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性肝炎，肝硬変例が含まれる可能性があるので肝臓専門医にコンサルトする必要がある．HBs抗原陽性例での再活性化のリスクは大きいので，基本的に核酸アナログの予防投与を実施する．但し，HBV再活性化のリスクが少ない悪性疾患以外の若年HBe抗原陽性無症候性キャリアに対するステロイド治療例などでは，核酸アナログ予防投与の有効性に関するエビデンスはなく経過観察など他の選択肢があり，適応は慎重に判断する必要がある．HBs抗原陰性でHBc抗体，HBs抗体いずれも陰性の場合は通常の対応とする．HBs抗原陰性でHBc抗体ないしHBs抗体が陽性，すなわち感染既往例と判断される場合は更にHBV-DNA定量検査を実施し，HBV-DNAが陽性の場合は核酸アナログの予防投与を行う．一方，HBV-DNAが陰性の場合はHBV-DNAを毎月モニタリングしながら，陽性化した時点で直ちに核酸アナログを投与する．特にリツキシマブ・ステロイド使用例，造血細胞移植例は再活性化のリスクが高いので慎重な対応が必要である．核酸アナログ予防投与例の投与中止時期に関する明確なエビデンスはないが，HBs抗原陰性，HBc抗体ないしHBs抗体陽性例では免疫抑制・化学療法終了後も12カ月間は投与を継続し，この継続期間中に一定の基準を満たせば投与終了も可能とした．以下にガイドライン作成にあたり論点になった事項を補足する．①スクリーニングにあたってはHBs抗原だけではなくHBc抗体，HBs抗体をできるだけ感度の高い検査法で実施する必要がある．HBs抗原陰性でHBc抗体，HBs抗体いずれも陰性の場合でも，患者が既に免疫抑制状態にある場合には抗体が検出されないことがあり，HBV-DNA定量検査まで測定することが望ましい．②B型キャリア例の急性増悪では発症後早期の核酸アナログ治療が有効であるが，HBV再活性化による劇症化例は発症後の核酸アナログ治療では予後不良であり，発症前の予防投与が必要である．しかし既往感染例でのHBV再活性化率は明らかでなく，また本邦におけるHBc抗体ないしHBs抗体陽性の既往感染例の頻度は高率であることより，全ての症例に核酸アナログの予防投与を実施するのは医療経済的にも困難である．Huiらの報告[16]ではHBs抗原陰性例のHBV再活性化では，HBV-DNAが陽性化し，肝炎が発症するまでに12～28週（平均18.5週）を要しており，したがってHBV-DNAをPCR法またはリアルタイムPCR法で毎月モニタリングし，検出感度以上になった時点で直ちに核酸アナログを投与しても肝炎の重症化は予防可能と推測される．③核酸アナログ製剤はB型慢性肝炎の治療ガイドライン[17]に準拠して，エンテカビル投与を推奨している．しかし，投与期間が長期に及ばない場合など，より安価なラミブジンへの代用も検討の余地がある．④核酸アナログ投与終了に関する明確な基準はない．HBs抗原陽性例では使用する各核酸アナログの投与終了基準に準ずる．HBs抗原陰性，HBc抗体ないしHBs抗体陽性例では免疫抑制・化学療法終了後も12カ月間は投与を継続し，この継続期間中にALTの正常化とHBV-DNAの持続陰性化が見られる場合は投与終了の検討も可能である．但し，HBV以外にALT異常の原因がある場合はALTの正常化は必須ではない．また，核酸アナログ予防投与終了後のHBV再活性化例の報告もあり，投与終了後も更に12カ月間は厳重な経過観察が必要である[18]．

本ガイドライン作成にあたってはワーキンググループ委員の他，名古屋市立大学腫瘍・免疫内科学および鹿児島大学大学院消化器疾患・生活習慣病学血液内科グループの協力および助言を得た．今後は本ガイドラインを血液内科をはじめとする関係領域に周知させていくとともに，各分野と協力して本ガイドラインの有効性を検証していくことが重要である．

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# Prevention of immunosuppressive therapy or chemotherapy-induced reactivation of hepatitis B virus infection —Joint report of the Intractable Liver Diseases Study Group of Japan and the Japanese Study Group of the Standard Antiviral Therapy for Viral Hepatitis—

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**Key words:** fulminant hepatitis　HBV reactivation　*de novo* hepatitis B　nucleoside analog　rituximab

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＜速　報＞

# 核酸アナログ療法中のB型関連肝癌に対する肝癌再発予測マーカーとしてのHBコア関連抗原の有用性

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荒瀬　康司[1)]　池田　健次[1)]　小林万利子[2)]　熊田　博光[1)]

緒言：B型肝疾患に対する核酸アナログ療法の有効性は広く知られており，ラミブジンにおいては投与により発癌率を抑制することが既に報告されている[1)2)]．しかしながら経過観察期間が長くなるにつれ肝発癌例も増加しつつある．また血中HBV-DNA量が抑制されているにもかかわらず，肝癌根治後の再発例も散見される．そこで今回我々は核酸アナログ投与中の肝癌について，肝癌根治療法後の再発予測マーカーとしてのHBコア関連抗原（HBcrAg）の有用性を検討した．

対象と方法：2001年～2008年までに当院で初発の肝細胞癌と診断されたB型肝癌症例で核酸アナログ投与中に肝発癌した54例を対象とした．肝癌発症時の核酸アナログ投与内容の内訳はラミブジン29例，ラミブジン＋アデフォビル併用17例，エンテカビル8例であった．肝癌治療法の内訳は外科切除36例，経皮的局所治療18例であった．HBcrAg測定は既報のごとくCLEIA法を[3)]，HBV-DNA量はアンプリコア法を用いた．肝癌根治後の再発に寄与する因子についてCox比例ハザードモデルを用いて，単変量及び多変量解析を行い検討した．

結果：発癌時のAST/ALT値は31/29 IU/l(中央値)，genotype Cが92.6%（50/54）で，HBe抗原陽性例は42.6%（23/54），血清HBV-DNA量は＜2.6 log copies/ml（中央値）であった．血清HBcrAg量は5.0 logU/ml（中央値）であった．血清HBV-DNA量＜2.6 log copies/mlであった症例35例中，HBcrAg量≧3.0 logU/mlであった症例が29例（82.9%），≧4.8 logU/mlであった症例は13例（37.1%）であった．核酸アナログ投与開始から発癌までの投与期間は2.2年（中央値）であった．

肝癌再発は38.9%（21/54）で認め，根治後から再発までの期間は14カ月（中央値）であった．再発に寄与する因子について単変量解析を行ったところ，HBV-DNA量≧3.0 log copies/ml，HBcrAg≧4.8 logU/ml，腫瘍数多発，門脈浸潤ありの4因子が抽出され，さらに多変量解析を行ったところ，独立因子としてHBcrAg≧4.8 logU/ml，門脈浸潤の2因子が抽出された（Table）．

考察：今回の検討では核酸アナログ投与中の発癌例は血清HBV-DNA量が低値に抑制されているにもかかわらず，HBcrAg量は十分抑制されていない例が認められた[4)]．核酸アナログが投与されていないB型肝癌において，血清HBV-DNA量が肝癌再発に関係するという報告はされている[5)]．しかしながら今回の対象症例のように核酸アナログ投与中の場合はHBV-DNA量よりHBcrAg量の方が肝癌根治後の再発予測マーカーとして有用であると考えられる．

索引用語：HBコア関連抗原，肝癌再発予測，核酸アナログ

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**Table** Factors associated with recurrence of HCC by univariate and multivariate analysis.

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| factors | Hazard Ratio (95%CI) | P | Hazard Ratio (95%CI) | P |
| HBeAg (Positive) | 1.53 (0.63-3.70) | 0.343 | | |
| HBV DNA ( $\geq$ 3.0 logcopies/mL) | 2.49 (1.03-6.00) | 0.042 | | |
| HBcrAg ( $\geq$ 4.8 logU/mL) | 10.4 (2.39-45.0) | 0.002 | 8.50 (1.95-37.1) | 0.004 |
| AST ( $\geq$ 50 IU/L) | 2.47 (0.98-6.20) | 0.055 | | |
| ALT ( $\geq$ 40 IU/L) | 2.37 (0.99-5.71) | 0.054 | | |
| Platelets count ( $< 10^5$ /mm$^3$) | 2.20 (0.81-6.02) | 0.123 | | |
| Serum Albumin ( $<$ 3.5 g/dl) | 1.39 (0.53-3.63) | 0.505 | | |
| Serum bilirubin ( $\geq$ 1.5 mg/dl) | 1.11 (0.62-2.00) | 0.713 | | |
| Prothorombin time ( $<$ 80%) | 2.23 (0.51-9.82) | 0.286 | | |
| ICG-R 15 ( $\geq$ 30%) | 0.54 (0.16-1.87) | 0.332 | | |
| AFP levels ( $\geq$ 100 ng/mL) | 1.81 (0.74-4.44) | 0.194 | | |
| DCP levels ( $\geq$ 100 mAU/mL) | 2.09 (0.81-5.39) | 0.129 | | |
| Tumor size ( $\geq$ 21 mm) | 2.02 (0.81-5.07) | 0.133 | | |
| Tumor number (multiple) | 4.03 (1.31-12.4) | 0.015 | | |
| Presence of portal vein invasion | 5.39 (1.69-17.2) | 0.004 | 3.63 (1.15-11.5) | 0.028 |

*Abbreviation*: AST, aspartate aminotransferase; ALT, alaine aminotransferase; ICG-R15: indocyanine green retention test at 15 min; AFP, alpha-fetoprotein; DCP, des-γ-carboxylprothorombin,

## 英文要旨

### Low hepatitis B virus core-related antigen is a predictor of absence in post-treatment recurrence of hepatocellular carcinoma during antiviral therapy

Tetsuya Hosaka[1]*, Fumitaka Suzuki[1], Masahiro Kobayashi[1], Miharu Hirakawa[1], Yusuke Kawamura[1], Hiromi Yatsuji[1], Hitomi Sezaki[1], Norio Akuta[1], Yoshiyuki Suzuki[1], Satoshi Saitoh[1], Yasuji Arase[1], Kenji Ikeda[1], Mariko Kobayashi[2], Hiromitsu Kumada[1]

The tumor recurrence rate of hepatocellular carcinoma (HCC) is still high even in patients who receive a curative therapy. We analyzed predictive value of HBV-related viral markers, including HBcrAg, HBV DNA, and HBeAg, for HCC recurrence in the patients who developed HCC during antiviral nucleot(s)ide analogues therapy. By univariate analysis, HBV DNA, HBcrAg, tumor number and presence of portal vein invasion were significant predictive factors. By multivariate analysis, HBcrAg and presence of portal vein invasion were independent and significant predictive factors of recurrence after curative therapy for HCC. We conclude that HBcrAg is useful as a predictor of post-treatment recurrence of HCC after curative therapy in patients who received antiviral therapy.

**Key words**: HB core-related antigen, prediction of recurrence of HCC, nucleot(s)ide analogues

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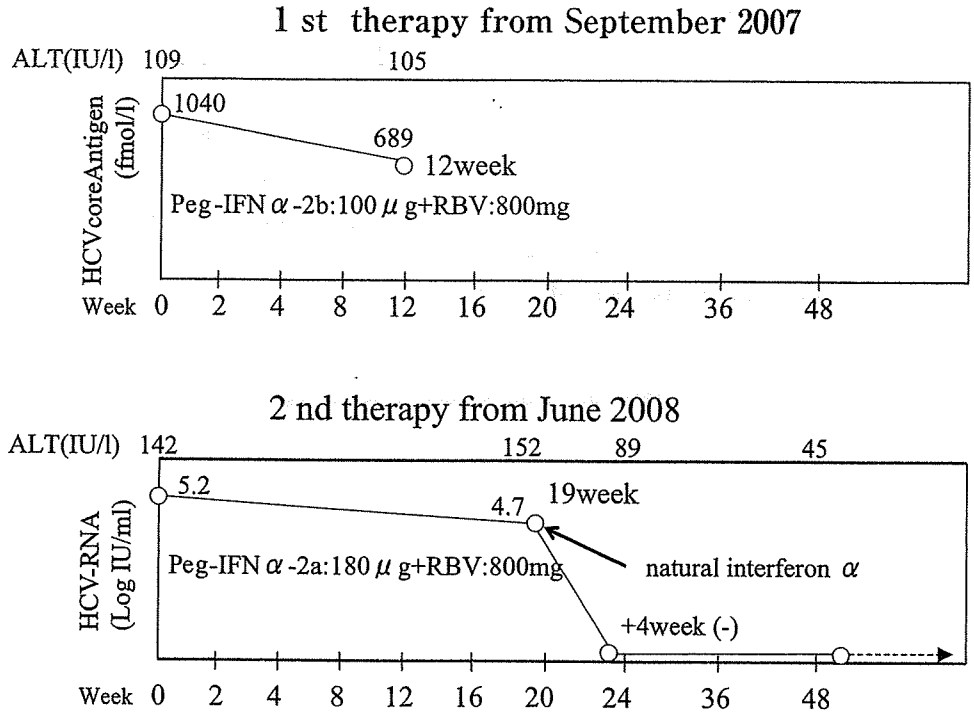


**Fig. 1** Clinical course

も最初は通常量の投与にてHCV-RNAの陰性化の有無をみることも必要であると思われる.

本症例報告の主旨は第13回日本肝臓学会大会(2009年10月)において発表した.

索引用語：C型慢性肝炎,
ペグインターフェロン＋リバビリン,
天然型インターフェロンα

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## 英文要旨

### Rapid virological response obtained by natural IFN α for a patient of chronic hepatitis C with a high viral load of HCV genotype 1b who is refractory to peg-interferon α+ribavirin combination therapy

Akira Kawano[1]*, Yuichiro Kado[1], Hirohisa Shigematsu[1], Koichiro Miki[1], Toshihiro Maruyama[1], Hideyuki Nomura[2], Shinji Shimoda[3]

Interferon monotherapy is considered to have limited effectiveness in patients with HCV of a high viral load. Here, we reported a 21-year old male of chronic hepatitis C with a high viral load of HCV genotype 1b. He received both peg-interferon α-2b plus ribavirin and peg-interferon α-2a plus ribavirin combination therapy. But there were no virological response. Nevertheless, after starting natural interferon α (human lymphoblastoid interferon (HLBI), Sumiferon; Dainippon Sumitomo Pharmaceutical Co., Osaka, Japan), he became HCV-RNA negative at 4 week. The therapy is continued and HCV-RNA negativity is sustained for over 40 weeks. Eradication of HCV might be expected.

Natural IFN α contains more than 20 subtypes, and one or more of them may have therapeutic effect against HCV virus of this patient.

**Key words**: chronic hepatitis C,
peg-interferon α plus ribavirin,
natural interferon α

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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. (J Rheumatol First Release Dec 23 2009; 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: $eGFR = 194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287}$ (× 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

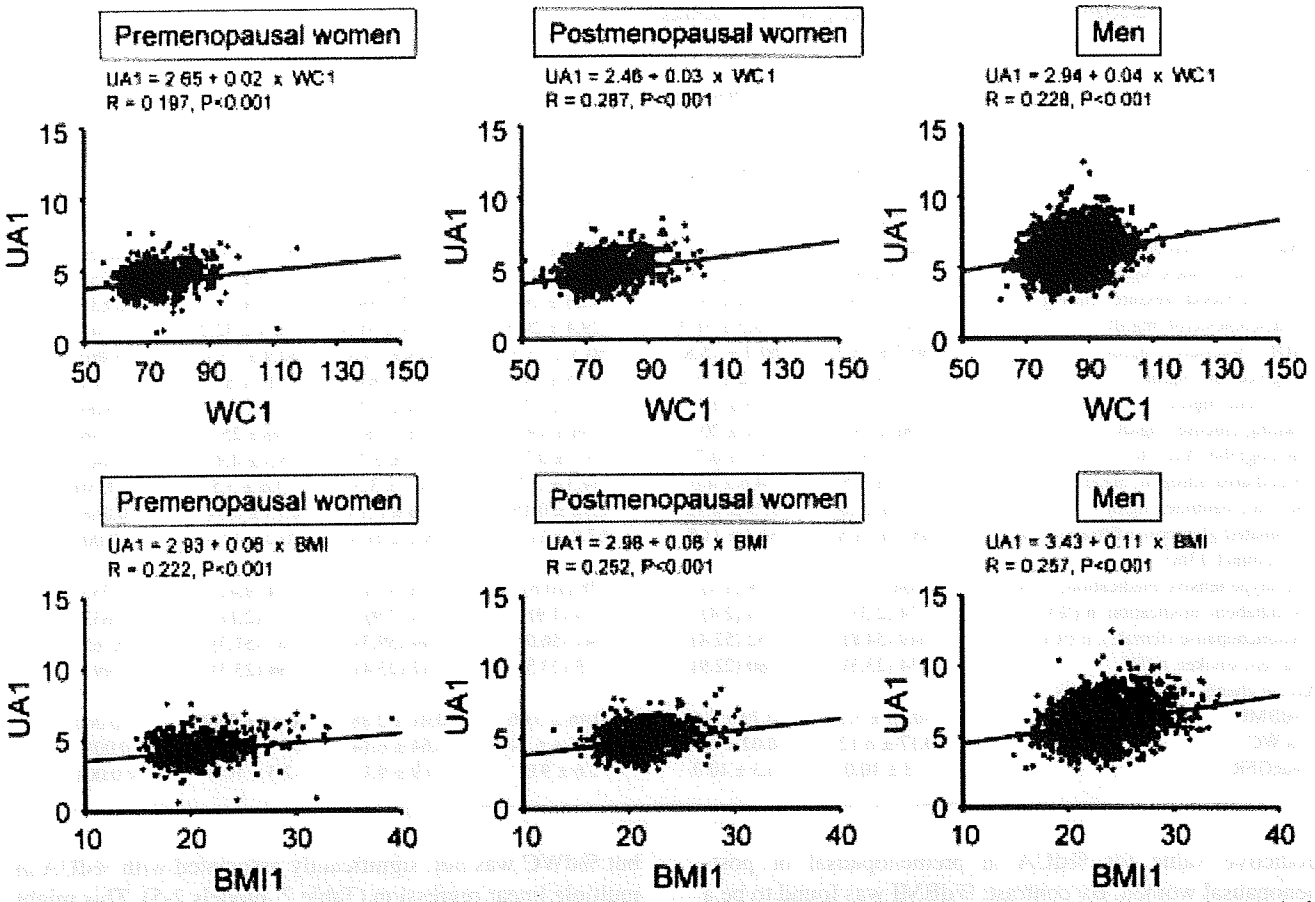


*Figure 1.* Scatterplot and linear regression between waist circumference at the first visit (WC1) and uric acid at the first visit (UA1) and those between body mass index at the first visit (BMI1) and UA1 in premenopausal and postmenopausal women and in men. Serum uric acid values were not adjusted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

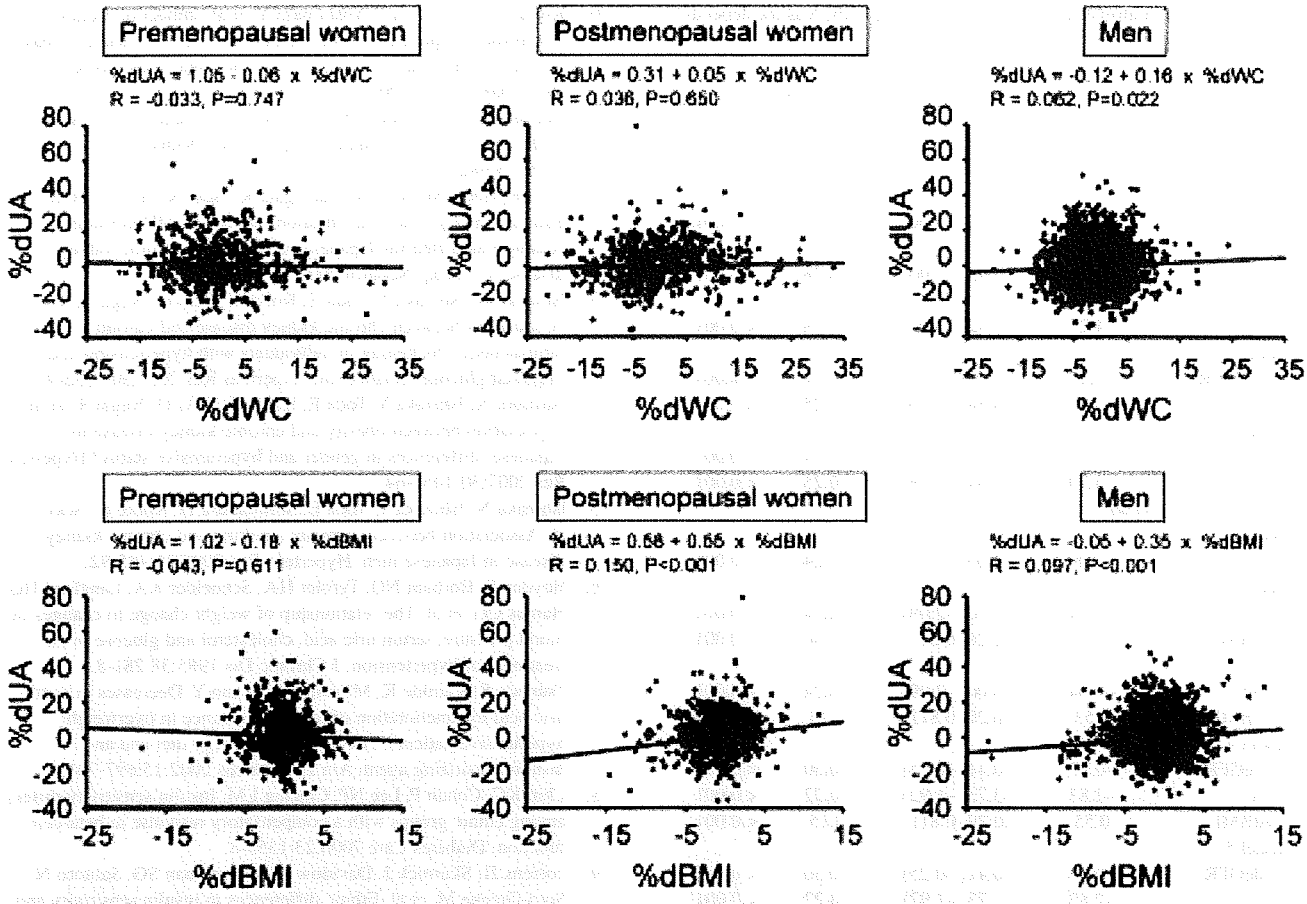


*Figure 2.* Scatterplot and linear regression between percentage change in waist circumference (%dWC) and percentage change in uric acid (%dUA), and those between percentage change in BMI (%dBMI) and %dUA in premenopausal and postmenopausal women and in men. Serum uric acid values were not adjusted for age or other possible confounders.

general/abdominal obesity, as no program to reduce weight was conducted by our institute. Second, we did not take into account participants' level of alcohol consumption or number of cigarettes smoked; both may affect serum UA levels[29,30]. Third, blood samples were taken from individuals in fasting condition, which may have affected their serum creatinine levels, and thus eGFR.

In summary, during a 1-year period, percentage changes in BMI (%dBMI) were associated positively with percentage changes in serum UA levels (%dUA) in postmenopausal women and men, but not in premenopausal women. This relationship was, at least in part, independent of changes in blood pressure and renal function. Weight loss may represent an effective strategy to decrease serum UA levels without use of antihyperuricemic medications, especially in postmenopausal women and men.

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*Table 2.* Stepwise multiple regression analysis using %dUA as the dependent variable.

| | ß | (95% CI) | Standardized ß | p |
|---|---|---|---|---|
| Premenopausal women | | | | |
| Model 1 | | | | |
| UA1 | −4.21 | (−5.42, −3.00) | −0.28 | < 0.001 |
| Model 2 | | | | |
| UA1 | −4.21 | (−5.42, −3.00) | −0.28 | < 0.001 |
| Model 3 | | | | |
| UA1 | −4.21 | (−5.42, −3.00) | −0.28 | < 0.001 |
| Model 4 | | | | |
| % deGFR | −0.43 | (−0.53, −0.33) | −0.34 | < 0.001 |
| UA1 | −3.70 | (−4.84, −2.56) | −0.25 | < 0.001 |
| Model 5 | | | | |
| %deGFR | −0.43 | (−0.53, −0.33) | −0.34 | < 0.001 |
| UA1 | −3.70 | (−4.84, −2.56) | −0.25 | < 0.001 |
| Postmenopausal women | | | | |
| Model 1 | | | | |
| UA1 | −3.09 | (−4.05, −2.13) | −0.24 | < 0.001 |
| Model 2 | | | | |
| UA1 | −3.04 | (−4.00, −2.09) | −0.24 | < 0.001 |
| %dBMI | 0.53 | (0.26, 0.81) | 0.14 | < 0.001 |
| Model 3 | | | | |
| UA1 | −3.04 | (−4.00, −2.09) | −0.24 | < 0.001 |
| %dBMI | 0.53 | (0.26, 0.81) | 0.14 | < 0.001 |
| Model 4 | | | | |
| %deGFR | −0.33 | (−0.41, −0.25) | −0.30 | < 0.001 |
| UA1 | −2.83 | (−3.73, −1.92) | −0.22 | < 0.001 |
| %dBMI | 0.55 | (0.29, 0.81) | 0.15 | < 0.001 |
| Model 5 | | | | |
| %deGFR | −0.33 | (−0.41, −0.25) | −0.30 | < 0.001 |
| UA1 | −2.83 | (−3.73, −1.92) | −0.22 | < 0.001 |
| %dBMI | 0.55 | (0.29, 0.81) | 0.15 | < 0.001 |
| Men | | | | |
| Model 1 | | | | |
| UA1 | −2.51 | (−2.90, −2.12) | −0.27 | < 0.001 |
| %dWC | 0.14 | (0.04, 0.25) | 0.06 | 0.008 |
| Model 2 | | | | |
| UA1 | −2.49 | (−2.88, −2.10) | −0.27 | < 0.001 |
| %dBMI | 0.32 | (0.17, 0.48) | 0.09 | < 0.001 |
| Model 3 | | | | |
| UA1 | −2.51 | (−2.89, −2.12) | −0.27 | < 0.001 |
| %dBMI | 0.38 | (0.22, 0.54) | 0.10 | < 0.001 |
| %dBPs | −0.06 | (−0.10, −0.02) | −0.06 | 0.006 |
| Model 4 | | | | |
| %deGFR | −0.36 | (−0.40, −0.31) | −0.32 | < 0.001 |
| UA1 | −2.29 | (−2.66, −1.92) | −0.25 | < 0.001 |
| %dBMI | 0.35 | (0.21, 0.50) | 0.10 | < 0.001 |
| Model 5 | | | | |
| %deGFR | −0.36 | (−0.40, −0.31) | −0.32 | < 0.001 |
| UA1 | −2.29 | (−2.66, −1.92) | −0.25 | < 0.001 |
| %dBMI | 0.35 | (0.21, 0.50) | 0.10 | < 0.001 |

Model 1. Independent variables include age, UA1, WC1, and %dWC. Model 2. Independent variables include Model 1 + BMI1 and %dBMI. Model 3. Independent variables include Model 2 + %dBPs. Model 4. Independent variables include Model 2 + %deGFR. Model 5. Independent variables include Model 2 + %dBPs and %deGFR. UA: uric acid; BMI: body mass index; BPs: systolic blood pressure; eGFR: estimated glomerular filtration rate.


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*Table 3.* Logistic regression analysis using the highest or lowest %dUA quartile as the dependent variable.

| | Independent Variable | | | |
|---|---|---|---|---|
| | %dUA ≥ 7.2% | | %dUA < −7.5% | |
| | OR (95% CI) | p | OR (95% CI) | p |
| Premenopausal women | | | | |
| Model 1 | | | | |
| %dBMI quartile | | | | |
| First | | | 1.19 (0.73, 1.94) | 0.474 |
| 2 and 3 | 1 Reference | | | |
| 4 | 0.65 (0.42, 0.99) | 0.046 | 1.00 Reference | |
| Model 2 | | | | |
| %dBMI quartile | | | | |
| First | | | 1.41 (0.85, 2.34) | 0.181 |
| 2 and 3 | 1.00 Reference | | | |
| 4 | 0.71 (0.45, 1.10) | 0.126 | 1.00 Reference | |
| %deGFR | 0.93 (0.91, 0.95) | < 0.001 | 1.06 (1.04, 1.08) | < 0.001 |
| %dBPs | 0.99 (0.97, 1.01) | 0.225 | 1.00 (0.98, 1.02) | 0.804 |
| Postmenopausal women | | | | |
| Model 1 | | | | |
| %dBMI quartile | | | | |
| First | | | 2.04 (1.37, 3.03) | < 0.001 |
| 2 and 3 | 1.00 Reference | | | |
| 4 | 1.60 (1.06, 2.41) | 0.025 | 1.00 Reference | |
| Model 2 | | | | |
| %dBMI | | | | |
| First | | | 2.04 (1.35, 3.07) | 0.001 |
| 2 and 3 | 1.00 Reference | | | |
| 4 | 1.72 (1.12, 2.63) | 0.013 | 1.00 Reference | |
| %deGFR | 0.95 (0.93, 0.97) | < 0.001 | 1.05 (1.03, 1.07) | < 0.001 |
| %dBPs | 0.98 (0.97, 1.00) | 0.039 | 1.00 (0.98, 1.01) | 0.684 |
| Men | | | | |
| Model 1 | | | | |
| %dBMI quartile | | | | |
| First | | | 1.35 (1.07, 1.69) | 0.011 |
| 2 and 3 | 1.00 Reference | | | |
| 4 | 1.38 (1.08, 1.76) | 0.010 | 1.00 Reference | |
| Model 2 | | | | |
| %dBMI quartile | | | | |
| First | | | 1.46 (1.14, 1.86) | 0.002 |
| 2 and 3 | 1.00 Reference | | | |
| 4 | 1.49 (1.15, 1.92) | 0.002 | 1.00 Reference | |
| %deGFR | 0.94 (0.92, 0.95) | < 0.001 | 1.07 (1.06, 1.08) | < 0.001 |
| %dBPs | 1.00 (0.99, 1.01) | 0.300 | 1.00 (0.99, 1.01) | 0.715 |

Model 1. Independent variables include age, UA1, BMI1, and %dBMI quartiles. Model 2. Independent variables include Model 1 + %dBPs and %deGFR. UA: uric acid; BMI: body mass index; BPs: systolic blood pressure; eGFR: estimated glomerular filtration rate.

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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 $\geq 0$, %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/m$^2$ | 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/m$^2$ | 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

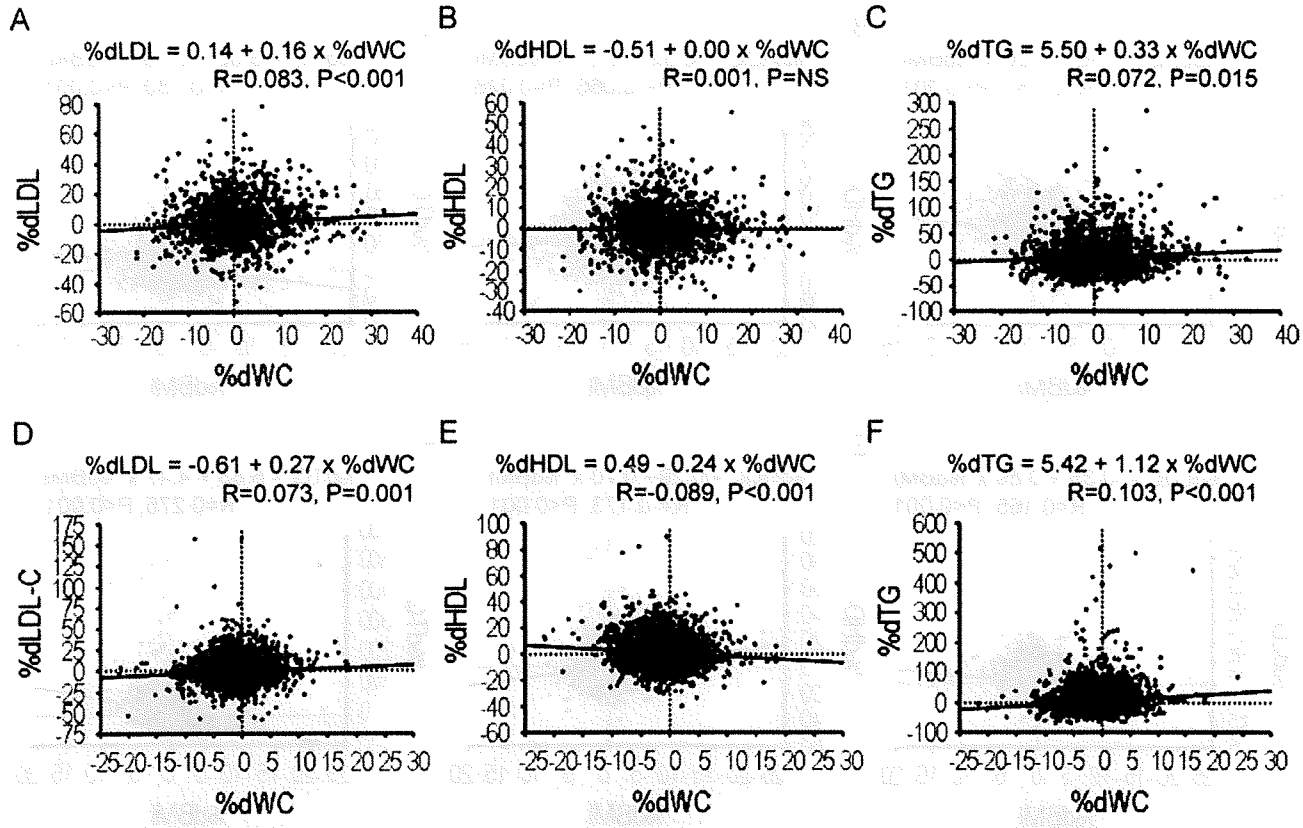


**Fig. 1.** Linear correlation between %dWC and %dLDL (A), %dHDL (B), and %dTG (C) in women and that between %dWC and %dLDL (D), %dHDL (E), and %dTG (F) in men.

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

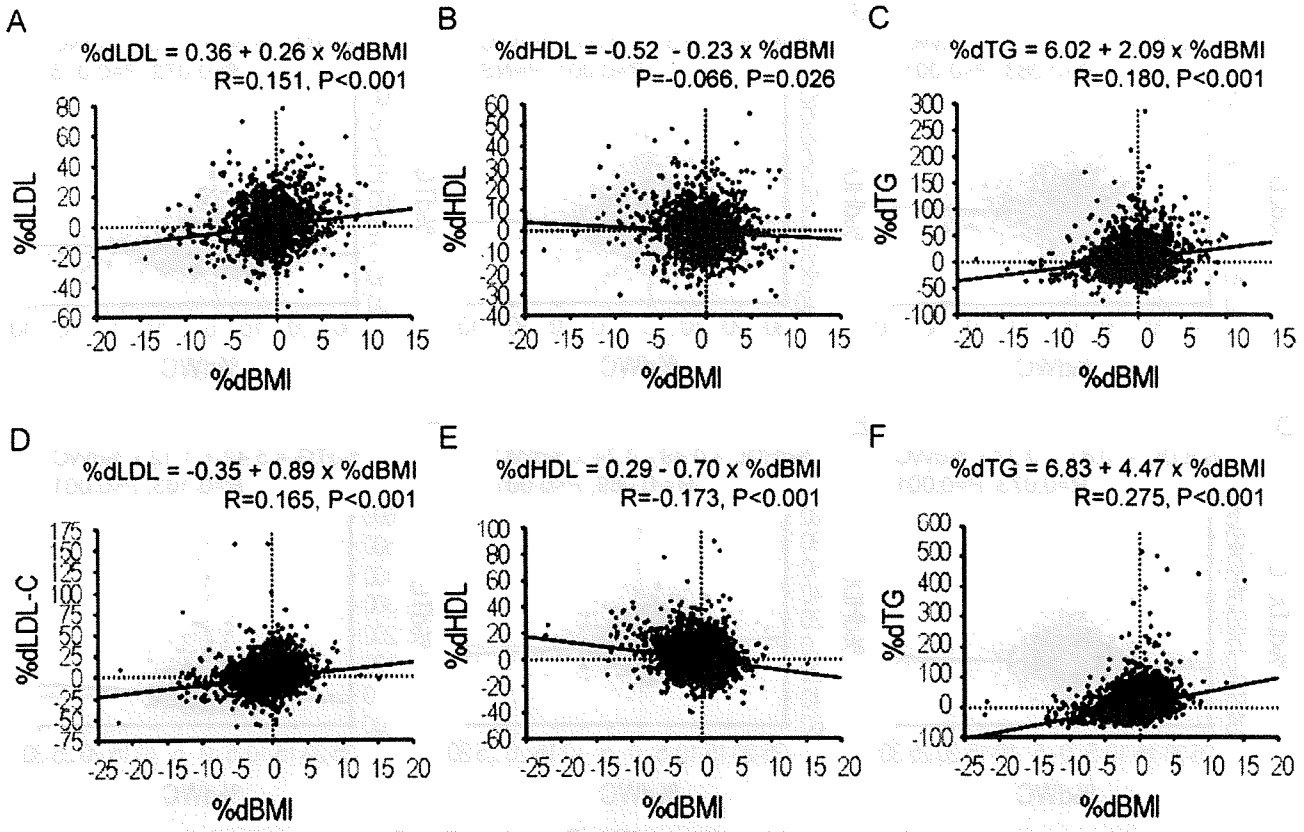


Fig. 2. Linear correlation between %dBMI and %dLDL (A), %dHDL (B), and %dTG (C) in women and that between %dBMI and %dLDL (D), %dHDL (E), and %dTG (F) in men.

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