症の危険性高く，特に若年者からの発症があることが判明した[5]．

また，HCV/HTLV-1 重複感染例では IFN 単独療法の有効率が有意に低く[6]，IFN 単独療法による肝癌発症抑制効果もみられなかった[5]．HTLV-1 が HCV に重複感染すると不利な状況に働く機序の詳細は不明であるが，HTLV-1 感染細胞から未感染細胞に感染する際には，細胞表面の gp46 を介して行われるが，肝病態が進行しているほど，この gp46 に対する抗体の出現頻度が高く，抗体価も高いことから[7]，HTLV-1 の外被蛋白の発現が肝病態に何らかの影響を与えているものと考えられる．

現在，PEG-IFN α-2b + ribavirin 療法が行われているが，この治療法では HCV/HTLV-1 重複感染例に対しても 34 例中 20 例，58.8% と HCV 単独感染 142 例中 80 例，56.3% とほぼ同等であり，当地区では今後は肝癌発症が減少するものと思われる[5]．

## おわりに

わが国は HCV の高浸淫国の一つであり，その原因としては医療行為による感染拡大が考えられた．また，HCV 感染者のうち肝機能異常者は高率に肝癌発症がみられた．HCV 感染者に対する PEG-IFNα + ribavirin 併用療法の有効性は genotype 1 型で 40%，2 型で 80% であった．有効例については HCV が完全に消失するため肝病態の著明な改善および肝癌発症抑制効果がみられた．また，HCV 感染者はインスリン抵抗性がみられる例があり，このような例では IFN 療法の有効性が低い．九州地区では成人 T 細胞白血病ウイルスの高浸淫地区でもあるため，HCV との重複感染例が高頻度にみられる．重複感染例では若年での肝癌発症があるため，有効性が高まった PEG-IFN-α + ribavirin 併用療法に期待しているところである．

本稿では九州大学大学院感染環境医学分野/九州大学病院総合診療科の方針である予防医学の実践の一つとして，HCV 感染を取り上げた．すなわち，著者らが取り組んだ HCV 感染の実態調査およびその感染防止対策とその効果，さらに感染患者対する肝癌発症抑制を目的とした IFN 療法の効果について述べた．

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（参考文献のうち，数字がゴシック体で表示されているものについては，著者により重要なものと指定された分です．）

# B型急性肝炎に対する核酸アナログ製剤の適応

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## はじめに

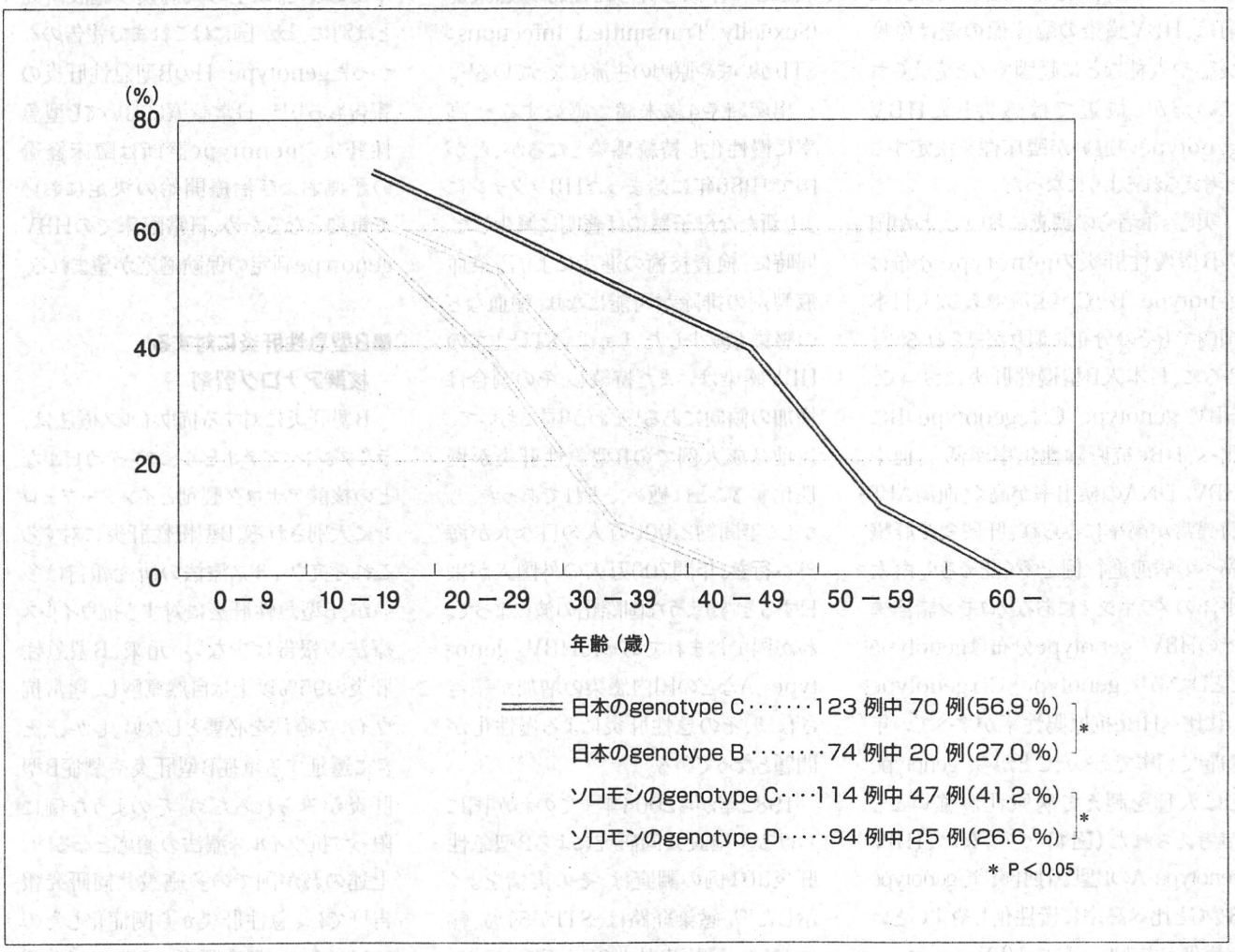
B型肝炎ウイルス(hepatitis B virus: HBV)感染は、世界で約3億人の持続感染(B型慢性肝炎)例がいるといわれ、第7位の死亡原因である。1980年代初頭のhepatitis B(HB)ワクチンの導入により新たな持続感染は減少している[1]。さらに、1998年より始まった(わが国の保険適応は2000年から)、B型慢性肝炎に対する核酸アナログ製剤による抗ウイルス療法は、ウイルス増殖の抑制、肝炎の沈静化をもたらし、肝病態進行を抑制し、B型慢性肝炎の管理に革命的なものとなった[2]。

一方、多くは自然寛解するB型急性肝炎において、慢性化する例やまれに劇症肝炎に移行する例もあるため、核酸アナログ製剤が必要となることがある。今回、わが国におけるB型急性肝炎の現状および特徴をふまえ同治療の適応について述べる。

## ■HBV genotypeと病原性

HBVは約3200塩基からなる部分

図1　B型慢性肝炎におけるHBV genotype 別・年齢別のHBe抗原陽性率　ーわが国およびソロモン諸島国の比較ー




(文献6, 9より改編)

環状二重鎖のDNAウイルスで、4つのopen reading flame (ORF) (S・C・X・P遺伝子)からなる。HBV遺伝子型(genotype)は、1980年代以降国際データベース化され、現在AからHの8つのgenotypeに分類される[3,4]。アジアには主にgenotypeBとC、アフリカにはgenotype A、西アフリカにはgenotype E、欧米にはgenotype AとD、南米にはgenotype FとHというように、世界中で主要なgenotype分布に違いがある。以前は、HBV感染の臨床像の差は免疫反応や人種などに起因すると考えられていたが、最近では感染したHBV genotypeの違いが臨床像を決定すると考えられるようになった。

実際、筆者らの調査において、わが国のB型慢性肝炎のgenotype分布はgenotype BとCが主流であるが、日本国内でもその分布に偏りがみられる[5,6]。さらに、日本人B型慢性肝炎において、HBV genotype Cは、genotype Bに比べ、HBe抗原陰性化率が低く、血中HBV DNAの検出率が高く、血清ALT値異常が高率にみられ、肝硬変や肝臓癌への病態進行例を多く認める[7]。南太平洋のメラネシアにあるソロモン諸島国でのHBV genotype分布はgenotype CとDであり、genotype Cはgenotype Dに比べHBe抗原陽性率がすべての年齢層で高率であったことから、genotype Cは人種を超えて病原性が強いことが考えられた(**図1**)[6,8,9]。なお、HBV genotype AのB型急性肝炎は、genotype BやCと比べ高率に慢性化しやすいという報告がある[10]一方で、HBV genotype AのB型慢性肝炎は肝臓癌発症が少なく[11]、インターフェロンによる治療効果が他genotypeに比べ良好である[12]。

以上のように、HBV感染の臨床においては、そのgenotypeを考慮することが重要である。

### ■B型急性肝炎

B型急性肝炎はHBVの初感染により生じる。同感染は、主に血液を介し、HBVに汚染された血液製剤・不法薬物静脈注射・注射針の再利用などにより起こるが、血液以外の精液・膣液・唾液などの体液を介した性行為感染症(Sexually Transmitted Infections: STI)がいまや原因の主流になっている[13]。

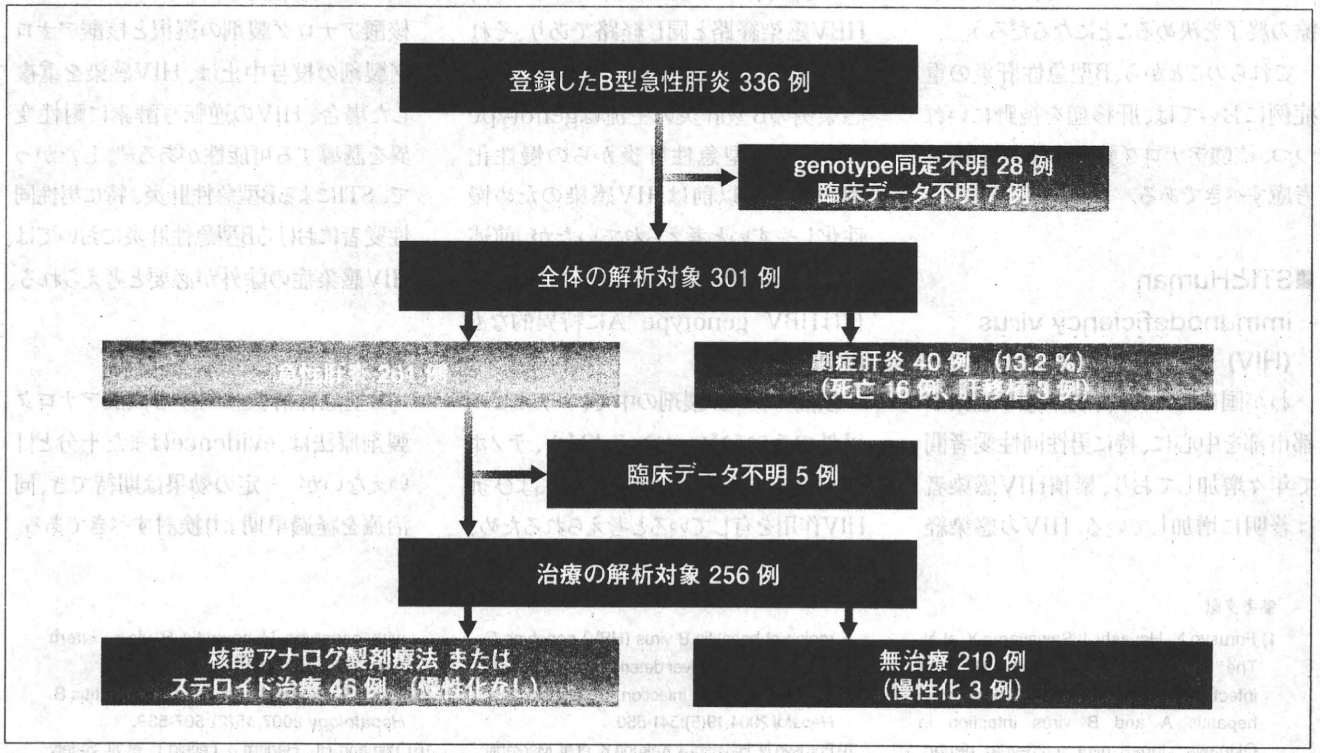
出産時や4歳未満で感染すると、高率に慢性化し持続感染となるが、わが国で1986年に始まったHBワクチンにより新たな母子感染は著明に減少した。同時に、検査技術の進歩により汚染血液製剤の排除が可能になり、輸血などの感染も減少した。しかし、STIとしてのHBV感染はいまだ持続し、その割合は増加の傾向にある[13]。わが国において、以前は成人例でのB型急性肝炎が慢性化することは極めてまれであった。しかし、年間約2,000万人の日本人が海外へ行き、年間700万人の外国人が来日するというような国際化の波によって、わが国ではまれであったHBV genotype Aなどの国内感染の増加が報告され[13]、その急性肝炎による慢性化が問題となっている。

1982年から2004年までのわが国における多施設共同研究によるB型急性肝炎301例の調査は、その実情をよく示した[10]。感染経路は、STIが57%、輸血が1%、医療事故が6%、不明が36%であった。原因となるgenotypeは、日本型のgenotype BとCは71%で、残りの29%は外国型のgenotype A、B、D、Gであり、日本人のB型慢性肝炎のgenotype報告とは大きく異なった。全体の1%が慢性化し、いずれも、抗ウイルス療法を受けず、かつ、欧米の genotype AとアジアのgenotypeBa(わが国のgenotype Bjではなく)で外国型のgenotypeであった。抗ウイルス療法を受けなかった症例での検討において、欧米のgenotype Aの慢性化率9%は、他のgenotypeの0.5%と比べ有意に高率であった。以上の大規模多施設研究とは別に、わが国にはこれまで報告のなかったgenotype HのB型急性肝炎の報告もあり[14]、日常診療においてB型急性肝炎のgenotype診断は臨床経過の予測および治療開始の決定において重要となるため、日常臨床でのHBV genotype判定の保険適応が望まれる。

### ■B型急性肝炎に対する核酸アナログ製剤

B型肝炎に対する抗ウイルス療法は、ラミブジン、アデホビル、エンテカビルなどの核酸アナログ製剤とインターフェロンに大別される。B型慢性肝炎に対するこれら抗ウイルス療法の研究報告は多いが、B型急性肝炎に対する抗ウイルス療法の報告は少ない。元来、B型急性肝炎の95%以上は自然寛解し、通常抗ウイルス療法を必要としない。しかし、ときに遷延する重症B型肝炎や劇症B型肝炎がみられるため、そのような例に限って抗ウイルス療法の適応となる[15]。上述のわが国での多施設共同研究報告[10]では、急性肝炎から劇症化したのは13.2%で、劇症肝炎のうち40%が死亡し、7.5%が肝臓移植を受けた。また、急性肝炎例のうち、血清ALT異常が24週間以上持続したのは3.1%であり、24

図2　わが国におけるB型急性肝炎の多施設共同研究報告




(文献6, 9より改編)

週までに99%がHBs抗原は陰性化したが、1%は慢性化した(**図2**)。慢性化例はいずれも、いかなる治療も行っていなかった。上述したように、HBV genotypeAによるB型急性肝炎は高率に慢性化するため、B型急性肝炎の抗ウイルス療法の適応は症例を選んで行うべきである。

近年、B型急性肝炎に対するラミブジンによる無作為比較研究が報告されている。十分早期にラミブジン投与を開始すると、肝不全や肝移植を回避することができるという報告もある[16]一方で、ラミブジン投与群はプラセボ群に比べ、HBV DNA量の早期低下を認めるものの、ALT値改善率やHBs抗原陰性化率において両群に有意差はなかったとの報告もある[17]。一部の専門家は、大規模かつ様々なHBV genotypeを含んだ比較研究が必要であると主張するかもしれないが、重症なB型急性肝炎やB型劇症肝炎において比較研究を行うのは倫理的ではないと考えられる。

イタリアからの報告では、血清ALT値、血清ビリルビン値、プロトロン時間を重視した重症B型肝炎に対し、慢性肝炎に対する2倍量のラミブジン200mg/日を投与し、少数例ながら全例完治し、入院期間13日、合併症はなく、血清ALT値および血清ビリルビン値の正常化はそれぞれ5.5週および3週間であり、血清HBV DNAは3ヵ月以内に検出されなくなり、経過は良好であった[18]。わが国においても、genotype AのB型急性肝炎に対し、インターフェロンとラミブジンの併用療法[19]やエンテカビルによる治療[20]で良好な効果を認めた報告がある。

B型急性肝炎への核酸アナログ製剤療法において、何を投与するか、そして、その投与量について一定の見解は出ていないが、腎障害のある例に対してはラミブジンおよびアデホビルは投与量を検討する必要があるかもしれない。また、核酸アナログ製剤による治療期間は、ウイルス増殖の停止を目標とすれば、HBs抗原陰性化またはHBs抗体陽転化を確認するまでとなるであろうが、その結論はまだ出ていない。実際、B型慢性肝炎においてHBV genotype AとBは自然HBs抗原陰性化率が他のgenotypeに比べ高率である[21]ので、B型急性肝炎においてもgenotype間の差があり得るかもしれないため、血清HBV

DNA量も検査をしながら、総合的に治療の終了を決めることになるだろう。

これらのことから、B型急性肝炎の重症例においては、肝移植を視野にいれつつ、核酸アナログ製剤の早期治療を考慮すべきである。

## ■STIとHuman immunodeficiency virus (HIV)

わが国において、新規のHIV感染が都市部を中心に、特に男性同性愛者間で年々増加しており、累積HIV感染者は著明に増加している。HIVの感染経路は、性行為や血液を介したもので、HBV感染経路と同じ経路であり、それら重複感染はよく認められる[22]。HIV感染例のB型肝炎の主流はgenotype Aであり、B型急性肝炎からの慢性化例が多い。以前はHIV感染のため慢性化しやすいと考えられていたが、前述のように非HIV感染の現象もあり、慢性化はHBV genotype Aに特異的なものである。

核酸アナログ製剤の中で、アデホビル以外のラミブジン、エンテカビル、テノホビル、エムトリシタビンは抗HBVおよび抗HIV作用を有していると考えられるため、STIにおけるB型急性肝炎の際に安易な核酸アナログ製剤の選択と核酸アナログ製剤の投与中止は、HIV感染を重複した場合、HIVの逆転写酵素に耐性変異を誘導する可能性がある[23]。したがって、STIによるB型急性肝炎、特に男性同性愛者におけるB型急性肝炎においては、HIV感染症の除外が必要と考えられる。

## おわりに

B型急性肝炎に対する核酸アナログ製剤療法は、evidenceはまだ十分とはいえないが、一定の効果は期待でき、同治療を経過早期より検討すべきである。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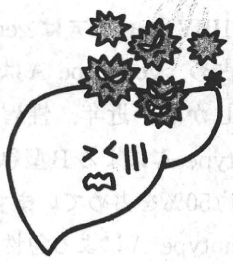
ミニレクチャー

# B型肝炎もSTI

九州大学病院総合診療科　林　純

## HBV感染の現状は？

B型肝炎ウイルス（HBV）の新たな感染は，血液センターにおけるスクリーニング検査の進歩および医療現場における感染対策の強化により，また，母子間感染対策の徹底などにより，ほとんど見られなくなりました．以上の現状を踏まえると，現在のHBVの急性感染であるB型急性肝炎の大部分は性行為によるものと考えられます．



## 性行為により感染した症例

B型急性肝炎はself limitedですが，HBe抗原を産生しない変異ウイルスに感染した場合，劇症化する例があるため，臨床的に注意を要します．B型慢性肝炎の婚約者との性行為により，同じgenotype CのHBVに感染し，劇症肝炎を発症した27歳の女性の例では，発熱，食欲不振を主訴とし，高度の肝機能障害がみられ，言動の異常，羽ばたき振戦が現れていたことから，肝性昏睡Ⅱ度と判定されました．

## B型急性肝炎あるいは劇症肝炎の治療は？

この症例では，血漿交換の導入により，1ヵ月後にはほぼ完治しましたが，劇症肝炎の生存率は30％以下と低いため，肝炎の状態が重症な場合，劇症化を予防するため核酸誘導体であるラミブジンやエンテカビルの投与，あるいはステロイド動注（保険適応外）などを試みることが多いです．さらに，HBV感染による劇症肝炎の肝移植による5年生存率は75％と良好な成績が報告されているため，肝移植を考慮に入れた治療を行うべきです．

HBV未感染者は，セックス・パートナーがHBV感染者の場合，感染防止のためのHBワクチンの接種が推奨されます．

## 一過性感染症としてのHBV感染症

いちど感染すると生涯持続して検出されるHBc抗体の陽性率は，筆者らが調査した特殊浴場女性従業員では，女性献血者に比べて有意に高率でした．すなわち，性行為によるHBV感染は，不顕性感染も含めるとかなりの頻度で存在する可能性があると思われます．

また，筆者らはヒト免疫不全ウイルス（HIV）およびHBVの重複感染があるセックス・

パートナーとのdeep kissのみで感染したgenotype AのB型急性肝炎を発症した男性同性愛者を経験しましたが，HIVには感染していませんでした．HBVはHIVに比較して，血液中だけでなく唾液中にもウイルス量が多いため，感染しやすいと考えられました．

### 広がりを見せるgenotype A


最近の話題としては，上記のようにgenotype AによるB型急性肝炎の頻度が増加してきていることが挙げられます．

genotypeの分布には地域差があり，わが国のHBVキャリアはgenotype BとCが大半を占め，genotype Aは本来極めて稀でした．しかし，近年，性習慣の変化や多様化から，欧米やフィリピンに多いとされるgenotype AによるB型急性肝炎が急速に都市部から広がりを見せ，最近ではB型急性肝炎の約50%を占めています．

genotype Aによる急性肝炎の特徴は，家族歴がなく，男性が90%以上を占め，感染経路としては性行為が疑われることが多く，同性愛者が約50%を占めるとされています．genotype BおよびCのHBVの成人感染は慢性化することはありませんが，genotype Aが感染した場合，約10%は慢性化することも特徴です．

**MINI LECTURE**

Original Article

# Impact of Changes in Obesity Parameters on Glucose Metabolism and Insulin Resistance Over a One-Year Period

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***Aim***: Changes in indexes of obesity, such as waist circumference (WC) and body mass index (BMI), may influence some glucose metabolism-related parameters in both obese and non-obese subjects. We have investigated the impact of changes in WC and in BMI on data related to glucose metabolism over a one-year period.

***Methods***: Data from 3213 individuals (2014 men, 1199 women) who underwent a general health screening two years running and were not taking antidiabetic medication were analyzed.

***Results***: In men, percent changes in WC (%dWC) and BMI (%dBMI) were both significantly correlated with percent changes in fasting glucose (%dFG), in hemoglobin $A_{1c}$ (%dHbA$_{1c}$), and in HOMA-IR (%dHOMA-IR). In women, these relationships were not significant except for the relationship between %dBMI and %dHOMA-IR. In a multivariate linear regression analysis using age, %dBMI, and %dWC as independent variables, %dBMI, but not %dWC, was found to be an independent predictor of %dHOMA-IR in both genders. Furthermore, in men, %dBMI was also an independent factor predicting %dFG and %dHbA$_{1c}$.

***Conclusion***: During the one-year period, a reduction in BMI, and thus weight loss, was found to be associated with the improvement of insulin sensitivity, especially in men. A reduction in WC was also associated with an improvement in insulin sensitivity in men; however, this relationship did not remain significant after controlling for changes in BMI.

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**Key words;** Waist circumference, Body mass index, Glucose metabolism, Insulin resistance, Health screening

## Introduction

Elevated fasting glucose (FG) and hemoglobin $A_{1c}$ (HbA$_{1c}$) concentarions, and enhanced insulin resistance are associated with an increased incidence of cardiovascular diseases[1]. Obesity, which may be reflected as an increase in waist circumference (WC) and in body mass index (BMI), is known to be associated with these glucose metabolism-related parameters[2-6]. In addition, the relative risk of developing type 2 diabetes increases with a gain in weight and BMI[7]. The relationship observed between insulin resistance and obesity may be explained by a disproportionate accumulation of visceral fat, leading to a change in levels of adipocytokines, which may underlie various metabolic disorders[8-10]. On the other hand, it has not been fully established whether changes in BMI or those in WC have the greater impact on glucose metabolism-related data. To this end, here we have analyzed the relationship between changes in obesity parameters and changes in diabetic parameters over a one-year period in Japanese individuals.

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

| variables | %dWC-Q1 (range: −21.3–−3.4) | %dWC-Q2 (range: −3.4–−0.1) | %dWC-Q3 (range: 0.0–3.3) | %dWC-Q4 (range: 3.3–33.4) | *p* value |
|---|---|---|---|---|---|
| Women | | | | | |
| *n* | 348 | 202 | 223 | 426 | |
| Age, years | 53 (52-54) | 53 (51-54) | 51 (50-53) | 51 (50-52) | 0.066 |
| Height, cm | 156 (156-157) | 157 (156-158) | 157 (156-158) | 157 (157-158) | 0.037 |
| Weight, kg | 50 (51-52) | 52 (52-54) | 52 (52-55) | 51 (51-53) | 0.009 |
| WC, cm | 79 (78-80) | 77 (77-80) | 76 (76-78) | 72 (73-74) | <0.001 |
| BMI, kg/m$^2$ | 20.7 (20.7-21.3) | 21.1 (21.2-22.2) | 21.1 (21.2-22.1) | 20.8 (20.8-21.3) | 0.028 |
| Systolic blood pressure, mmHg | 115 (116-119) | 118 (118-123) | 114 (115-120) | 113 (115-118) | 0.129 |
| Diastolic blood pressure, mmHg | 72 (72-75) | 73 (73-76) | 72 (72-75) | 71 (71-74) | 0.198 |
| Pulse rate, bpm | 63 (63-64) | 63 (62-65) | 63 (63-65) | 63 (63-64) | 0.937 |
| LDL-cholesterol, mg/dL | 131 (127-134) | 130 (125-134) | 127 (124-133) | 122 (121-127) | 0.021 |
| HDL-cholesterol, mg/dL | 68 (68-71) | 66 (66-70) | 68 (67-70) | 68 (68-70) | 0.329 |
| Trigryceride, mg/dL | 77 (81-91) | 77 (84-99) | 77 (79-93) | 69 (76-83) | 0.026 |
| Uric acid, mg/dL | 4.5 (4.5-4.7) | 4.5 (4.4-4.7) | 4.6 (4.5-4.7) | 4.4 (4.4-4.5) | 0.076 |
| Fasting glucose, mg/dL | 87 (87-90) | 89 (89-93) | 88 (88-91) | 88 (88-91) | 0.149 |
| Hemoglobin A1c, % | 5.1 (5.1-5.2) | 5.2 (5.1-5.2) | 5.1 (5.1-5.2) | 5.1 (5.1-5.2) | 0.284 |
| Blood urea nitrogen, mg/dL | 13.0 (13.0-13.8) | 13.0 (13.2-14.2) | 13.0 (12.9-13.7) | 13.0 (13.2-13.8) | 0.705 |
| Serum creatinine, mg/dL | 0.60 (0.61-0.70) | 0.60 (0.62-0.65) | 0.60 (0.61-0.63) | 0.60 (0.62-0.64) | 0.408 |
| Anti-dyslipidemic medication, *n* (%) | 13 (3.7) | 11 (5.4) | 6 (2.7) | 16 (3.8) | 0.526 |
| Anti-hypertensive medication, *n* (%) | 27 (7.8) | 18 (8.9) | 9 (4.0) | 17 (4.0) | 0.022 |
| Current smoker, *n* (%) | 36 (10.3) | 15 (7.4) | 12 (5.4) | 44 (10.3) | 0.117 |
| Men | | | | | |
| *n* | 462 | 589 | 600 | 363 | |
| Age, years | 54 (53-55) | 54 (53-54) | 54 (53-54) | 53 (51-53) | 0.040 |
| Height, cm | 169 (169-170) | 170 (169-170) | 169 (169-170) | 169 (169-170) | 0.975 |
| Weight, kg | 68 (68-70) | 68 (68-69) | 67 (68-69) | 67 (67-68) | 0.328 |
| WC, cm | 88 (87-89) | 87 (86-87) | 85 (85-86) | 82 (82-84) | <0.001 |
| BMI, kg/m$^2$ | 23.8 (23.6-24.2) | 23.7 (23.6-24.0) | 23.6 (23.6-24.0) | 23.3 (23.2-23.8) | 0.150 |
| Systolic blood pressure, mmHg | 128 (127-131) | 125 (127-130) | 124 (125-127) | 121 (121-124) | <0.001 |
| Diastolic blood pressure, mmHg | 81 (81-83) | 80 (80-82) | 79 (79-81) | 77 (77-79) | <0.001 |
| Pulse rate, bpm | 62 (62-64) | 62 (62-64) | 62 (62-64) | 61 (61-63) | 0.347 |
| LDL-cholesterol, mg/dL | 132 (129-134) | 130 (128-133) | 129 (127-132) | 125 (124-131) | 0.225 |
| HDL-cholesterol, mg/dL | 54 (55-58) | 54 (54-57) | 53 (54-56) | 55 (55-58) | 0.328 |
| Trigryceride, mg/dL | 111 (122-136) | 111 (123-134) | 111 (126-140) | 100 (115-133) | 0.037 |
| Uric acid, mg/dL | 6.1 (6.0-6.2) | 6.1 (6.1-6.3) | 6.0 (6.0-6.2) | 6.2 (6.0-6.2) | 0.290 |
| Fasting glucose, mg/dL | 95 (97-100) | 95 (97-99) | 94 (95-97) | 93 (94-97) | 0.008 |
| Hemoglobin A1c, % | 5.3 (5.3-5.4) | 5.3 (5.3-5.4) | 5.2 (5.2-5.3) | 5.2 (5.2-5.3) | 0.005 |
| Blood urea nitrogen, mg/dL | 14.0 (14.3-15.0) | 14.0 (14.4-14.9) | 14.0 (14.0-14.6) | 14.0 (14.1-14.7) | 0.405 |
| Serum creatinine, mg/dL | 0.80 (0.83-0.92) | 0.80 (0.85-0.87) | 0.85 (0.85-0.87) | 0.80 (0.84-0.86) | 0.647 |
| Anti-dyslipidemic medication, *n* (%) | 18 (3.9) | 25 (4.2) | 28 (4.7) | 16 (4.4) | 0.942 |
| Anti-hypertensive medication, *n* (%) | 58 (12.6) | 77 (13.1) | 84 (14.0) | 42 (11.6) | 0.736 |
| Current smoker, *n* (%) | 137 (29.7) | 194 (32.9) | 175 (29.2) | 121 (33.3) | 0.352 |

## Methods

### Study Population

The study was approved by The Ethics Committee of Mitsui Memorial Hospital. Between October 2005 and October 2006, 11558 individuals underwent a general health screening at our institute. Of these, 3325 (2113 men, 1212 women) individuals

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

| variables | %dBMI-Q1 (range: −21.8–−1.9) | %dBMI-Q2 (range: −1.9–−0.2) | %dBMI-Q3 (range: −0.2–1.4) | %dBMI-Q4 (range: 1.4–15.7) | *p* value |
|---|---|---|---|---|---|
| Women | | | | | |
| *n* | 284 | 268 | 305 | 342 | |
| Age, years | 53 (52–54) | 54 (52–54) | 52 (51–53) | 49 (49–51) | 0.002 |
| Height, cm | 156 (156–157) | 157 (156–157) | 158 (157–158) | 157 (157–158) | 0.005 |
| Weight, kg | 52 (52–54) | 51 (52–53) | 51 (51–53) | 51 (51–53) | 0.325 |
| WC, cm | 77 (76–78) | 76 (76–78) | 75 (75–77) | 75 (75–77) | 0.115 |
| BMI, kg/m$^2$ | 21.3 (21.3–22.0) | 20.9 (21.1–21.8) | 20.5 (20.6–21.2) | 20.7 (20.7–21.3) | 0.002 |
| Systolic blood pressure, mmHg | 117 (118–123) | 115 (115–119) | 114 (115–119) | 113 (115–118) | 0.060 |
| Diastolic blood pressure, mmHg | 74 (73–76) | 73 (72–75) | 71 (72–74) | 71 (71–74) | 0.057 |
| Pulse rate, bpm | 63 (63–65) | 64 (63–65) | 61 (62–64) | 63 (63–65) | 0.106 |
| LDL-cholesterol, mg/dL | 133 (127–135) | 132 (129–136) | 125 (123–129) | 117 (119–125) | <0.001 |
| HDL-cholesterol, mg/dL | 67 (66–70) | 68 (67–71) | 69 (68–71) | 67 (67–70) | 0.647 |
| Trigryceride, mg/dL | 79 (87–102) | 76 (80–89) | 74 (79–89) | 68 (73–81) | 0.002 |
| Uric acid, mg/dL | 4.5 (4.4–4.7) | 4.4 (4.4–4.6) | 4.6 (4.5–4.7) | 4.4 (4.4–4.6) | 0.408 |
| Fasting glucose, mg/dL | 88 (88–91) | 88 (88–93) | 88 (88–91) | 88 (88–90) | 0.933 |
| Hemoglobin A1c, % | 5.1 (5.1–5.2) | 5.2 (5.1–5.3) | 5.1 (5.1–5.2) | 5.1 (5.0–5.1) | 0.028 |
| Blood urea nitrogen, mg/dL | 13.0 (13.2–14.0) | 13.0 (13.1–13.9) | 13.0 (13.3–14.2) | 13.0 (12.8–13.4) | 0.174 |
| Serum creatinine, mg/dL | 0.60 (0.61–0.63) | 0.60 (0.61–0.63) | 0.60 (0.62–0.73) | 0.60 (0.61–0.63) | 0.002 |
| Anti-dyslipidemic medication, *n* (%) | 12 (4.2) | 10 (3.7) | 12 (3.9) | 12 (3.5) | 0.972 |
| Anti-hypertensive medication, *n* (%) | 23 (8.1) | 15 (5.6) | 16 (5.2) | 17 (5.0) | 0.352 |
| Current smoker, *n* (%) | 21 (7.4) | 22 (8.2) | 23 (7.5) | 41 (12.0) | 0.130 |
| Men | | | | | |
| *n* | 504 | 531 | 495 | 484 | |
| Age, years | 54 (53–55) | 55 (54–55) | 54 (53–54) | 51 (51–52) | <0.001 |
| Height, cm | 169 (169–170) | 169 (168–169) | 170 (169–170) | 170 (169–171) | 0.012 |
| Weight, kg | 69 (68–70) | 67 (67–68) | 68 (68–69) | 68 (67–69) | 0.097 |
| WC, cm | 87 (86–87) | 85 (85–86) | 86 (85–87) | 85 (85–86) | 0.011 |
| BMI, kg/m$^2$ | 24.0 (23.8–24.3) | 23.4 (23.4–23.9) | 23.7 (23.6–24.1) | 23.5 (23.3–23.8) | 0.012 |
| Systolic blood pressure, mmHg | 126 (127–130) | 124 (125–128) | 126 (125–129) | 123 (123–126) | 0.011 |
| Diastolic blood pressure, mmHg | 81 (81–83) | 79 (79–81) | 80 (80–82) | 78 (78–80) | 0.019 |
| Pulse rate, bpm | 62 (62–64) | 62 (62–63) | 62 (63–64) | 62 (61–63) | 0.106 |
| LDL-cholesterol, mg/dL | 133 (130–135) | 129 (128–133) | 130 (126–132) | 125 (125–130) | 0.014 |
| HDL-cholesterol, mg/dL | 54 (54–56) | 54 (55–57) | 54 (55–58) | 54 (54–57) | 0.437 |
| Trigryceride, mg/dL | 111 (126–141) | 108 (123–136) | 111 (120–135) | 107 (118–132) | 0.285 |
| Uric acid, mg/dL | 6.1 (6.1–6.3) | 6.1 (6.0–6.2) | 6.0 (6.0–6.2) | 6.1 (6.0–6.3) | 0.344 |
| Fasting glucose, mg/dL | 95 (97–100) | 95 (97–100) | 95 (95–97) | 93 (94–96) | 0.002 |
| Hemoglobin A1c, % | 5.3 (5.3–5.5) | 5.3 (5.3–5.4) | 5.2 (5.2–5.3) | 5.2 (5.2–5.3) | <0.001 |
| Blood urea nitrogen, mg/dL | 14.0 (14.3–15.0) | 14.0 (14.3–14.8) | 14.0 (13.9–14.4) | 14.0 (14.3–15.0) | 0.130 |
| Serum creatinine, mg/dL | 0.80 (0.84–0.92) | 0.80 (0.85–0.87) | 0.80 (0.83–0.86) | 0.90 (0.85–0.87) | 0.303 |
| Anti-dyslipidemic medication, *n* (%) | 20 (4.0) | 18 (3.4) | 28 (5.7) | 21 (4.3) | 0.334 |
| Anti-hypertensive medication, *n* (%) | 72 (14.3) | 81 (15.3) | 47 (9.5) | 61 (12.6) | 0.035 |
| Current smoker, *n* (%) | 155 (30.8) | 167 (31.5) | 148 (29.9) | 157 (32.4) | 0.851 |

underwent a general health screening during this period (first visit) and again the following year (second visit). Among these 3325 individuals, 3213 (2014 men, 1199 women) who reported not taking antidiabetic drugs at either visit were enrolled in the current study. The mean ± standard deviation (SD) of the interval between the two visits of the individuals enrolled was 356 ± 51 days. The percent difference in

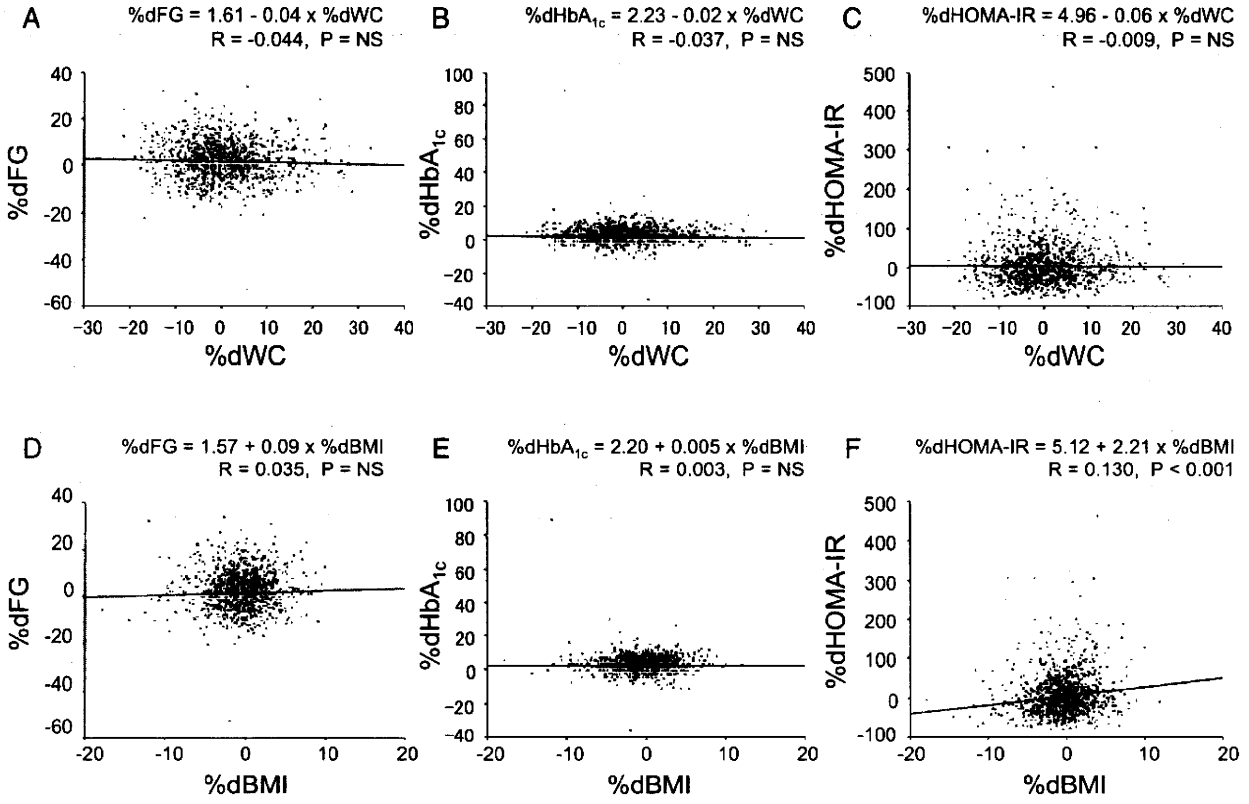


**Fig. 1.** Scatter plot and linear regression between %dWC and %dFG (A), %dHbA1c (B), and %dHOMA-IR (C) and between %dBMI and %dFG (D), %dHbA1c (E), and %dHOMA-IR (F) in women.

the value of WC, BMI, serum levels of fasting glucose (FG), HbA1c, and HOMA-IR between the first and second visits was designated %dWC, %dBMI, %dFG, %dHbA1c, and %dHOMA-IR, respectively. Blood samples were taken from all subjects after an overnight fast. BMI was expressed as weight (in kilograms) divided by the square of height (in meters). WC was measured at the umbilical level to the nearest 1 cm by trained physicians and technicians[11].

**Laboratory Analysis**

Serum levels of TC, HDL-C, and TG were determined enzymatically. Serum uric acid was measured by the uricase-peroxidase method; hemoglobin A1c was determined by a latex agglutination immunoassay. Creatinine was measured by TBA-200FR (Toshiba Medical Systems, Tochigi, Japan) using a commercial kit. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by the equation: HOMA-IR = (immunoreactive insulin (IRI)) × FBS/405. Blood pressure was measured after about 10 min of rest by an automated sphygmomanometer.

**Statistical Analysis**

Data are expressed as the median (95% confidence interval (95%CI)) unless stated otherwise. The Kruskal-Wallis test, $\chi^2$ test, logistic regression analysis, and multivariate linear regression analysis were applied as appropriate to assess the statistical significance of differences between groups using computer software, Dr. SPSS II (SPSS Inc., Chicago, IL). A value of $p < 0.05$ was taken to be statistically significant.

## Results

**Baseline Characteristics**

We enrolled 1199 women and 2014 men in this study. The mean age of the individuals enrolled was 51.9 years in women and 53.4 years in men at the first visit. The sex-nonspecific range of the first to fourth %dWC quartiles was −21.3/−3.4, −3.4/−0.1, 0.0/3.3, and 3.3/33.4, respectively, and that of the first to fourth %dBMI quartiles was −21.8/−1.9, −1.9/−0.2, −0.2/1.4, and 1.4/15.7, respectively. Subject characteristics at the first visit are shown according to the

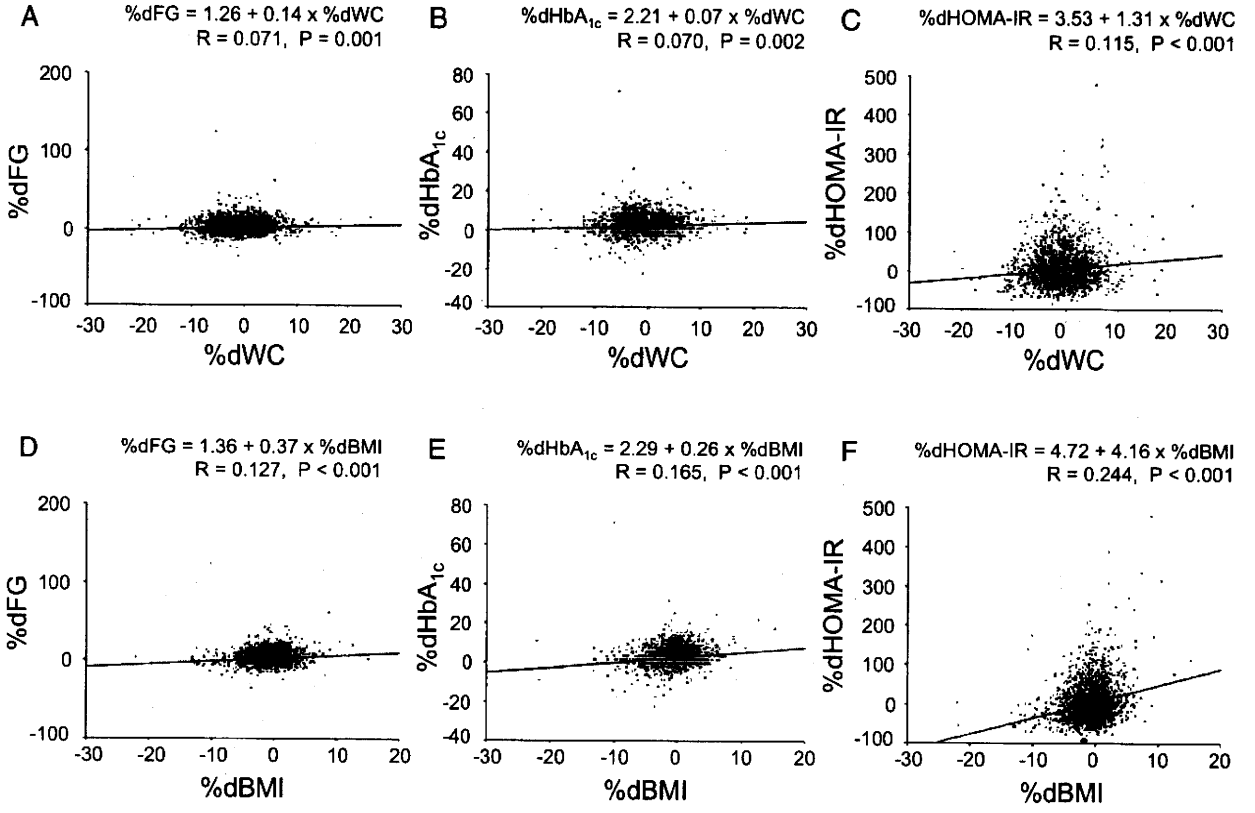


**Fig. 2.** Scatter plot and linear regression between %dWC and %dFG (A), %dHbA1c (B), and %dHOMA-IR (C) and between %dBMI and %dFG (D), %dHbA1c (E), and %dHOMA-IR (F) in men.

%dWC and %dBMI quartiles in **Table 1**. No statistically significant trends in the rate of anti-dyslipidemic medication or of current smoking were found across the four %dWC or %dBMI quartiles in either gender. The correlation coefficient between %dWC and %dBMI was 0.24 in women and 0.46 in men.

### Association between Percent Changes in Obesity Parameters and Percent Changes in Diabetic Parameters

Scatter plots of %dWC and %dBMI versus %dFG, %dHbA1c and %dHOMA-IR, coupled with results of linear regression analyses, are shown in **Fig. 1** and **2**. In women, only the relationship between %dBMI and %dHOMA-IR was significant. In men, by contrast, the relationship was significant between both %dWC and %dBMI and the percent change in each of the diabetic parameters.

**Fig. 3** and **4** show the percent changes in diabetic parameters according to the %dWC and %dBMI quartiles. In women, %dHOMA-IR increased with increasing %dBMI. In men, not only %dHOMA-IR but also %dFG and %dHbA1c increased with increasing %dWC and %dBMI.

### Logistic Regression Analysis

A multivariate logistic regression analysis, adjusted for age at the first visit, of the second, third, and fourth %dBMI quartiles, showed that the first, second, third, and fourth %dBMI quartiles in men were associated with the highest %dHOMA-IR quartile (%dHOMA-IR >24.3%) with an odds ratio of 1.00 (reference), 1.47 (95%CI 1.08-2.01), 1.51 (95%CI 1.11-2.07), and 2.87 (95%CI 2.13-3.87), respectively. In women, on the other hand, the first, second, third, and fourth %dBMI quartiles were not significantly related to the highest %dHOMA-IR quartile (%dHOMA-IR >24.3%) with an odds ratio of 1.00 (reference), 1.23 (95%CI 0.82-1.85), 1.45 (95%CI 0.98-2.14), and 1.89 (95%CI 1.30-2.74), respectively.

### Multivariate Linear Regression Analysis

In a multivariate linear regression analysis with age at the first visit and %dWC as independent vari-

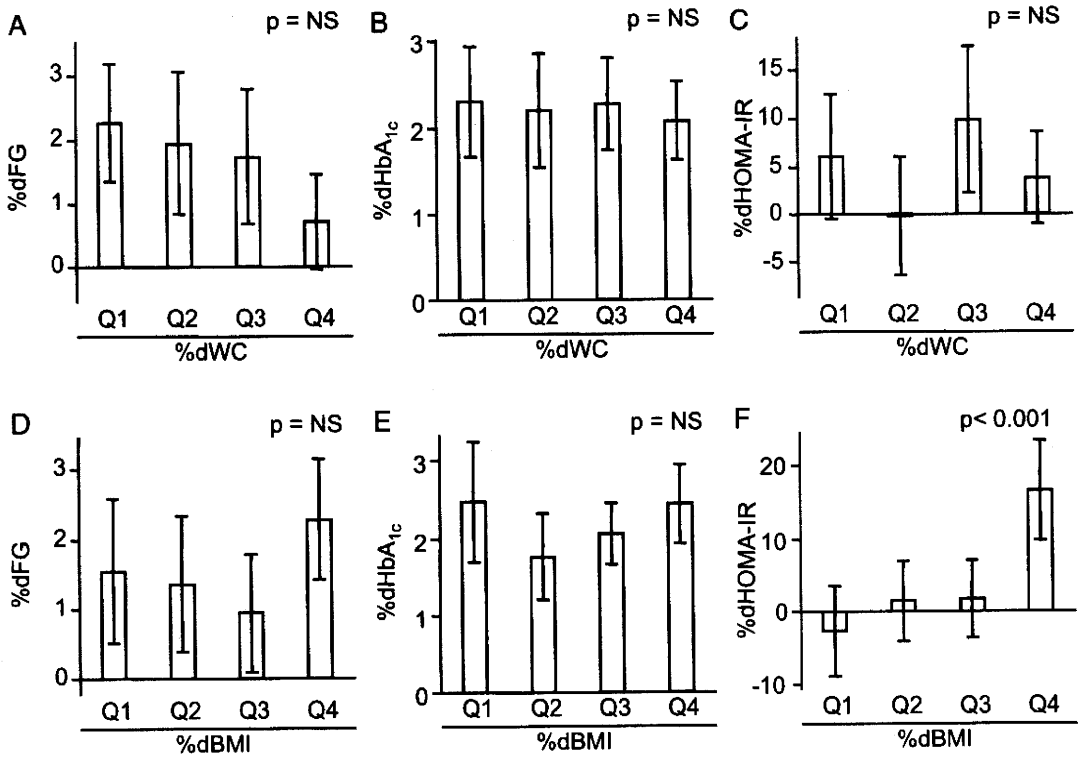


**Fig. 3.** %dFG (A), %dHbA$_{1c}$ (B), and %dHOMA-IR (C) according to %dWC quartiles, and %dFG (D), %dHbA$_{1c}$ (E), and %dHOMA-IR (F) according to %dBMI quartiles in women. The mean ± 95% confidence interval is shown in each group.

ables (**Table 2**, model 1), %dWC was an independent predictor for %dHOMA-IR in men, but not in women. However, when %dBMI was used as an additional covariate in the statistical model, %dWC did not remain significant (**Table 2**, model 2). In model 2, %dBMI was found to be an independent predictor for %dHOMA-IR, %dFG and %dHbA$_{1c}$ in men, but for only %dHOMA-IR in women.

## Discussion

In the current study, we demonstrated that percent changes in obesity parameters (%dWC, %dBMI) were positively correlated with percent changes in glucose metabolism-related parameters (%dFG, %dHbA$_{1c}$, %dHOMA-IR) in men. In women, by contrast, there was no significant relationship between %dWC and percent changes in diabetic parameters, and %dBMI was not significantly associated with %dFG or %dHbA$_{1c}$. In the multivariate linear regression analysis, %dWC was a predictor for %dHOMA-IR in men, although it did not remain significant when %dBMI was used as an additional covariate in the statistical model, suggesting that changes in WC are not a predictor for changes in glucose-metabolism-related parameters independent of changes in BMI.

Obesity is associated with a cluster of specific metabolic abnormalities that may be related to cardiovascular risk factors[8, 12]. Wahrenberg *et al.* have reported that WC, which was found to be the strongest regressor among WC, BMI, log-plasma triglycerides, systolic blood pressure, and high-density lipoprotein cholesterol, is a risk factor for insulin resistance[13]. On the other hand, Onat *et al.* prospectively analyzed 1638 men and found that the age-adjusted waist-to-hip ratio (WHR) was significant in predicting diabetes mellitus[14]. Furthermore, Colditz *et al.* analyzed data from 114281 women who did not have diagnosis of diabetes mellitus, coronary heart disease, stroke, or cancer, and showed that BMI was the dominant predictor of risk for diabetes mellitus, although weight gain was also a risk factor for diabetes[15]. It has been shown that even small gains in weight during adulthood lead to a significantly increased risk of many chronic diseases[16]. Several studies showed that weight loss reduced regional depots of adipose tissue and

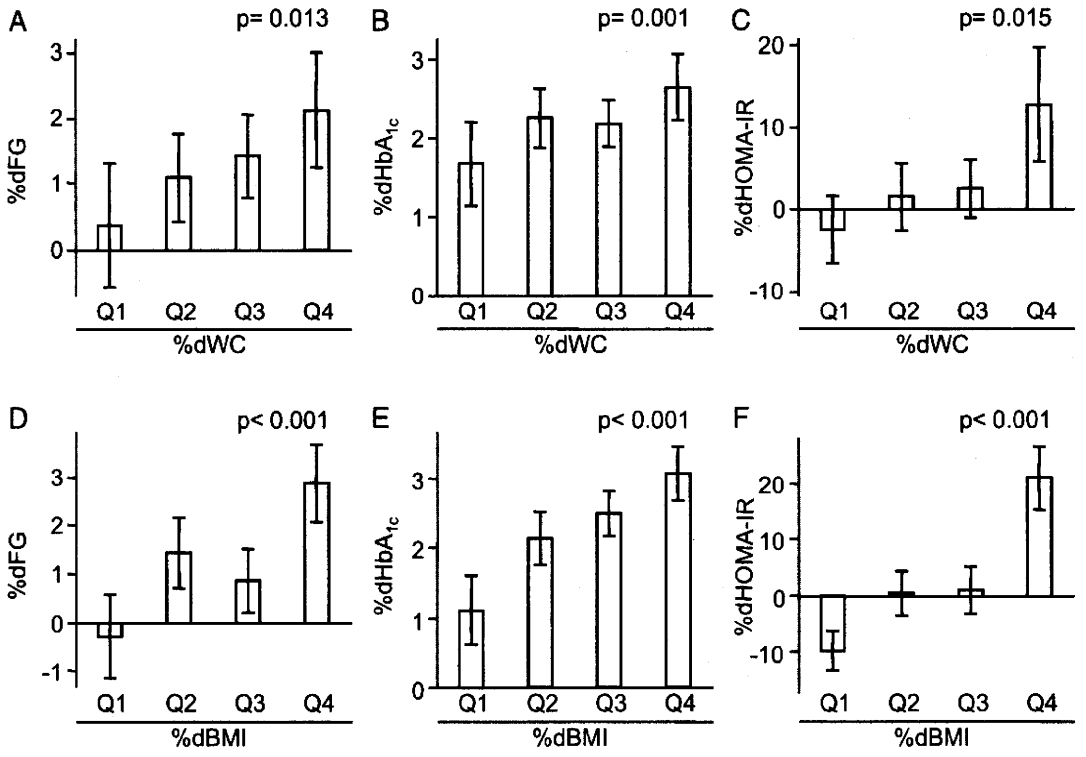


**Fig. 4.** %dFG (A), %dHbA1c (B), and %dHOMA-IR (C) according to %dWC quartiles, and %dFG (D), %dHbA1c (E), and %dHOMA-IR (F) according to %dBMI quartiles in men. The mean ± 95% confidence interval is shown in each group.

improved insulin sensitivity and cardiovascular risk factors[17, 18]. Pascale *et al.* analyzed 60 women and 33 men participating in a year-long weight loss program and concluded that improvements in FG, fasting insulin, and HbA1c were significantly related to weight loss[19].

Besides body weight, visceral fat has also been reported to be associated with β-cell function in individuals with impaired fasting glycemia and impaired glucose tolerance[9]. In general, BMI is strongly associated with subcutaneous fat area. As parameters of obesity, BMI and WC may have different meanings but similar associations. BMI may have a weaker association with visceral fat; by contrast, WC has a stronger correlation with visceral fat area in both genders[10]. It has been suggested that WC better reflects the accumulation of visceral fat than WHR[20, 21]. Therefore, it is possible that changes in WC have a stronger impact on changes in glucose metabolism as compared with changes in BMI.

In the current study, however, %dBMI was an independent factor predicting %dFG, %dHbA1c, and %dHOMA-IR in men, and %dHOMA-IR in women. %dWC was an independent factor predicting %dHOMA-IR in men, only without adjustment for %dBMI. Why %dBMI had a stronger association with %dFG, %dHbA1c and %dHOMA-IR is not clear.

Because Asian women are relatively lean, subcutaneous fat may have a relatively greater influence on WC[22]. For example, Sakurai *et al.* analyzed 2935 men and 1622 women between 35 and 59 years of age: in a multiple logistic regression analysis, WC was associated with FG in both genders. However, the risk ratio of having two or more metabolic disorders was higher for BMI than for WC in women, suggesting WC to be a relatively poor discriminator of visceral fat, and BMI to be a more appropriate index of total and abdominal fat, especially in women[22, 23].

It has recently been demonstrated that the association between WC and cardiovascular risk markers, such as insulin resistance, weakens with age[24]. Janssen *et al.* reported that, although individuals with a moderate and high WC were likely to have elevated cardiometabolic risk markers irrespective of age, there seemed to be a significant correlation between age and WC, indicating that the relation between WC and insulin

**Table 2.** Multivariate linear regression analysis between percent changes in diabetic parameters and age, %dWC, and %dBMI

| | | $\beta$ | 95% CI | | Standardized $\beta$ | $p$ value |
|---|---|---|---|---|---|---|
| Women | Model 1 | | | | | |
| | Dependent variable, %dFG | | | | | |
| | age | −0.02 | −0.06 | 0.03 | −0.02 | 0.494 |
| | %dWC | −0.05 | −0.10 | 0.01 | −0.05 | 0.118 |
| | Dependent variable, %dHbA$_{1c}$ | | | | | |
| | age | −0.01 | −0.04 | 0.01 | −0.03 | 0.353 |
| | %dWC | −0.02 | −0.06 | 0.01 | −0.04 | 0.181 |
| | Dependent variable, %dHOMA-IR | | | | | |
| | age | 0.00 | −0.30 | 0.31 | 0.00 | 0.993 |
| | %dWC | −0.06 | −0.44 | 0.32 | −0.01 | 0.753 |
| | Model 2 | | | | | |
| | Dependent variable, %dFG | | | | | |
| | age | −0.01 | −0.06 | 0.03 | −0.02 | 0.605 |
| | %dWC | −0.06 | −0.12 | 0.00 | −0.06 | 0.059 |
| | %dBMI | 0.12 | −0.03 | 0.27 | 0.05 | 0.119 |
| | Dependent variable, %dHbA$_{1c}$ | | | | | |
| | age | −0.01 | −0.04 | 0.02 | −0.03 | 0.374 |
| | %dWC | −0.03 | −0.06 | 0.01 | −0.04 | 0.168 |
| | %dBMI | 0.02 | −0.08 | 0.11 | 0.01 | 0.741 |
| | Dependent variable, %dHOMA-IR | | | | | |
| | age | 0.08 | −0.22 | 0.38 | 0.01 | 0.610 |
| | %dWC | −0.28 | −0.67 | 0.10 | −0.04 | 0.152 |
| | %dBMI | 2.41 | 1.42 | 3.40 | 0.14 | <0.001 |
| Men | Model 1 | | | | | |
| | Dependent variable, %dFG | | | | | |
| | age | −0.02 | −0.06 | 0.01 | −0.03 | 0.223 |
| | %dWC | 0.14 | 0.05 | 0.22 | 0.07 | 0.002 |
| | Dependent variable, %dHbA$_{1c}$ | | | | | |
| | age | −0.01 | −0.03 | 0.01 | −0.03 | 0.250 |
| | %dWC | 0.07 | 0.03 | 0.12 | 0.07 | 0.002 |
| | Dependent variable, %dHOMA-IR | | | | | |
| | age | −0.08 | −0.29 | 0.14 | −0.02 | 0.479 |
| | %dWC | 1.30 | 0.80 | 1.80 | 0.11 | <0.001 |
| | Model 2 | | | | | |
| | Dependent variable, %dFG | | | | | |
| | age | −0.01 | −0.05 | 0.02 | −0.02 | 0.434 |
| | %dWC | 0.03 | −0.07 | 0.13 | 0.02 | 0.544 |
| | %dBMI | 0.35 | 0.20 | 0.49 | 0.12 | <0.001 |
| | Dependent variable, %dHbA$_{1c}$ | | | | | |
| | age | −0.01 | −0.03 | 0.01 | −0.01 | 0.592 |
| | %dWC | −0.01 | −0.06 | 0.04 | −0.01 | 0.740 |
| | %dBMI | 0.26 | 0.18 | 0.34 | 0.17 | <0.001 |
| | Dependent variable, %dHOMA-IR | | | | | |
| | age | 0.02 | −0.19 | 0.23 | 0.00 | 0.840 |
| | %dWC | 0.02 | −0.52 | 0.57 | 0.00 | 0.932 |
| | %dBMI | 4.15 | 3.33 | 4.97 | 0.24 | <0.001 |

For model 1, independent variables include age at the first visit and %dWC. For model 2, independent variables include age at the first visit, %dWC, and %dBMI.

resistance was attenuated in the elderly[24]. With regard to our study, the mean age of the individuals enrolled was 51.9 years in women and 53.4 years in men at the first visit. We may have to analyze the relationship between %dWC or %dBMI and changes in glucose metabolism in a younger population in future studies. In addition, WC measurements may be less reliable or reproducible than weight and height measurements, which might relate to the finding that although %dWC is a predictor for the change in diabetic parameters, the correlation between %dWC and %dBMI was weaker in women, the latter of which is a predictor for the changes in diabetic parameters also in women.

In the current study, interestingly, there was a gender difference in the relationship between %dWC and changes in diabetic parameters. Wing *et al.* reported that the relationship between changes in WHR and changes in lipid parameters differed between women and men: they showed that changes in WHR were associated with changes in total cholesterol and triglycerides levels in men, but not in women[18].

Although we did not look into the mechanisms that may explain the differences in the association of changes in obesity indexes and those in glucose metabolism-related markers between men and women, several explanations may exist. Adipose tissue has been recognized as a significant endocrine organ that releases biologically important cytokines, such as adiponectin, leptin, and vaspin[25, 26]. In several clinical studies, certain gender differences have existed in the serum levels of such adipokines (adiponectin[27, 28], leptin[29], and vaspin[30]), which may account, in part, for the difference in the association between changes in obesity indexes and those in glucose metabolism-related parameters in the current study. Such sexual dimorphism in adipocytokines may be related to the difference in the levels of sex hormones, such as dehydro-epiandrosterone-sulphate (DHEAS), oestradiol, and testosterone[27, 31, 32].

We previously analyzed the relationship between percent changes in obesity parameters and percent changes in serum lipid parameters, uric acid, and systolic blood pressure[33-35]. We found that, as in the current study, the impact of %dBMI was greater than that of %dWC from the viewpoint of changes in serum uric acid and blood pressure.

Our study has several potential limitations. First, we enrolled only individuals who underwent a general health screening at our institute for 2 consecutive years. Second, we analyzed data from participants without considering alcohol consumption or the number of cigarettes smoked. Third, we excluded individuals who were taking antidiabetic drugs at either visit. It has been suggested that these individuals are generally more motivated to improve their own health than those who are not taking such drugs. In addition, a longer follow-up would be required to draw more convincing conclusions in future studies.

In summary, over a one-year period, %dBMI was found to be an independent predictor for %dHOMA-IR in both genders and for %dFG and %dHbA$_{1c}$ only in men. Although %dWC was also associated with percent changes in these diabetic parameters, this relationship did not remain significant after controlling for %dBMI. Conversely, the relationship between %dBMI and percent changes in glucose-related metabolism parameters, especially in men, was independent of %dWC. These findings collectively suggest that controlling body weight, rather than WC, may be the primary target for improving glucose metabolism at least over a one-year period.

## Acknowledgements

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Original Article

# Association between Gamma-Glutamyltransferase Levels and Insulin Resistance According to Alcohol Consumption and Number of Cigarettes Smoked

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***Aim*:** Alcohol intake may increase serum gamma-glutamyltransferase (GGT) but reduce insulin resistance. We analyzed the association between GGT and a marker of insulin resistance, homeostasis model assessment for insulin resistance (HOMA-IR), according to the drinking and smoking status.
***Methods*:** After excluding former smokers and/or former drinkers, the data of 10,482 men who underwent general health screening were analyzed.
***Results*:** Alcohol consumption showed a graded association with GGT. In men with current alcohol consumption of ≥40 g per day, ≥20 cigarettes per day further increased GGT levels. Alcohol consumption showed a U-shaped association with HOMA-IR. In contrast, smoking 20–39 and ≥40 cigarettes per day increased HOMA-IR as compared with never smokers. An interaction between alcohol consumption and smoking was present for GGT ($p<0.001$) and HOMA-IR ($p=0.059$). GGT was not a significant negative predictive value for HOMA-IR regardless of the drinking or smoking status.
***Conclusions*:** Although alcohol intake showed a graded association with GGT and a U-shaped association with HOMA-IR, serum GGT can be utilized as a predictor of insulin resistance in current drinkers.

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**Key words;** Drinking, Cigarette smoking, Epidemiology, Insulin resistance, Liver function

## Introduction

Recent epidemiological studies have shown that, besides being a biomarker of alcohol intake[1-4], elevated gamma-glutamyltransferase (GGT) may be a predictor of cardiovascular events[5], stroke[6], liver cancer[7], metabolic syndrome and type 2 diabetes[8], associations that may also be present in nondrinkers[9]. Several factors other than alcohol are known to affect serum GGT levels, including coffee consumption[10, 11] and obesity[12]. In addition, a recent study has demonstrated that cigarette smoking may also increase serum GGT levels, especially in men with moderate to heavy alcohol consumption[13]. Furthermore, alcohol consumption may improve insulin sensitivity and lower the incidence of metabolic syndrome[14-19]; therefore, drinking may increase GGT and decrease insulin resistance. On the other hand, it has been reported that serum GGT has a positive association with insulin resistance[20, 21]. To this end, we investigated the effect of drinking and smoking on GGT and HOMA-IR values, and whether the mode of association between GGT and insulin resistance was affected by drinking and smoking in Japanese men who underwent general health screening.

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## Methods

### Study Population

The study was approved by the Ethics Commit-