750	48.0	0.7	2688	
	15-17Y	2450	2750	3100	58.4	0.6	2803	
	18-28Y	2250	2650	3000	63.0	0.5	2520	2520
	30-49Y	2300	2650	3050	68.5	0.4	2192	2740
	50-69Y	2100	2450	2800	65.0	0.4	2080	2600
	70<	1850	2200	2500	59.7	0.4	1910	2388
Female	0-5M		500					
	6-8M		600					
	9-11M		650					
	1-2Y		900		11.0	1.0	880	
	3-5Y		1250		16.2	1.0	1296	
	6-7Y	1250	1450	1650	22.0	0.9	1584	
	8-9Y	1500	1700	1900	27.2	0.9	1958	
	10-11Y	1750	2000	2250	34.5	0.8	2208	
	12-14Y	2000	2250	2550	46.0	0.7	2576	
	15-17Y	2000	2250	2500	50.6	0.6	2429	
	18-28Y	1700	1950	2250	50.6	0.5	2024	2024
	30-49Y	1750	2000	2300	53.0	0.4	1696	2120
	50-69Y	1650	1950	2200	53.6	0.4	1715	2144
	70<	1450	1700	2000	49.0	0.4	1568	1960

Recommended energy intake by physical activity (PA) is referred from DRI2010
*1Standard body weight in DRI2010 in Japan[2]
Energy is expressed by calorie in the table.