Table 3. Incidence of All-Cause Death and Cardiac Death With or Without Sulfonylurea Treatment

	Control (n=2,558)	Nicorandil (n=2,558)	HR (95%CI)	P value
	Rate per 1,000 patient-years	Rate per 1,000 patient-years		
All-cause deaths	22.61	15.23	0.65 (0.51–0.84)	0.0008
Sulfonylurea (–)	23.03 (139/2,258)	16.16 (97/2,228)	0.68 (0.52–0.88)	0.0034
Sulfonylurea (+)	19.53 (16/300)	8.98 (8/330)	0.46 (0.20–1.07)	0.0719
Cardiac deaths	11.23	4.93	0.44 (0.29–0.66)	0.0001
Sulfonylurea (–)	11.93 (72/2,258)	5.00 (30/2,228)	0.42 (0.27–0.64)	0.0001
Sulfonylurea (+)	6.10 (5/300)	4.49 (4/330)	0.73 (0.20–2.73)	0.6441

HR, hazard ratio; CI, confidence interval.

Discussion

Our findings from the JCAD study show that in patients with coronary artery disease confirmed by coronary angiography, which is generally associated with a high risk of cardiovascular events, treatment with 15 mg nicorandil conferred a 35% reduction in all-cause deaths compared with the control group. This difference was mainly because of a significant reduction in cardiac deaths, especially fatal MI. In this study, in-hospital deaths because of MI or CPAOA were defined as fatal MI. It has been reported in population-based studies that half of acute MIs are fatal before hospitalization, and that most such deaths occurred within the first hour after onset of acute symptoms.[13,14] In the present study, the majority of cases of CPAOA might have been related to MI, because all of the patients had significant stenosis of a major coronary artery on coronary angiography.

Our results confirm and extend observations of the effects of nicorandil on coronary events in patients with stable angina (IONA study).[8] In an on-treatment analysis of IONA, 40 mg nicorandil yielded a 17% significant reduction in the primary composite endpoint of coronary heart disease deaths, nonfatal MI, and unplanned hospital admission for chest pain, as well as a 14% significant reduction in all cardiovascular events. Clinical characteristics such as age and sex were almost the same in our study and in IONA.[8] Medications such as β-blockers and statins were less frequently used and angiotensin II receptor blockers more frequently used in our study than in IONA. Although 60% of patients had previously undergone coronary angiography and some had a positive exercise test with additional risk factors in IONA, in our study all patients underwent coronary angiography, and the mean number of significant coronary artery stenosis was almost 1.9. Moreover, the inclusion criterion in IONA was recently diagnosed stable angina that was neither unstable nor chronic. Some patients with acute MI (21.4%) or unstable angina (14.8%) were included in our study, so coronary artery lesions might have been more severe and vulnerable in the present patients than in those in IONA. Furthermore, the mean follow-up period was longer in JCAD than in IONA, at 2.7 and 1.6 years, respectively. Rates of all-cause mortality were 129/2561 patients (5.0%) and 156/2,558 patients (6.1%) in the IONA placebo and JCAD control groups, respectively. The reason for the higher rate of mortality in JCAD than in IONA might thus have been that IHD was more severe and the observational period longer. The subgroup analysis of IONA also suggested that nicorandil treatment of high-risk patients who were taking more anti-anginal medications or who had higher Canadian Cardiovascular Society (CCS) functional status scores would achieve the greatest absolute risk reduction.[15]

Nicorandil is a hybrid drug that functions as a K-ATP channel opener and nitric oxide releaser.[1] It suppresses not only myocardial stunning but also myocardial necrosis in ischemic reperfusion.[3–5] Pretreatment with K-ATP channel openers maintains mitochondrial respiration without inhibiting the increase in intracellular sodium and decrease in intracellular ATP and phosphocreatine during ischemia, and accelerates recovery of ATP concentration in tissues after ischemia.[16,17] Moreover, K-ATP channel openers protect endothelial function in the coronary arteries from ischemic reperfusion injury via activation of mitochondrial K-ATP channels.[18,19] The mitochondrial K-ATP channel may thus be an important mediator of protection of myocardial cells and coronary endothelium, and these mechanisms may thus have significantly reduced cardiovascular deaths associated with fatal MI and other ischemic events in the present nicorandil group compared with the control group. The early dissociation of the Kaplan-Meier curve in the case of cardiac deaths as well as all-cause deaths also suggests pharmacological preconditioning rather than stabilization of plaque and/or improvement of endothelial function with nicorandil, because the latter mechanisms are unlikely to function in the early phase.

Interestingly, there was no significant difference between the nicorandil and control groups in the incidence of acute MI in this study. Fatal MI significantly decreased and nonfatal MI slightly increased in the nicorandil group compared with the control. These findings also suggest that nicorandil had a pharmacological preconditioning effect, which salvages the ischemic myocardium and reduces necrosis of infarct-related myocardium in patients with acute MI. Moreover, on detailed analysis of the type of fatal MI, we found that CPAOA itself was significantly reduced in the nicorandil group compared with the control. The cause of these deaths before hospitalization is often ventricular fibrillation or cardiogenic shock. It has been reported that nicorandil reduces lethal ventricular arrhythmia in the initial phase after acute coronary syndrome.[20] This mechanism might also play a role in reducing fatal MI.

In this study, the dose of nicorandil (15 mg/day) was smaller than that used in IONA (40 mg/day). The recommended dosage in Europe and Oceania is 10–40 mg twice daily, and 7.5–30 mg three times daily in Asia.[21] It has been found that oral nicorandil (15 mg/day) may have preconditioning effects in patients with stable angina undergoing coronary angioplasty.[22] Ishii et al also reported that nicorandil (15 mg/day) improved clinical outcomes in patients with IHD receiving hemodialysis following coronary angioplasty.[23] These findings thus suggest that 15 mg/day of nicor-

andil is adequate to activate K-ATP channels. However, the optimal dosage of nicorandil remains to be determined.

In this study, the incidence of congestive heart failure as a secondary endpoint was significantly reduced in the nicorandil group compared with the control group. The pharmacological preconditioning induced by nicorandil does not explain this suppressive effect, suggesting that another mechanism is responsible for it. Possible mechanisms include improvements of endothelial function and left ventricular function through improved microvascular circulation and/or cardiac sympathetic nerve activity.[24,25] Sanada et al reported that nicorandil attenuated cardiac remodeling by inhibiting 70-kd S6 kinesis in long-term inhibition of nitric oxide synthase with N^{ω}-nitro-L-arginine methyl ester rats.[26] We also reported that nicorandil prevented left ventricular remodeling and loss of cardiac function in Dahl salt-sensitive hypertensive rats with congestive heart failure; these effects were mediated in part by enhanced endothelial nitric oxide synthase expression via activated K-ATP channels in the heart.[27] These mechanisms are also suggested by the finding that the Kaplan-Maier curves for the incidence of congestive heart failure in the 2 groups in this study gradually dissociated (data not shown). Recently, Kitakaze et al demonstrated that oral administration of nicorandil in the chronic phase after acute MI with successful catheter intervention increased left ventricular ejection fraction.[28] These findings may explain the significant reduction in the incidence of congestive heart failure in the nicorandil group in this study.

One important issue, whether the sulfonylureas eliminate the effects of nicorandil, remained following IONA. Concomitant treatment with a sulfonylurea was excluded in IONA, because these drugs inhibit the opening of K-ATP channels. One-third of patients with IHD have diabetes, and this complication augments cardiovascular events. Sulfonylureas may eliminate the myocardial and vascular protective effects of nicorandil when adequate dosages of them, which inhibit SUR2 or mitochondrial K-ATP channels, are administered. Recently, it was demonstrated that differences in selectivity for SUR type exist among the various types of sulfonylureas. Gliclazide did not inhibit the reconstructed cardiac and vascular type of K-ATP channel via activation of nicorandil,[29] whereas glimepiride did not inhibit the mitochondrial K-ATP channel in isolated myocardial cells.[30] Our findings also demonstrated that sulfonylureas did not absolutely eliminate the favorable effects of nicorandil, because nicorandil treatment with sulfonylureas tended to reduced all-cause deaths but not cardiac deaths. Lee et al also reported that ischemic preconditioning could be induced by nicorandil in diabetic glibenclamide-treated patients, although it was attenuated by impairment of intrinsic activation of cardiac K-ATP channels.[31] These findings suggest that the cardioprotective effect of nicorandil mediated via activated K-ATP channels is partially impaired in diabetic patients being treated with sulfonylureas. However, because the mortality rates in the present study for the relatively few patients treated with nicorandil and sulfonylureas (630 patients) might have failed to exhibit significant differences from those in other groups, our findings need to be confirmed in additional studies.

In this study, slightly higher mortality rates were observed in the non-sulfonylureas than in the sulfonylureas group, which finding might be related to the poor prognosis of patients with diabetes not on sulfonylureas observed in this study or/and improvement of prognosis with sulfonylureas.

Study Limitations

This was a multicenter collaborative prospective observational study in a large cohort of coronary artery patients with similar clinical treatments based on coronary angiographic data, with data on clinical outcome collected in blind fashion. However, it was an observational and not a randomized, double-blind, controlled study. Thus, control was limited to variables for which data were available, although propensity score analysis was performed to reduce the conditional probability of taking a medication using covariates between the nicorandil and control groups. Moreover, precise information on the timing of nicorandil initiation, duration of treatment, and extent of compliance during the follow-up period could not be obtained. Categorization under a specific diagnostic label might also not be possible in the early stage of cardiac illness during the prehospital phase in patients with CPAOA. Nevertheless, the results obtained for various endpoints were internally consistent in this study, and mortality was a completely unbiased endpoint.

In conclusion, the reductions observed in cardiovascular deaths with nicorandil in this study were large, given the short period of follow-up, in patients with IHD, which has important implications for their treatment.

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Review Article

Nucleic Acid Drugs for Prevention of Cardiac Rejection

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Heart transplantation has been broadly performed in humans. However, occurrence of acute and chronic rejection has not yet been resolved. Several inflammatory factors, such as cytokines and adhesion molecules, enhance the rejection. The graft arterial disease (GAD), which is a type of chronic rejection, is characterized by intimal thickening comprised of proliferative smooth muscle cells. Specific treatments that target the attenuation of acute rejection and GAD formation have not been well studied in cardiac transplantation. Recent progress in the nucleic acid drugs, such as antisense oligodeoxynucleotides (ODNs) to regulate the transcription of disease-related genes, has important roles in therapeutic applications. Transfection of cis-element double-stranded DNA, named as "decoy," has been also reported to be a useful nucleic acid drug. This decoy strategy has been not only a useful method for the experimental studies of gene regulation but also a novel clinical strategy. In this paper, we reviewed the experimental results of NF-κB, E2F, AP-1, and STAT-1 decoy and other ODNs using the experimental heart transplant models.

1. Introduction

Heart transplantation is a common surgical procedure in humans. However, acute rejection and graft arterial diseases (GADs), which are a phenomenon of chronic rejection, have not yet been resolved [1, 2]. Several inflammatory factors (e.g., cytokines and adhesion molecules) enhance acute and chronic rejection. GAD is characterized by intimal thickening comprised of proliferative smooth muscle cells (SMCs) [3, 4]. Specific treatments that target the attenuation of acute rejection and GAD were not studied in depth in cardiac transplantation. Nucleic acid drugs, such as antisense oligodeoxynucleotides (ODNs) to regulate the transcription of disease-related genes, have an important role in therapeutic applications. Transfection of cis-element double-stranded DNA, named "decoy," has also been reported to be a useful nucleic acid drug [5, 6]. The nucleic acid drugs have been not only a useful method for the experimental studies of endogenous gene regulation, but also a novel clinical strategy [7, 8]. In this paper, we reviewed the experimental results of nucleic acid drugs using the experimental heart transplant models.

2. Antisense Cyclin-Dependent Kinase (cdk) 2 Kinase ODN

The enzyme cdk2 kinase plays an important role in cell transition through the G1-S phase [9]. Recent progress in the regulation of cell cycle progression has reinforced the importance of the G1-S phase in the process of cell proliferation [10]. However, the role of these cell cycle regulatory genes in the pathophysiology of GAD was not investigated. The antisense method, which uses a single-strand DNA, is an innovative and attractive strategy to block the transcription or translation of specific genes [5]. To test the effect of antisense cdk2 kinase ODN on the inhibition of GAD formation, we performed ODN transfer into murine cardiac allografts. Donor hearts were infused with the antisense cdk2 kinase ODN-HVJ-liposome complex

solution from the descending aorta; the hearts were then immediately transplanted into recipients. Treatment with antisense cdk2 kinase ODN dramatically reduced arterial intimal thickening with suppression of vascular cell adhesion molecule (VCAM)-1. In the study, we clearly demonstrated for the first time that a single intraluminal administration of antisense cdk2 kinase ODN prevents GAD formation [11].

3. Antisense Proliferating-Cell Nuclear Antigen (PCNA) ODN

Cell growth and proliferation are dependent on the coordinated actions of multiple cell cycle regulatory genes. Among many cell cycle regulatory genes, PCNA plays a critical role in the SMC proliferation [12]. Although inhibition of arterial neointimal formation by antisense PCNA ODN after balloon angioplasty in a rat carotid injury model was reported [13], the effect of antisense PCNA ODN in preventing GAD was not tested. Therefore, we performed single intraluminal delivery of the antisense PCNA ODN into murine cardiac allografts. In the group of no ODN or sense PCNA ODN transfection, the graft coronary arteries were severely thickened. However, limited neointimal formation was observed in antisense PCNA ODN-transfected allografts. The cell cycle regulatory gene PCNA plays an essential role in cell transition through both the G1/S and G2/M phases [13]. Therefore, blocking PCNA activation using antisense ODN regulates multiple cell cycle phases, thus it prevents GAD formation effectively [14].

4. Antisense bcl-x ODN

Apoptosis is a prominent feature of atherosclerosis [15]; however, the role in GAD formation remains to be elucidated. It is postulated that the regulation of apoptosis involves the balance between proapoptotic mediators such as *bax*, and antiapoptotic mediators such as bcl-x [16, 17]. However, the role of bcl-x in the pathophysiology of GAD remains unclear. Recently, it was reported that antisense bcl-x ODN is an efficient therapeutic strategy for prevention of neointimal formation after balloon injury of rat carotid arteries [18]. We therefore hypothesized that GAD could also be prevented by antisense bcl-x ODN. Histologically, heavy neointimal thickening had formed in the coronary arteries of sense bcl-x ODN transfected or untreated allograft recipients; however in recipients treated with antisense bcl-x ODN, arterial neointimal formation was dramatically suppressed. Regarding apoptosis, limited TUNEL positive cells were observed in the arterial thickened intima of allografts from nontreated or sense bcl-x ODN-treated recipients. However, increased TUNEL positive cells were seen in the mildly thickened intima of the allografts treated with antisense bcl-x ODN. In the study, we revealed that antisense bcl-x ODN inhibits arterial neointimal formation through the induction of apoptosis [19].

5. E2F Decoy

The transcription factor E2F regulates multiple cell-cycle regulatory genes, which are critical to the process of cell growth and proliferation [20, 21]. Double-stranded DNA with high affinity for E2F acting as a decoy (E2F decoy) inhibits cell-cycle regulatory gene expression and SMC proliferation in rat carotid injury models [22]. However, the effect of E2F decoy in preventing GAD formation was not investigated. To clarify the effects, we used both murine and monkey cardiac transplant models. Immunohistochemically, PCNA, c-myb, cdk2, or cdc2 were expressed diffusely and strongly in the thickened allograft arterial intima of untreated allografts; whereas treatment with E2F decoy resulted in suppressed expression in the endothelial cells of the mildly thickened allograft intima. We revealed that E2F decoy transfer into the allografts specifically abolished E2F activity and inhibited intimal hyperplasia (Figure 1). In addition, it was more effective than antisense ODN, because E2F decoy blocked multiple cell cycle regulatory genes that bind to the same *cis* element [23]. In the investigation of E2F decoy, we used both rodent and nonhuman primate heart transplant models. Although the rodent models could not exactly represent human GAD, the animal models have been used as appropriate investigation for long time. Because the primate model demonstrated similar findings to both rodents and humans, rodent allograft models are useful to analyze the pathophysiology of human heart transplantation.

6. NF-κB Decoy

Antisense cdk2 kinase ODN and E2F decoy inhibit GAD formation by suppressing cell cycle regulatory gene expression as demonstrated above. However, these nucleic acid drugs could not attenuate acute rejection [11, 23]. Nuclear factor-kappa B (NF-κB) plays a pivotal role in the coordinated transcription of multiple inflammatory genes [24–26]. However, the role of NF-κB in the pathophysiology of acute rejection and GAD was not investigated. Since NF-κB decoy inhibits the expression of several inflammatory genes, we hypothesized that NF-κB decoy could attenuate both acute rejection and GAD after transplantation. To analyze the graft survival, donor hearts were infused with NF-κB decoy-HVJ-AVE-liposome complex and transplanted into recipients. In the major mismatch murine combination group, nontreated or scrambled decoy transfected allografts were acutely rejected, while NF-κB decoy transfection significantly prolonged allograft survival. Histologically, moderate myocardial cell infiltration and heavy GAD formation was observed in nontreated or scrambled decoy transfected allografts, while NF-κB decoy markedly attenuated cell infiltration and GAD formation. Immunohistochemically, intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 were enhanced in nontreated or scrambled ODN transfected allografts, while NF-κB decoy transfection markedly suppressed the expression. In this study, we demonstrated that NF-κB decoy inhibits intimal hyperplasia effectively; the prevention of neointimal formation was associated with suppressed expression of adhesion

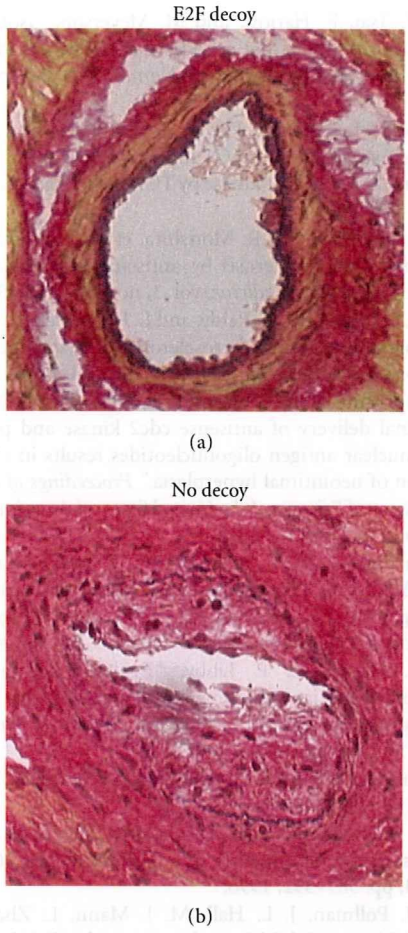

FIGURE 1: Representative findings of allograft coronary arteries are shown. (a) demonstrates the effects of E2F decoy compared to controls (b) on the intimal hyperplasia which defines cardiac allograft vasculopathy. (Modified from reference [23].)

molecules which are directly affected by NF-κB decoy. It is also noteworthy that NF-κB decoy attenuates both chronic rejection (GAD) and acute rejection in cardiac allografts. Suppressed cell cycle regulatory genes, growth factors and adhesion molecule expression were also observed in the NF-κB decoy treated allografts; the phenomena may be controlled directly and/or indirectly by NF-κB decoy throughout the cytokine and chemokine network [27]. In the network, ICAM-1, interferon-gamma and monocyte chemoattractant protein-1 are the common factors to suppress these diseases [2, 4]. Because NF-κB decoy regulates these factors, the treatment has a significant effect for both acute and chronic rejection.

7. AP-1 and STAT-1 Decoy

Other transcription factors, signal transducer and activator of transcription-1 (STAT-1) and activator protein-1 (AP-1), are also important in the process of acute rejection and GAD by regulating vascular adhesion molecule expression [28, 29]. Hölschermann et al. and Stadlbauer et al. investigated the effects of STAT-1 decoy and AP-1 decoy to prevent acute rejection and GAD using rat transplant models [30, 31]. They transplanted rat allografts after perfusion with STAT-1 or AP-1 decoy. In acute rejection models, transfection with AP-1 and STAT-1 decoy significantly prolonged cardiac allograft survival. Immunohistochemistry revealed a marked reduction of myocardial infiltrating T-cells and adhesion molecule expression on the endothelium in the decoy transfected allografts [30]. In chronic rejection models, rat cardiac allografts were perfused ex vivo with AP-1 decoy ODN, STAT-1 decoy ODN, or buffer solution and transplanted into the abdomen of recipients with cyclosporine immunosuppression. Treatment with both decoy attenuated the incidence and severity of CAV. Histological analyses revealed that AP-1 or STAT-1 decoy ODN treatment primarily attenuated CD40 expression in the coronary endothelial cells and medial smooth muscle cells [31]. They concluded that treating donor hearts with decoy that is neutralizing AP-1 or STAT-1 at the time of transplantation prevents both acute and chronic rejection.

8. ODN Transfer Methods

Although a number of viral and nonviral vectors were reported, no ideal vector has been established at this point. Each system has unique characters and properties that can be used for specific conditions [32]. We have developed a gene transfer vector by combining the hemagglutinating virus of Japan (HVJ) and liposome. Using the system, we developed an effective method of gene transfer into the vessel wall and myocardium [11, 14, 19]. It was also revealed that ultrasound can increase cell membrane permeability to macromolecules such as plasmid DNA. Thus, we found that this approach is applicable to decoy transfer into the arteries and other organs [33–35].

9. Summary

In this paper, we demonstrated that transfection of nucleic acid drugs attenuates both acute and chronic rejection. We added an illustration that depicts the molecular pathways targeted and how they fit into the pathophysiology of the diseases targeted (Figure 2). Recently, clinical trials have been performed in cardiovascular diseases. For example, ex vivo E2F decoy transfection in vascular grafts suppressed neointimal hyperplasia after cardiac bypass surgery in humans [36, 37]. We also tried the NF-κB decoy transfection in the site of coronary arteries after stent implantation in humans [38–40]. The results demonstrated that the strategy is clinically promising. However, collateral and/or adverse effects by nuclear acid drugs have not yet been completely resolved. We reported some possible collateral and/or adverse effects, such as chest pain, skin rush, decreasing platelets, and liver dysfunction, in the NF-κB decoy treated patients [39]. Antisense bcl-2 oligonucleotide in patients with advanced solid tumors showed liver dysfunction that was considered as an adverse effect [41]. Cursiefen et al. reported that an

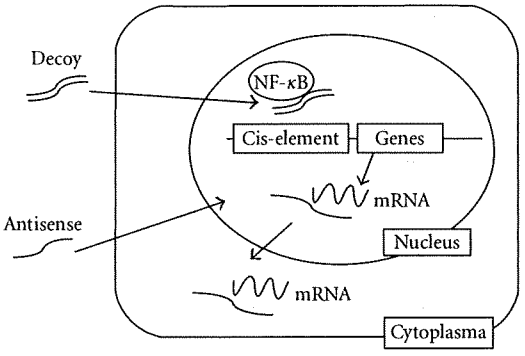

FIGURE 2: An *illustration* which depicts the molecular pathways targeted and how they fit into the immunopathophysiology of the diseases targeted is shown. (Modified from [6].)

antisense oligonucleotide against insulin receptor substrate-1 to inhibit corneal neovascularization had some adverse effects such as painful eye and pressure sensation [42]. Thus, further studies of nucleic acid drugs should be conducted in other transplant models to explore the clinical utility for prevention of acute rejection and GAD.

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Original Article

Impact of Changes in Waist Circumference and BMI over One-Year Period on Serum Lipid Data in Japanese Individuals

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Aim: Loss or gain in obesity indexes, such as body mass index (BMI) and waist circumference (WC), may affect serum lipid parameters. We therefore analyzed the impact of changes in WC and BMI over a one-year period on serum levels of LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), and triglycerides (TG).
Methods: We analyzed the data of 3,111 individuals who were not on lipid- lowering medication and who underwent general health screening two years running.
Results: The correlation between percent changes of WC (%dWC) and BMI (%dBMI) were both statistically significantly correlated with percent changes in LDL-C (%dLDL), HDL-C (%dHDL), and TG (%dTG) except that between %dWC and %dHDL in women. In multiple regression analysis, %dBMI, but not %dWC, was found to be an independent predictor of %dLDL, %dHDL, and %dTG. When %dBMI was excluded from the variables, %dWC was identified as an independent factor predicting %dLDL and %dTG; however, in individuals with %dBMI of ≥ 0, %dWC was not found to be a predictor of percent changes in any lipid parameters tested in this model.
Conclusion: Percent changes in BMI were found to be an independent predictor of adverse changes in lipid parameters in both genders. Although percent changes in WC (%dWC) also tended to confer adverse changes in lipid parameters, this relationship did not remain statistically significant after controlling for %dBMI. It is suggested that changes in obesity parameters are an important goal to avoid adverse lipid changes, although there might be some gender differences.

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Key words; Waist circumference, Body mass index, LDL-C, Health screening

Introduction

It is well known that obesity parameters, such as body weight, body mass index (BMI), and waist circumference (WC), may be related with values of serum lipid parameters, including low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG) as well as other established cardiovascular risk factors[1, 2]. Although there are in general substantial correlations among various obesity parameters, some parameters may provide better prediction of insulin resistance than others[3, 4]. On the other hand, fewer studies have analyzed the effect of changes in obesity parameters on changes in these lipid parameters in the general population[5]. To this end, the aim of the current study was to investigate the relationship between changes in obesity parameters over a one-year period and changes in lipid parameters over the same period in Japanese individuals.

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Table 1a. Baseline Characteristics at the First Visit According to %dWC

Variables	%dWC quartiles				*p* for trend
	First (range: −21.2–−3.4)	Second (range: −3.4–−0.1)	Third (range: 0.0–3.2)	Fourth (range: 3.2–33.3)	
Women					
n	324	193	216	407	
Age, years	52.2±10.2	51.4±10.2	51.4±9.8	50.4±9.3	0.110
Height, cm	156±5	159±6	157±6	158±6	0.021
Weight, kg	51.3±7.5	53.2±8.6	53.7±8.5	52.2±6.9	0.002
WC, cm	78.9±8.5	77.9±9.4	76.8±8.5	73.5±7.9	<0.001
BMI, kg/m²	21.0±2.9	21.6±3.3	21.7±3.2	21.0±2.7	0.003
Systolic blood pressure, mmHg	117±18	120±20	117±17	116±19	0.242
Diastolic blood pressure, mmHg	73±10	74±12	73±11	72±12	0.225
Pulse rate, bpm	64±8	64±8	64±9	63±9	0.614
LDL-cholesterol, mg/dL	129±32	130±33	129±33	123±32	0.036
HDL-cholesterol, mg/dL	70±14	68±15	68±14	69±15	0.582
riglyceride (interquartile range), mg/dL	75 (55.5–98.5)	75 (55–108)	77 (54–103)	69 (54–90)	0.040
Uric acid, mg/dL	4.6±1.0	4.5±1.0	4.6±0.9	4.4±0.9	0.156
Fasting glucose, mg/dL	89±15	92±18	92±22	90±17	0.188
Haemoglobin A1C, %	5.1±0.5	5.2±0.5	5.2±0.8	5.1±0.6	0.602
Anti-hypertensive medication, n (%)	17 (5.3)	11 (5.7)	6 (2.8)	14 (3.4)	0.306
Anti-diabetic medication, n (%)	1 (0.3)	0	1 (0.5)	4 (1.0)	0.400
Blood urea nitrogen, mg/dL	13.3±3.7	13.5±3.4	13.3±3.1	13.4±3.2	0.928
Serum creatinine, mg/dL	0.66±0.48	0.63±0.09	0.62±0.09	0.63±0.09	0.368
Current smoker, n (%)	35 (10.8)	14 (7.3)	11 (5.1)	44 (10.8)	0.056
Men					
n	453	571	574	373	
Age, years	54.3±10.2	53.2±10.0	53.5±10.5	51.8±10.1	0.008
Height, cm	170±6	169±6	169±6	169±5	0.919
Weight, kg	68.7±10.0	68.3±9.2	68.2±9.1	67.4±8.8	0.246
WC, cm	88.0±7.8	86.7±7.1	85.3±7.2	82.9±7.5	<0.001
BMI, kg/m²	23.8±3.0	23.8±2.7	23.8±2.8	23.5±2.8	0.278
Systolic blood pressure, mmHg	129±20	128±20	126±18	122±16	<0.001
Diastolic blood pressure, mmHg	82±12	81±12	80±11	78±10	<0.001
Pulse rate, bpm	64±10	63±9	63±9	62±10	0.185
LDL-cholesterol, mg/dL	131±30	130±30	130±30	127±30	0.291
HDL-cholesterol, mg/dL	57±14	55±14	55±13	57±13	0.280
riglyceride (interquartile range), mg/dL	109 (76–154)	109 (79–157)	110 (77–160)	98 (73–143)	0.287
Uric acid, mg/dL	6.1±1.3	6.1±1.2	6.1±1.2	6.1±1.2	0.628
Fasting glucose, mg/dL	102±24	99±20	98±18	99±24	0.013
Haemoglobin A1C, %	5.5±0.8	5.4±0.8	5.3±0.7	5.4±0.9	0.022
Anti-hypertensive medication, n (%)	51 (11.3)	70 (12.6)	74 (12.9)	39 (10.5)	0.676
Anti-diabetic medication, n (%)	17 (3.8)	10 (1.8)	15 (2.6)	15 (4.0)	0.128
Blood urea nitrogen, mg/dL	14.7±4.2	14.6±3.5	14.3±3.2	14.3±3.0	0.144
Serum creatinine, mg/dL	0.87±0.52	0.85±0.13	0.86±0.13	0.84±0.11	0.429
Current smoker, n (%)	140 (30.9)	193 (33.8)	172 (30.0)	127 (34.0)	0.407

Methods

Study Population

The study was approved by the Ethics Committee of Mitsui Memorial Hospital. Between October 2005 and October 2006, 11,558 individuals underwent general health screening at our institute. Of these, 3,312 individuals (1,203 women, 2,109 men)

Table 1b. Baseline Characteristics at the First Visit According to %dBMI

Variables	%dBMI quartiles				*p* for trend
	First (range: −21.8–−1.8)	Second (range: −1.8–−0.2)	Third (range: −0.2–1.4)	Fourth (range: 1.4–15.6)	
Women					
n	267	263	290	320	
Age, years	51.9 ± 10.1	52.7 ± 9.9	51.2 ± 9.2	49.6 ± 9.9	0.001
Height, cm	156 ± 5	156 ± 6	158 ± 6	158 ± 6	0.005
Weight, kg	53.0 ± 7.7	52.7 ± 8.1	51.9 ± 7.4	52.2 ± 7.7	0.290
WC, cm	77.1 ± 8.6	77.1 ± 9.1	75.6 ± 9.0	75.9 ± 8.2	0.076
BMI, kg/m^2	21.6 ± 3.0	21.5 ± 3.1	20.8 ± 2.8	21.1 ± 3.0	0.002
Systolic blood pressure, mmHg	120 ± 20	118 ± 18	116 ± 18	116 ± 18	0.054
Diastolic blood pressure, mmHg	75 ± 12	74 ± 11	73 ± 11	72 ± 11	0.041
Pulse rate, bpm	64 ± 9	64 ± 8	63 ± 9	64 ± 9	0.171
LDL-cholesterol, mg/dL	132 ± 37	132 ± 30	125 ± 29	121 ± 31	< 0.001
HDL-cholesterol, mg/dL	68 ± 14	69 ± 15	70 ± 15	69 ± 14	0.293
riglyceride (interquartile range), mg/dL	78 (58–104)	75 (56–105)	72 (53–100)	67 (51.5–91)	< 0.001
Uric acid, mg/dL	4.5 ± 1.0	4.5 ± 0.9	4.6 ± 0.9	4.5 ± 1.0	0.470
Fasting glucose, mg/dL	90 ± 17	93 ± 27	89 ± 13	89 ± 12	0.038
Haemoglobin A1C, %	5.1 ± 0.5	5.2 ± 0.8	5.2 ± 0.5	5.1 ± 0.5	0.012
Anti-hypertensive medication, n (%)	11 (4.1)	13 (4.9)	12 (4.1)	12 (3.8)	0.913
Anti-diabetic medication, n (%)	0	3 (1.1)	1 (0.3)	2 (0.7)	0.315
Blood urea nitrogen, mg/dL	13.5 ± 3.0	13.3 ± 3.3	13.7 ± 3.9	13.1 ± 3.1	0.181
Serum creatinine, mg/dL	0.62 ± 0.09	0.62 ± 0.10	0.68 ± 0.51	0.62 ± 0.09	0.022
Current smoker, n (%)	19 (7.1)	22 (8.4)	23 (7.9)	40 (12.5)	0.095
Men					
n	510	515	488	458	
Age, years	54.0 ± 10.2	54.5 ± 10.0	53.4 ± 10.2	51.1 ± 10.3	< 0.001
Height, cm	169 ± 6	169 ± 6	170 ± 6	170 ± 6	0.190
Weight, kg	68.7 ± 9.7	67.5 ± 9.0	68.8 ± 9.5	67.7 ± 8.8	0.050
WC, cm	87.0 ± 7.6	85.5 ± 7.3	86.4 ± 7.7	84.9 ± 7.5	0.002
BMI, kg/m^2	23.9 ± 2.8	23.6 ± 2.9	23.9 ± 2.8	23.5 ± 2.7	0.020
Systolic blood pressure, mmHg	128 ± 19	126 ± 19	127 ± 18	124 ± 18	0.004
Diastolic blood pressure, mmHg	81 ± 12	80 ± 12	81 ± 11	79 ± 11	0.010
Pulse rate, bpm	63 ± 9	63 ± 9	64 ± 9	62 ± 9	0.231
LDL-cholesterol, mg/dL	132 ± 31	130 ± 29	129 ± 29	127 ± 31	0.026
HDL-cholesterol, mg/dL	55 ± 13	56 ± 14	56 ± 13	56 ± 14	0.774
riglyceride (interquartile range), mg/dL	111 (79–158)	107 (75–158)	110 (76–153)	102 (75–148)	0.253
Uric acid, mg/dL	6.2 ± 1.3	6.0 ± 1.2	6.0 ± 1.1	6.1 ± 1.2	0.312
Fasting glucose, mg/dL	100 ± 21	101 ± 23	99 ± 18	98 ± 23	0.088
Haemoglobin A1C, %	5.5 ± 0.8	5.4 ± 0.8	5.3 ± 0.7	5.4 ± 0.8	0.049
Anti-hypertensive medication, n (%)	67 (13.1)	70 (13.6)	42 (8.6)	55 (12.0)	0.065
Anti-diabetic medication, n (%)	16 (3.1)	14 (2.7)	11 (2.3)	16 (3.5)	0.692
Blood urea nitrogen, mg/dL	14.6 ± 4.1	14.5 ± 3.2	14.2 ± 3.2	14.5 ± 3.4	0.307
Serum creatinine, mg/dL	0.88 ± 0.50	0.86 ± 0.13	0.84 ± 0.12	0.85 ± 0.13	0.245
Current smoker, n (%)	162 (31.8)	163 (31.7)	151 (30.9)	156 (34.1)	0.758

underwent general health screening during this period (first visit) and again the following year (second visit). Among these 3,312 individuals, 3,111 (1,140 women, 1,971 men) who reported not taking anti-hyperlipidemic drugs at both visits were enrolled in the present study. The mean ± standard deviation (SD) of the interval between the two visits of the individuals enrolled was 355 ± 52 days. The percent difference in

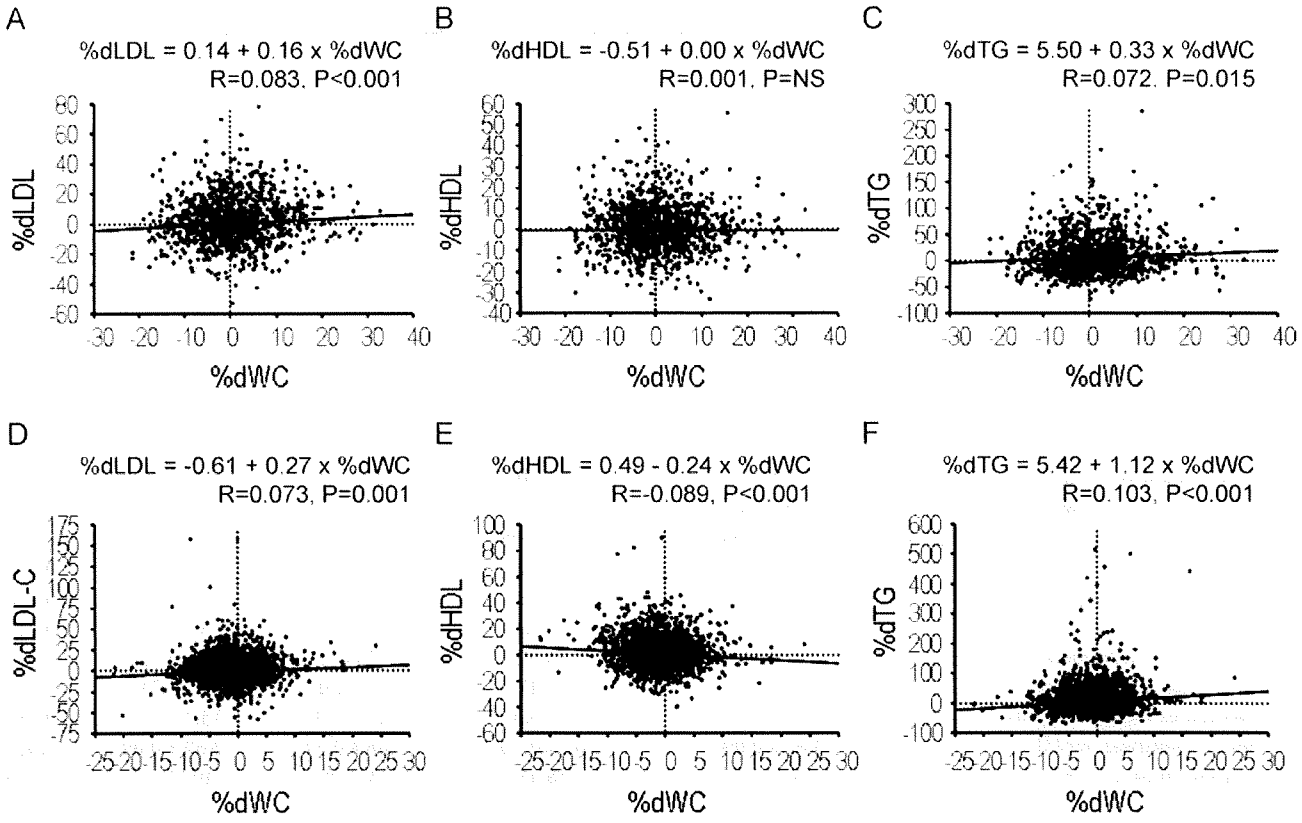

Fig. 1. Linear correlation between %dWC and %dLDL (A), %dHDL (B), and %dTG (C) in women and that between %dWC and %dLDL (D), %dHDL (E), and %dTG (F) in men.

the value of WC, BMI, serum levels of LDL-C, HDL-C, and TG between first and second visits was designated as %dWC, %dBMI, %dLDL, %dHDL, and %dTG respectively. All subjects were seen after an overnight fast. Height and weight were determined, and BMI was expressed as weight (in kilograms) divided by the square of the height (in meters). Waist circumference was measured at the umbilical level to the nearest 1 cm by trained physicians and technicians with the subject standing[6].

Laboratory Analysis

Blood samples were taken from the subjects after an overnight fast. Serum levels of TC, HDL-C, and TG were determined enzymatically. Serum uric acid was measured by the uricase-peroxidase method and hemoglobin A1C was determined using the latex agglutination immunoassay. Blood pressure was measured after about 10 min of rest using an automated sphygmomanometer.

Statistical Analysis

Data are expressed as the mean ± SD unless otherwise stated. Analyses of variance with trend analysis, linear regression analysis and stepwise multiple regression analysis were conducted as appropriate to assess the statistical significance of differences between groups using computer software, StatView ver. 5.0 (SAS Institute, NC) and Dr. SPSS II (SPSS Inc., Chicago, IL). A value of $p<0.05$ was taken to be significant.

Results

Baseline Characteristics

The mean ± SD age of the individuals enrolled was 51.3 ± 9.8 years in women and 53.3 ± 10.2 years in men at the first visit. The sex-nonspecific ranges (min/max) was −21.2/−3.4, −3.4/−0.1, 0.0/3.2, and 3.2/33.3 for each %dWC quartile, and −21.8/−1.8, −1.8/−0.2, −0.2/1.4, and 1.4/15.6 for each %dBMI quartile. Baseline characteristics of the subjects according to %dWC quartile and %dBMI quartile are described in **Table 1a**, **1b**. There was no statistically

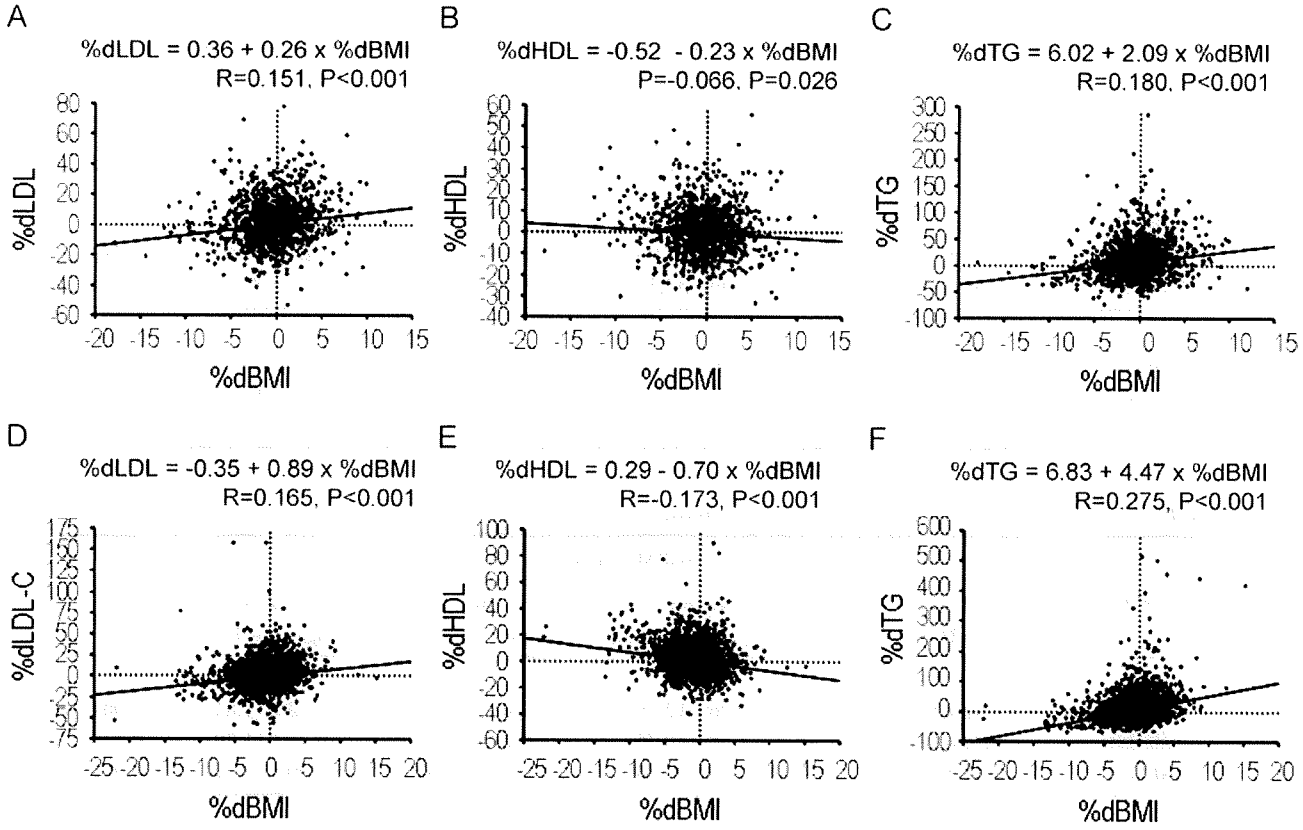

Fig. 2. Linear correlation between %dBMI and %dLDL (A), %dHDL (B), and %dTG (C) in women and that between %dBMI and %dLDL (D), %dHDL (E), and %dTG (F) in men.

significant trend in the rate of anti-hypertensive and anti-diabetic medications across four %dWC or %dBMI quartiles.

Association between Percent Changes in Obesity Parameters and Percent Changes in Lipid Parameters

Scatter plots of %dWC and percent changes in lipid parameters (**Fig. 1**) and %dBMI and percent changes in lipid parameters (**Fig. 2**) are shown. Except between %dWC and %dHDL in women, the correlation was found to be statistically significant between percent changes in obesity parameters and percent changes in lipid parameters; however, the coefficients of correlation were relatively small.

Table 2 describes the percent changes in lipid parameters by %dWC and %dBMI quartiles. In women, %dTG increased with increasing %dWC and with %dBMI. In men, %dLDL and %dTG increased and %dHDL decreased with increasing %dWC (**Table 2a**) and with %dBMI (**Table 2b**). Kappa coefficient between %dWC quartiles and %dBMI quartiles were found to be slight (women, 0.079, $p<0.001$; men, 0.171, $p<0.001$).

Stepwise Multiple Regression Analysis

The correlation coefficient between %dWC and %dBMI was 0.24 in women and 0.47 in men. The regression equation in each gender is as follows: $\%dBMI = -0.181 + 0.096 \times \%dWC$ (women), $\%dBMI = -0.287 + 0.319 \times \%dWC$ (men). We put both %dBMI and %dWC together with age into the statistical model of stepwise multiple regression analysis (**Table 3**, model 1) and it was found that %dBMI, but not %dWC, significantly predicts percent changes in all lipid parameters tested. When %dBMI was excluded from the independent variables, %dWC was identified as an independent factor predicting percent changes in lipid parameters, except for %dHDL in women (**Table 3**, model 2). In women or men with %dBMI of ≥0 (580 women, 890 men), %dWC was not found to be a predictor of percent changes in any lipid parameters tested (data not shown).

Table 2a. Percent changes in lipid parameters according to %dWC quartiles

Variables	%dWC quartiles				*p* for trend
	First (range: −21.2–−3.4)	Second (range: −3.4–−0.1)	Third (range: 0.0–3.2)	Fourth (range: 3.2–33.3)	
Women					
%dLDL	−1.24±14.32	0.44±14.68	0.39±15.80	1.43±15.31	0.127
%dHDL	−0.41±10.97	−0.35±11.93	−0.53±11.02	−0.64±10.90	0.989
%dTG	2.92±35.05	1.49±33.53	9.02±40.49	8.60±37.33	0.034
Men					
%dLDL	−0.26±17.05	−0.36±15.56	−0.31±17.25	0.38±14.93	0.040
%dHDL	2.15±13.23	0.36±11.83	0.08±12.17	−0.21±11.35	0.016
%dTG	−1.25±39.56	5.17±47.12	6.67±53.51	9.66±53.00	0.009

Table 2b. Percent changes in lipid parameters according to %dBMI quartiles

Variables	%dBMI quartiles				*p* for trend
	First (range: −21.8–−1.8)	Second (range: −1.8–−0.2)	Third (range: −0.2–1.4)	Fourth (range: 1.4–15.6)	
Women					
%dLDL	−1.48±16.44	−1.26±12.79	−0.06±14.24	3.42±15.81	<0.001
%dHDL	0.78±12.40	−1.38±10.75	−0.62±9.46	−0.76±11.59	0.147
%dTG	−2.31±33.46	3.58±33.84	6.59±41.32	13.90±35.91	<0.001
Men					
%dLDL	−4.34±16.61	−0.96±15.58	0.01±15.69	2.80±16.68	<0.001
%dHDL	2.94±13.12	0.75±11.37	−0.40±10.50	−1.18±13.29	<0.001
%dTG	−10.21±33.76	1.90±40.05	7.07±48.69	23.13±63.63	<0.001

Discussion

In the current study, both %dWC and %dBMI were positively associated with %dLDL and %dTG in both genders. In addition, %dWC and %dBMI were inversely associated with %dHDL in men, but not in women; however, the association between percent changes in these obesity parameters and percent changes in lipid parameters, when present, was weak. Similar results were obtained when either %dWC or %dBMI was used as a potent predictor of percent changes in lipid data; however the correlation between %dWC and %dBMI was found to be relatively weak, especially in women; the correlation coefficient was 0.47 in men and 0.24 in women. Stepwise multiple regression analysis showed that %dBMI, but not %dWC, was identified as an independent factor predicting % changes in lipid data tested. Notably, even when %dBMI was excluded from the variables, %dWC was not identified as a predictor of %dHDL in women.

Several previous studies showed an association between changes in obesity indexes and lipid parameter changes. For example, in a community-based sample of 3,325 young adults, a 10-year weight gain tended to confer adverse changes in levels of LDL-C, HDL-C, and TG[7]. Bonithon-Kopp *et al.* reported that changes in BMI and the waist to hip ratio (WHR) were positively associated with changes in TG[8]. Williams *et al.* reported that changes in BMI as well as WC had a greater probability of inducing hypercholesterolemia during 7 years of follow-up[9]. In middle-aged subjects free from known cardiovascular diseases and diabetes[10], a gain or loss of WC over 9 years significantly affected serum lipid data and the incidence of metabolic syndrome[11].

On the other hand, only a few studies have investigated whether WC change was associated with changes in lipid parameters independent of BMI. Wing *et al.* analyzed whether changes in WHR led to improvements in serum lipid concentrations independent of weight change in subjects with no history of

Table 3. Stepwise multiple regression analysis between percent changes in lipid parameters and age, %dWC, and %dBMI

	Women					Men				
	β	95%CI		Standardized β	p value	β	95%CI		Standardized β	p value
Model 1										
Dependent variable, %dLDL										
%dBMI	0.72	0.44	0.99	0.15	<0.001	0.86	0.62	1.10	0.16	<0.001
age						−0.08	−0.15	−0.01	−0.05	0.019
Dependent variable, %dHDL										
%dBMI	−0.23	−0.43	−0.03	−0.07	0.026	−0.70	−0.88	−0.53	−0.17	<0.001
Dependent variable, %TG										
%dBMI	2.08	1.42	2.75	0.18	<0.001	4.47	3.78	5.16	0.28	<0.001
Model 2										
Dependent variable, %dLDL										
%dWC	0.16	0.05	0.26	0.08	0.005	0.25	0.09	0.41	0.07	0.002
age						−0.11	−0.18	−0.04	−0.07	0.003
Dependent variable, %dHDL										
%dWC						−0.24	−0.36	−0.12	−0.09	<0.001
Dependent variable, %TG										
%dWC	0.33	0.06	0.60	0.07	0.015	1.12	0.64	1.60	0.10	<0.001

Model 1. Independent variables include age, %dWC, and %dBMI. For model 2, independent variables included age and %dWC. Standardized β values are the estimates resulting from analysis performed on standardized variables.

heart disease or hypertension[12]. They found that changes in WHR were associated with changes in total cholesterol and triglycerides in men; however, statistical significance was lost after controlling for changes in BMI. On the other hand, after controlling for changes in WHR, changes in BMI remained to be associated with changes in total cholesterol and triglycerides in both genders. Of note, even before controlling for changes in BMI, WC change was not found to be associated with either total cholesterol or triglycerides in women. Wing *et al.* concluded that changes in WHR may not be independently related to changes in cardiovascular risk factors. Pascale *et al.* showed that in subjects participating in a year-long weight loss program, weight loss, but not reductions in WHR, was significantly related with improvements in fasting glucose, fasting insulin, and HbA1, although the magnitude of WHR reduction was strongly related to the amount of weight lost especially in men[13].

Similar to Wing *et al.*'s study, the current study indicated certain gender differences in the association between WC change and lipid parameter change, especially in the model not controlled for BMI. As HDL-C and TG are closely related to insulin sensitivity, and thus visceral fat mass, the closer relationship of %dBMI than %dWC with %dHDL and %dTG was rather unexpected. It is possible that WC measurements may be less reliable than weight and height measurements, which reduced the predictive power of %dWC for lipid changes. The correlation between %dWC and %dBMI was relatively weak, especially in women. This finding may indicate that a loss (gain) of BMI did not necessarily result in a loss (gain) in WC over a one-year period, and that men appear to lose (or gain) weight in their abdominal area more readily than women, which was consistent with previous observations[8, 12]. The finding that %dWC did not predict lipid changes independently of %dBMI may suggest that changes in BMI might be a more reliable goal to avoid adverse lipid changes than changes in WC.

It has recently been demonstrated that measuring both general and abdominal adiposity provides a better assessment of the risk of death[14]; therefore, we cannot lessen the importance of reducing WC and thus control visceral adiposity; in this sense, whether percent changes in abdominal fat demonstrated by computed tomography will have a greater impact on serum lipid data than %dWC should be examined in future studies[15].

The current study has several potential limitations. First, individuals who, for unknown reasons, did not visit our institute in the second year were not enrolled in the current study, which may cause some bias. Second, we do not have sufficient information

on the extent to which modifications of lifestyle and dietary habits affect the observed changes in general/abdominal obesity[16]. Third, we excluded subjects who were taking lipid-lowering drugs at either visit, and these individuals may, in general, have higher motivation to obtain information on how to improve serum lipid levels effectively as compared with those not taking such drugs. Finally, a longer follow-up should be performed in future studies.

In summary, during a one-year period, percent changes in BMI (%dBMI) were associated positively with percent changes in LDL-C and TG and negatively with those in HDL-C, especially in both genders. Although percent changes in WC (%dWC) also tended to confer adverse changes in lipid parameters, this relationship did not remain significant after controlling for %dBMI.

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Changes in Waist Circumference and Body Mass Index in Relation to Changes in Serum Uric Acid in Japanese Individuals

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ABSTRACT. ***Objective.*** Studies have shown that obesity is associated with an increase in serum uric acid; and few data are available on the relationship between changes in measures of obesity and changes in uric acid concentrations. We investigated the relationship among percentage changes in waist circumference (%dWC), body mass index (%dBMI), and serum uric acid (%dUA).

Methods. The data of 3153 individuals [1968 men, 1185 women (536 premenopausal, 649 postmenopausal)] who underwent general health screening over a 2-year period and were not taking antihyperuricemic medication were analyzed.

Results. Stepwise multiple regression analysis showed that %dBMI was associated positively with %dUA in postmenopausal women and men, and the association retained statistical significance after adjustment for changes in blood pressure and in renal function. Association between %dBMI and %dUA was not significant in premenopausal women. In men, %dWC was a predicting factor for %dUA, although it did not remain significant when %dBMI was used as a covariate in the statistical model. Multivariate logistic regression analysis showed that the odds ratio of the association between the lowest %dBMI quartile (%dBMI < –1.86) and the lowest %dUA quartile (%dUA < –7.41) was 2.04 (95% CI 1.35–3.07) in postmenopausal women and 1.46 (95% CI 1.14–1.86) in men.

Conclusion. Weight loss may represent an effective nonmedical strategy for reducing serum UA levels, especially in postmenopausal women and men. (First Release Dec 23 2009; J Rheumatol 2010;37:410–6; doi:10.3899/jrheum.090736)

Key Indexing Terms:
WAIST CIRCUMFERENCE BODY MASS INDEX URIC ACID
GLOMERULAR FILTRATION RATE BLOOD PRESSURE

Obesity and serum uric acid (UA) are both associated with enhanced insulin resistance and incidence of metabolic syndrome[1-3]. In addition, measures of obesity have been reported to be positively associated with serum levels of UA[4,5], an association that may be caused by impaired renal clearance of UA in the condition of obesity[6]. The finding that a reduction in weight, and thus in body mass index (BMI), may have a significant effect on serum UA[7] and renal urate excretion[6] suggests that changes in weight may play a role in the regulation of serum UA levels, although the reverse scenario might also be possible[8]. In our study, by analyzing individuals who underwent general health screening, we examined the influence of changes in waist circumference (WC) and BMI on changes in UA, and the dependency/independency on changes in either blood pressure or renal function, which is the possible critical factor affecting serum UA levels in healthy subjects[9].

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MATERIALS AND METHODS

Study population. The study was approved by The Ethical Committee of Mitsui Memorial Hospital. Between October 2005 and October 2006, 11,558 individuals underwent general health screening at our institute. Of these, 3326 individuals (2113 men, 1213 women) underwent general health screening during this period (first visit) and again the following year (second visit). Among these 3326 individuals, 3179 (1968 men, 1211 women) reported taking no antihyperuricemic drugs at either visit. Among the 1211 women, 1185 (98%) answered the questionnaire concerning whether they still had menstruation, and were enrolled for study. Therefore, we analyzed data of 3153 individuals (1968 men, 1185 women). The mean ± standard deviation (SD) interval between the 2 visits of the individuals enrolled was

356.2 ± 51.7 days. WC, BMI, UA, systolic blood pressure, and estimated glomerular filtration rate (eGFR) at the first visit were designated WC1, BMI1, UA1, BPs1, and eGFR1, respectively, and at the second visit WC2, BMI2, UA2, BPs2, and eGFR2.

The percentage differences between values of WC1 and WC2, BMI1 and BMI2, UA1 and UA2, BPs1 and BPs2, and eGFR1 and eGFR2 were designated %dWC, %dBMI, %dUA, %dBPs, and %deGFR. All participants were seen after an overnight fast. Height and weight were determined, and BMI was expressed as weight (kilograms) divided by the square of height (meters). With the subject standing, waist circumference was measured at the umbilical level to the nearest 1 cm by trained physicians and technicians[10].

Laboratory analysis. Blood samples were taken after an overnight fast. Serum levels of low density lipoprotein (LDL), high density lipoprotein (HDL) cholesterol, and triglycerides were determined enzymatically. Serum UA was measured by the uricase-peroxidase method, and hemoglobin A_{1C} by latex agglutination immunoassay. Creatinine was measured by TBA-200FR (Toshiba Medical Systems, Tochigi, Japan) using a commercial kit. Accuras Auto CRE (Shino-test, Tokyo, Japan) eGFR was calculated by the equation: eGFR = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$ (× 0.739 if female)[11]. This equation was recently determined by a multicenter study, and differs from the equation[12] that we used in previous studies[13-15]. Blood pressure was measured after about 10 min of rest with an automated sphygmomanometer.

Statistical analysis. Data are expressed as the mean ± SD unless stated otherwise. Analyses of variance with trend analysis and stepwise multiple regression analysis were conducted as appropriate to assess the statistical significance of differences between groups using SPSS II (SPSS Inc., Chicago, IL, USA). A value of $p < 0.05$ was taken to be statistically significant.

RESULTS

Baseline characteristics. We enrolled 536 premenopausal women, 649 postmenopausal women, and 1968 men for study. At the first visit the mean age of premenopausal women was 43.1 ± 5.51 years, postmenopausal women 59.1 ± 6.8 years, and men 53.3 ± 10.2 years. The sex-nonspecific range of the first to the fourth %dUA quartiles (maximum/minimum) was –47.2/–7.5, –7.4/–1.2, 0.0/7.1, and 7.2/77.8 (Table 1). A plot of WC1 and BMI1 compared to UA1 is shown in Figure 1. In both men and women, there was a statistically significant correlation between WC1 or BMI1 and UA1. The correlation coefficient between WC1 and BMI1 was 0.626 ($p < 0.001$) in premenopausal women, 0.563 ($p < 0.001$) in postmenopausal women, and 0.838 ($p < 0.001$) in men.

Relationship between %dWC, %dBMI, and %dUA. The relationship between %dBMI and %dUA, although very weak, was significant in postmenopausal women and men, and the relationship between %dWC and %dUA was significant only in men (Figure 2). In premenopausal women, the relationships between %dWC and %dUA and between %dBMI and %dUA were not statistically significant. The correlation coefficient between %dWC and %dBMI was 0.267 ($p < 0.001$) in premenopausal women, 0.221 ($p < 0.001$) in postmenopausal women, and 0.484 ($p < 0.001$) in men.

We next performed stepwise multiple regression analysis (Table 2). In a model in which age, UA1, WC1, and %dWC were used as independent variables (model 1), %dWC was found to have independent predictive value for %dUA in men, but not in women. However, after adding BMI1 and %dBMI as independent variables, %dWC in men was no longer a predictor for %dUA (model 2). %dBMI was found to be a predictor for %dUA in postmenopausal women and men even after using either or both %dBPs and %deGFR as independent variables (models 3-5). On the other hand, in premenopausal women, %dBMI was not a significant predictor value for %dUA in any of these models. In addition, in a model in which age, UA1, BMI1, and %dBMI were used as independent variables, %dBMI again was not found to have significant predictive value for %dUA (data not shown). In model 5, variance inflation factor (VIF) scores of all the independent variables were less than 10 (data not shown).

Logistic regression analysis. When the highest %dUA quartile (%dUA ≥ 7.25) was used as a dependent variable, logistic regression analysis showed that the highest %dBMI quartile (%dBMI ≥ 1.47) had a significant positive association in postmenopausal women and in men after adjusting for UA1 and BMI1 (Table 3, model 1). In these groups, statistical significance was retained even after further adjustment for %dBPs and %deGFR (model 2). On the other hand, in premenopausal women, the highest %dBMI quartile was, unexpectedly, negatively associated with the highest %dUA quartile, although statistical significance was lost after further adjustment for %dBPs and %deGFR. In all 3 subgroups tested, %deGFR was negatively associated with the highest quartile of %dUA.

Logistic regression analysis showed that the lowest %dBMI quartile (%dBMI < –1.86) had a significant positive association with the lowest %dUA quartile (%dUA < –7.41) in postmenopausal women and men, and this remained statistically significant even after further adjustment for %dBPs and %deGFR (model 2). But in premenopausal women, association between the lowest %dBMI quartile and lowest %UA was not statistically significant regardless of this further adjustment.

DISCUSSION

Analyzing data of individuals who underwent general heath screening and who were taking no antihyperuricemic medication, we found that correlation between percentage changes in BMI (%dBMI) and in UA (%dUA) was statistically significant in postmenopausal women and in men, but not in premenopausal women.

Stepwise multiple regression analysis showed that %dWC is a significant independent variable for %dUA in men, where UA1, WC1, and %dWC was used as possible independent variables (model 1); however, the relationship lost statistical significance after further adjustment for BMI1 and %dBMI (Table 3). %dWC was not found to be a

Table 1. Baseline characteristics at the first visit according to %dUA quartiles.

Variables	Total, n	%dUA Quartile				p for Trend
		First (range –47.2/–7.5)	Second (range –7.4/–1.2)	Third (range 0.0/7.1)	Fourth (range 7.2/77.8)	
Women/men	1185/1968	290/496	252/483	327/514	316/475	
Baseline data at visit 1						
Age, yrs	52.8 ± 10.2	52.6 ± 10.6	53.3 ± 10.1	52.9 ± 10.0	52.3 ± 10.2	0.225
Waist circumference, cm	82.3 ± 9.2	82.8 ± 9.6	82.7 ± 9.1	82.2 ± 8.7	81.7 ± 9.3	0.074
Body mass index, kg/m^2	22.8 ± 3.1	23.0 ± 3.3	22.8 ± 3.0	22.8 ± 3.0	22.6 ± 3.1	0.056
Systolic blood pressure, mmHg	123 ± 19	124 ± 20	123 ± 19	122 ± 19	123 ± 19	0.636
LDL-cholesterol, mg/dl	129.1 ± 31.2	130.2 ± 31.3	129.4 ± 29.5	129.8 ± 31.3	126.9 ± 32.2	0.147
HDL-cholesterol, mg/dl	60.7 ± 15.3	60.7 ± 15.8	60.5 ± 15.5	60.8 ± 14.8	60.9 ± 15.1	0.980
Triglyceride, mg/dl	111 ± 72	112 ± 75	115 ± 81	109 ± 67	109 ± 65	0.249
Uric acid, mg/dl	5.5 ± 1.3	5.8 ± 1.5	5.7 ± 1.2	5.4 ± 1.3	5.1 ± 1.2	< 0.001
Fasting glucose, mg/dl	96 ± 21	97 ± 20	96 ± 19	95 ± 18	96 ± 25	0.486
Hemoglobin A1c, %	5.3 ± 0.7	5.3 ± 0.7	5.3 ± 0.7	5.3 ± 0.7	5.3 ± 0.9	0.941
Blood urea nitrogen, mg/dl	14.1 ± 3.5	14.6 ± 4.0	14.3 ± 3.2	14.1 ± 3.3	13.6 ± 3.5	< 0.001
Serum creatinine, mg/dl	0.77 ± 0.29	0.79 ± 0.42	0.78 ± 0.15	0.76 ± 0.15	0.75 ± 0.34	0.068
Estimated glomerular filtration rate, ml/min/1.73m^2	68.3 ± 11.8	67.3 ± 11.8	67.8 ± 11.5	68.1 ± 11.4	70.2 ± 12.4	< 0.001
Antihypertensive medication, n (%)	306 (9.7)	78 (9.9)	78 (10.6)	76 (9.0)	74 (9.4)	0.736
Antidiabetic medication, n (%)	74 (2.3)	19 (2.4)	14 (1.9)	24 (2.9)	17 (2.1)	0.632
Postmenopause (female), n (%)	649 (54.8)	152 (52.4)	141 (56.0)	194 (59.3)	162 (51.3)	0.165
Current smoker, n (%)	734 (23.3)	180 (22.9)	173 (23.5)	197 (23.4)	184 (23.3)	0.992
Percent change between 2 visits						
%dBMI	–0.28 ± 3.1	–0.70 ± 3.41	–0.46 ± 3.06	0.01 ± 2.88	–0.03 ± 2.98	< 0.001
%dWC	0.17 ± 6.12	–0.02 ± 6.33	–0.35 ± 6.14	0.64 ± 6.14	0.35 ± 5.83	0.008
%deGFR	1.8 ± 10.0	6.3 ± 10.0	2.6 ± 9.0	0.9 ± 9.1	–2.5 ± 10.0	< 0.001

predictive value for %dUA in premenopausal or postmenopausal women. By contrast, %dBMI was found to be a predictor for %dUA, even after adjustment for WC1, %dWC, %dBPs, and %deGFR in postmenopausal women and men, although it was not significant in premenopausal women. In premenopausal women, %dBMI was not a significant predictive value for %dUA in the model in which age, UA1, BMI1, and %dBMI were used as independent variables; therefore, failure of %dBMI as a predictor for %dUA in premenopausal women may not fully be explained by the multicollinearity between %dWC and %dBMI. These findings collectively indicate that mode of association between change in BMI and change in UA differs between premenopausal and postmenopausal women.

There are several previous studies in which changes in obesity measures have been analyzed in relation to the changes in UA over a certain period of time. For example, Heyden, *et al* showed that there was a stepwise progression from decreased UA levels associated with maximum weight loss to increased levels with maximum weight gain[16]. In addition, Rathmann, *et al*[7] analyzed the data of 1249 male and 1362 female subjects aged 17–35 years from the Coronary Artery Risk Development in Young Adults (CARDIA) Study who attended a 10-year followup. They reported that changes in BMI and WC were associated with changes in UA in a statistical model adjusted for age and baseline UA levels[7]. In contrast, we found that %dBMI was, but %dWC was not, significantly associated with %dUA in multiple linear regression (Table 2, models 2-5). This might be because statistical significance had been weakened after %dWC and %dBMI were simultaneously included into the statistical model; however, %dWC was not significantly associated with %dUA in women even before the adjustment for %dBMI (model 1). From our epidemiological study, we cannot determine what would have caused the different observations between the findings of Rathmann, *et al*[7] and our own. However, considering that circulating insulin levels may have potential to regulate serum UA levels[17], the difference might derive from the difference in insulin sensitivity[18,19] and/or difference in the effect of obesity on insulin resistance[20] among various ethnicities. This possibility should be investigated in future studies. Choe, *et al* found that mean changes in BMI, but not in WC, were statistically different between subjects who had decreased or had no change in UA and those with increased UA during a 1-year followup in men who underwent health promotion screening[9]. They also found that changes in serum creatinine levels, but not in systolic or diastolic blood pressure, were significantly different between subjects who had decreased or unchanged UA levels and those with increased UA[9] — a finding that is, in one sense, in agreement with our observations.

What would be the possible underlying mechanisms that explain the difference in the mode of association between

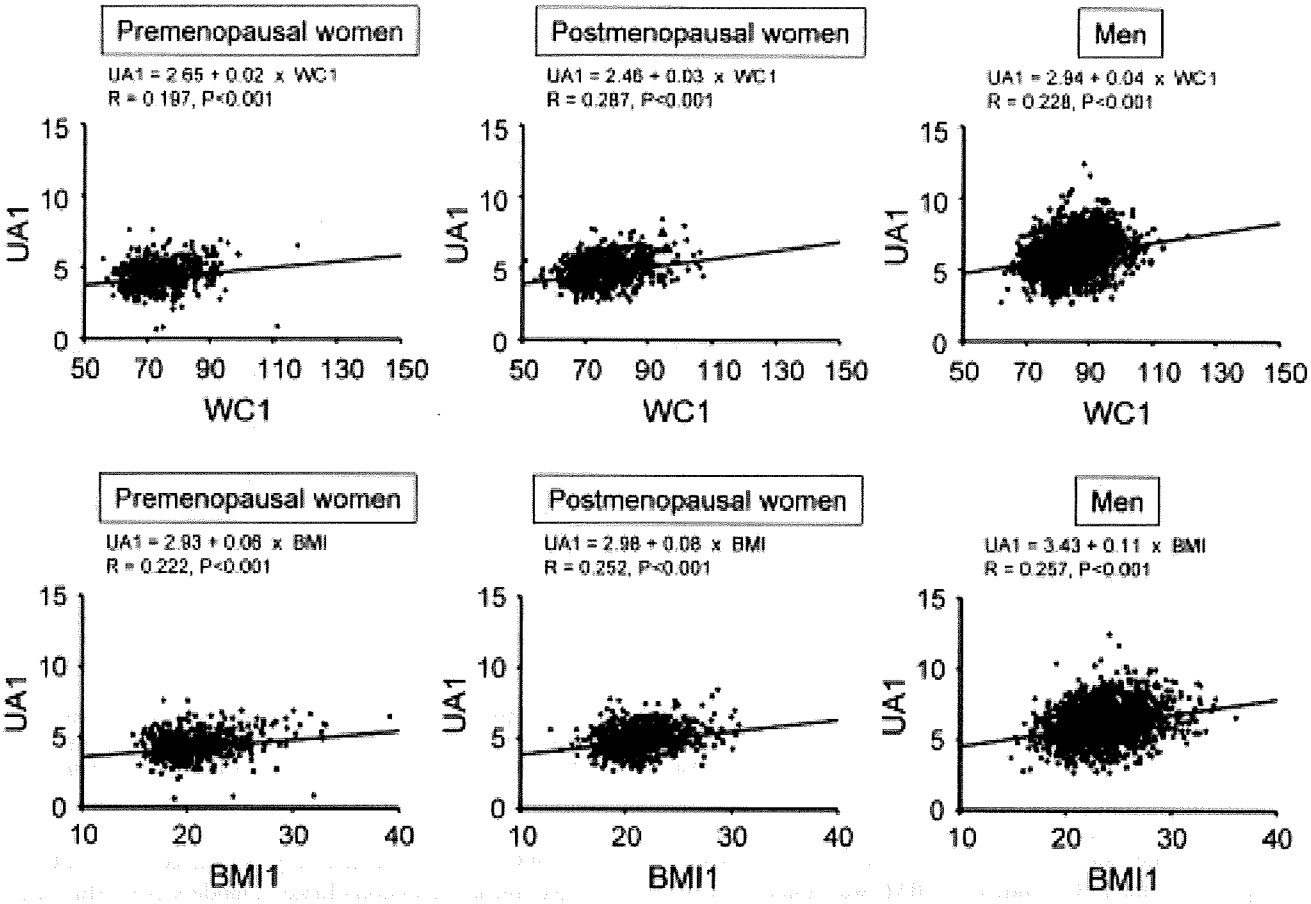

Figure 1. Scatterplot and linear regression between waist circumference at the first visit (WC1) and uric acid at the first visit (UA1) and those between body mass index at the first visit (BMI1) and UA1 in premenopausal and postmenopausal women and in men. Serum uric acid values were not adjusted for age or other possible confounders.

%dBMI and %dUA between premenopausal and postmenopausal women? It has been reported that certain alterations in UA metabolism may occur after the menopause; menopause leads to an increase in serum UA levels[21,22], and this may be in part attributed to decreased estrogen production and subsequent reduction of the fractional excretion of UA[23]. In addition, a recent study suggested that association between insulin resistance and serum UA levels may be greater in postmenopausal women than premenopausal women[24]. Whether these phenomena are related to the difference in the mode of association between %dBMI and %dUA of premenopausal and postmenopausal women remains to be investigated.

We previously showed that obesity or overweight was significantly associated with chronic kidney disease[14], and that changes in obesity measures may be associated with changes in eGFR and urinary excretion of albumin[25]. The strength of the current study was that we demonstrate that change in BMI was positively associated with change in UA in postmenopausal women and men independent of change in eGFR. In addition, we show that mode of association between %dBMI and %dUA was different between premenopausal and postmenopausal women, which may have relation with the fact that menopause causes the elevation of serum UA[21,22,26]. However, controlling BMI is neither unnecessary nor ineffective in keeping the metabolic measures in optimal ranges in "premenopausal" women, because weight gain may result in the reduced insulin sensitivity and aggravation of cardiovascular risk also in premenopausal women[27].

Data for visceral fat volume measured by computed tomography were not available in our study. Recent reports showed that subcutaneous fat accumulation is related to impaired urinary UA excretion[6], whereas visceral fat accumulation is linked closely to the overproduction of uric acid[28], and that serum UA levels are increased both in individuals with subcutaneous fat obesity and in those with visceral fat obesity[28]. It remains to be determined whether changes of WC will lead to an increase in urinary UA excretion in our population, and whether there is a relationship between %dUA and change in visceral fat volume.

Our study has several potential limitations. First, we had no information on the extent to which modifications of lifestyle and dietary habits affected observed changes in