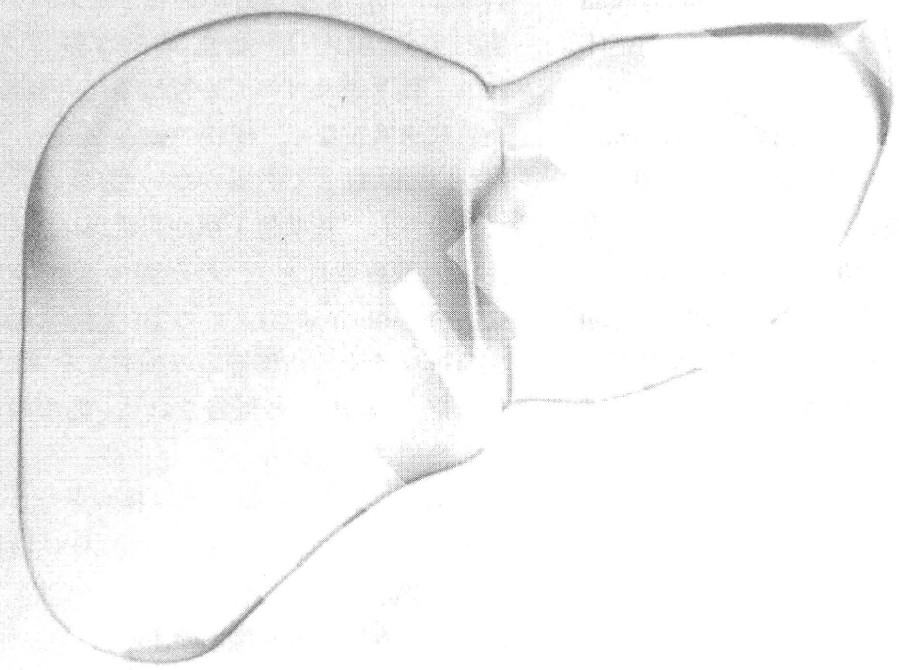
NASH/NAFLDの診断・治療

Diagnosis and Treatment



Diagnosis and Treatment

診断法：血液・生化学的検査

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KEY WORD
血清トランスアミナーゼ，HOMA-IR，
血清フェリチン，非侵襲的肝線維化評価指数

1980 年に Ludwig らが NASH（nonalcoholic steatohepatitis）という疾患概念を提唱し，1986 年に Schaffer らが非飲酒者で単純性脂肪肝，NASH を含むアルコール性肝障害類似の肝病変を呈するものを総称して NAFLD（nonalcoholic fatty liver disease）とした．今のところ NASH/NAFLD 診断のための高感度で特異的なマーカーはなく，確定診断，ステージ診断のためには疾患定義からわかるように病理組織診断が必須である．しかし，肝生検の侵襲性とコストの問題，患者数の多さからすべての症例に対し病理診断を確認することは不可能である．腹部超音波検査は肝組織に中性脂肪が過剰に蓄積した脂肪性肝疾患を高感度に検出するよい代替検査であるが，炎症の活動性，肝線維化ステージの診断に対しては有用とはいえない．最近，肝線維化ステージ評価検査として Fibroscan® などの elastography が実用化されはじめているが，広く普及するに至っていない．現在はこれらをカバーするために血液・生化学検査を適切に評価することが必要である．

拾い上げ検査

2006 年人間ドック全国集計では肝機能障害は 26.3%で，現在も増加傾向にある．このなかにはウイルス性肝炎，アルコール性肝障害も多数含まれるが，NASH/NAFLD の頻度が少なくはない．NASH/NAFLD 疑い例を拾い上げるため，健診，人間ドックでどのような検査項目に注意すべきであろうか．

●血清トランスアミナーゼ（AST：aspartate aminotransferase，ALT：alanine aminotransferase）

まず最初に，血清 ALT の基準値を考慮する必要がある．血清 ALT 基準値に関しては初回献血者 9,221 人による検討がある．従来の ALT 基準値，男性 40 IU/*l*，女性 30 IU/*l* 以下で，HBV，HCV，HIV 感染すべてが除外され，服薬歴，糖・脂質代謝異常なく，Body mass index（BMI）が 24.9 kg/m^2 以下で肥満のない 3,925 人を対象として検討され，基準値上限が男性 30 IU/*l*，女性 19 IU/*l* と報告された[1]．わが国では PNALT（persistently normal ALT）の HCV 持続感染者に対する抗ウイルス治療適応の検討から ALT の基準値上限が 30 IU/*l* と報告され[2]，他の慢性肝疾患でも使用されている．

血清 ALT による拾い上げ検査を行ったときの一般人口における NASH/NAFLD の頻度は，米国が 7.3%，中国が 10.1%，日本が 9.3%[3]であり，超音波検査などの画像診断よりも拾い上げの率が低い（米国 33%，中国 15%，日本 14%）．よって，NASH/NAFLD のなかで血清 AST/ALT 値がわずかでも上昇していれば，活動性が低いとはいえない可能性がある．

●γ-GTP（gamma-glutamyltranspeptidase）

γ-GTP は胆汁うっ滞，飲酒のマーカーであるだけでなく，酸化ストレスまたはメタボリック

ファクターを反映するマーカーでもある．飲酒歴がないにもかかわらず，他の胆道系酵素に比べγ-GTPが高い症例では心血管系疾患，メタボリック症候群，糖尿病の合併頻度が高い[4]．このようにγ-GTPは肥満，インスリン抵抗性との関連が強いため，NASH/NAFLD診断において有用な検査である．一般的に基準値上限が男性50 IU/*l*，女性30 IU/*l*である．

●末梢血検査

NASH/NAFLD疑い例において喫煙などの要素がないにもかかわらず多血症の場合には，睡眠時無呼吸症候群の合併がないか病歴を聴取する．また，血小板数はC型慢性肝炎ほどではないが，血小板数が肝線維化進展と相関すると考えられる．C型慢性肝炎で血小板数15万/mm^{3}は線維化ステージF2の目安であるが，NASH/NAFLDにおいては血小板15万/mm^{3}はさらに進行している可能背が高い．

●脂質代謝異常

LDL-コレステロール140 mg/d*l*以上，HDL-コレステロール40 mg/d*l*未満，トリグリセライド150 mg/d*l*以上の基準のいずれかがあると脂質代謝異常である．NASH/NAFLDではインスリン抵抗性を背景に食事性の脂質吸収の亢進，脂肪細胞からの遊離脂肪酸分泌亢進，肝細胞への取り込み亢進，肝細胞での脂肪酸の合成亢進となり，肝細胞脂肪沈着とともに高頻度に高トリグリセライド血症となっている．肝機能障害に脂質代謝異常が合併している場合は，強くNASH/NAFLDを疑う．

診断のための検査

病歴聴取で飲酒量がエタノール換算で1日20 g（日本酒1合相当）以下であれば非飲酒者であり，非アルコール性と診断される．また，HBV，HCV肝炎ウイスルマーカー陰性をもって非ウイルス性と診断する．自己免疫性の鑑別は抗核抗体が160倍以上の場合は自己免疫性の可能性のほうが高いといえる．しかし，HBVキャリア，抗核抗体陽性例であってもHBV-DNA値が5 Log IU/m*l*未満の場合，抗核抗体が80倍以下の場合で，腹部超音波検査上脂肪肝の所見があり，肥満，脂質代謝異常などを合併している場合はウイルス性，自己免疫の要素が強いか，代謝異常の要素が強いか判断がむずかしい．最終的には肝生検による確認を含めた総合的判断が必要である．

●高インスリン血症

NASH/NAFLDの基本病態であるインスリン抵抗性を確認することはNASH/NAFLDの診断のうえで必須といえる．空腹時の血中インスリン値（IRI：immune reactive insulin）やC-ペプチド，またはHOMA-IR（Homeostasis model assessment-insulin resistance）＝｛（空腹時血糖×空腹時IRI）÷405｝はインスリン抵抗性のよいマーカーである．HOMA-IRが2以上でインスリン抵抗性があり，5以上で高度インスリン抵抗性である．そして，HOMA-IRが高いほど肝線維化が進展するという報告もある[5]．

血液生化学検査で，単純性脂肪肝かNASHかの鑑別はある程度可能である．NASHの多くは線維化をともない，炎症や肝細胞変性・壊死も存在するので，単純性脂肪肝に比べ，炎症を反映する血清トランスアミナーゼ（ALT値）がより高値で，線維増生のために血小板低下や線維化マーカー（ヒアルロン酸やⅣ型コラーゲン）高値例が多く，鉄蓄積の指標である血清フェリチン高値例が多くみられる．

ステージ診断・フォローアップのための検査

NASH/NAFLDと診断した場合，すべて一律のフォローアップでよいだろうか．どういった症例に対して肝生検を考慮し，フォローアップを強化し，治療介入が必要か重要である．肝線維化進展例はもちろんであるが，将来，線維化が進展し発がんリスク群となる可能性の高い症例を予測できないだろうか．

●鉄関連マーカー

NASH/NAFLDの病態に肝組織の酸化ストレスが増強が指摘されているが，本疾患ではしばしば軽度から中等度の肝内鉄過剰蓄積が認められ，酸化ストレスを増強する因子と考えられている．また，健診，人間ドック，一般内科で経験される高フェリチン血症例のほとんどが，体重オーバーの中年男性であり，BMI高値，拡張期血圧上昇，空腹時C-ペプチド高値などのメタボリック因子を合併していることが多い．肝生検を行うと65%以上で脂肪肝，核糖原などのNAFLDに矛盾しない所見が認められ，これらの症例では高フェリチン血症とインスリン抵抗性の関連が示唆された[6]．

最近では，高フェリチン血症と複数の代謝異常の合併がNASH/NAFLD診断の重要な因子といわれており，Yonedaらの報告ではNASHでは単純性脂肪肝に比べ有意に血清フェリチンが高値であり，わが国の単純性脂肪肝とNASHの鑑別診断に有用であることが示されている[7]．

●血清フェリチン

鉄過剰状態でフェリチンは増加し，フェリチン鉄が凝集して不溶性のヘモジデリンを形成する．フェリチンは細胞内に発現する鉄貯蔵蛋白で，3価の鉄を内包し，鉄の貯蔵および血清鉄濃度の維持を行う．フェリチンはさまざまな細胞に発現しているが，主に肝，脾，骨髄に発現している．正常成人の肝臓における鉄貯蔵量はおおよそ1,000 mgである．血清フェリチンの正常値は男性で40～128 ng/ml，女性で12～53 ng/mlとなっている．その値は鉄貯蔵状態を反映し，古くから慢性肝疾患において血清フェリチン値は血清トランスアミナーゼ値レベルおよび肝内鉄濃度によく相関し，診断的有用性が報告されていた．

●鉄過剰と耐糖能異常

NASH/NAFLDの鉄過剰症のメカニズムは明らかではない．炎症が強い場合は炎症サイトカインによって肝細胞，kupffer細胞におけるフェリチン産生の増加が考えられるが，炎症のさほど強くないNAFLDにおいても血清フェリチンが高い場合もある．NASH/NAFLDの患者において，高フェリチン血症とインスリン抵抗性，または高血糖とが相関することが報告されている．肝内鉄沈着とインスリン抵抗性との関連に関しては不明な点が多いが，鉄過剰が肝内酸化ストレスを増強し，インスリンシグナルに影響し，肝臓におけるインスリン抵抗性をもたらすと考えられている．

NAFLDの病態に関連して，Iwasakiらは日本人において血清フェリチンとさまざまな脂肪分布つまり内臓脂肪（VFA），皮下脂肪（SFA），インスリン抵抗性そして肝脂肪化と関連することを報告している[8]．さらに，Yonedaらは正常肝，単純性脂肪肝，NASHの比較検討で，血清フェリチンがNASH診断に有用であることを報告している．そして，血清フェリチンとインスリン抵抗性の関連性を示している[7]．NAFLDにおいてもC型慢性肝炎のように血清フェリチンが上昇している症例では，瀉血療法が肝機能およびインスリン抵抗性を改善すると報告されている[9]．このことから肝内の鉄過剰蓄積とインスリン抵抗性との関連と両者の肝細胞障害への関与が示唆されている．

NASH/NAFLDの病態における重要性が認知されているが，実地臨床で測定できる酸化ストレスマーカーはない．鉄過剰は肝内酸化ストレスに関与することから，貯蔵鉄マーカーである血清フェリチンを測定することによって，間接的に肝内酸化ストレスを推定することは可能である．実際に血清フェリチンの上昇にともない酸化ストレスマーカーである血清チオレドキシンの上昇，肝組織のHNE，8OHdGの発現上昇が認められる[5]，肝内の鉄の過剰蓄積によってROS産生が増加し，肝細胞障害の増強，肝線維化の亢進の重要な因子の1つと考えられている．

●線維化マーカー

Ⅲ型プロコラーゲンN末端ペプチド（PⅢNP），4型コラーゲン7S，ヒアルロン酸はウイル

表　一般血液・生化学検査項目を用いた非侵襲的肝線維化評価指数

肝線維化評価指数	評価項目と計算式またはスコア	文献
AAR	AST/ALT	11
Forns Index	7.811−3.131・ln(血小板)+0.781・ln(γ-GTP)+3.467・ln(年齢)−0.014・(総コレステロール)	12
APRI	(AST/基準値上限/血小板[$10^3/\mu l$])×100	11
FPI	FPI = e/(1+e) e =−10.929+(1.827×Ln・AST)+(0.081×年齢)+(0.768×飲酒グレード)+(0.385×HOMA-IR)+(0.447 総コレステロール)	13
CDS	各3スコアの合計 ① 血小板($10^3/\mu l$)スコア：≥340=0；280−339=1；220−279=2；160−219=3；100−159=4；40−99=5；<40=6 ② AARスコア：>1.7 = 0；1.2−1.7 = 1；0.6−1.19 = 2；<0.6 = 3 ③ INRスコア：<1.1 = 0；1.1−1.4 = 1；>1.4 = 2	11
HALT-C Index	HALT-C Index=exp(log odds)/(1+exp(log odds)) log odds=−5.56−0.0089×血小板($10^3/\mu l$)+1.26×AST/ALT+5.27×INR	11
FIB-4	(年齢)×(AST)/(血小板[$10^3/\mu l$]×(ALT)$^{1/2}$	14
FibroIndex	1.738−0.064(血小板[$10^4/\mu l$])+0.005(AST)+0.463(γ-グロブリン[g/dl])	15

ス性慢性肝炎，肝硬変の肝線維化の評価だけでなく，NASH/NAFLDの線維化の評価にも有用である[10]．

●非侵襲的肝線維化評価指数

AAR(AST/ALT ratio)，Forns Index，APRI (AST-to-platelet ratio index)，FPI (Fibrosis predict index)，CDS (Cirrhosis discriminant score)，HALT-C (Hepatitis C antiviral long-term treatment against cirrhosis) Index，FIB-4，FibroIndex[11~15]などの非侵襲的肝線維化評価指数は，もともとC型慢性肝炎の線維化ステージ予測のために考案されたものがほとんどであるが，侵襲的な肝生検を施行することなく，また，特殊検査である線維化マーカーを測定することなく，通常診療で行われる血液・生化学検査からステージが予測できることから，その有用性が報告されている．Fujiiらはこれらの指数でとくにCDSとHALT-C IndexがNASH/NAFLDに対しても有用であることを報告している[11]（**表**）．今後さらに検討されることが期待される．

●高感度CRP

高感度CRPは心血管系イベントのリスク因子，メタボリック症候群との関連性からNASH/NAFLDとの関連も指摘されている．さらに高感度CRPはNASH/NAFLDの線維化進展度と相関すると報告されている[16]．

●アディポサイトカイン

脂肪細胞が産生するサイトカインであるアディポサイトカインとNASH/NAFLDの病態との関連は強い．アディポサイトカインの分泌異常が病態に関与している．アディポネクチンはインスリン抵抗性を改善させる．NASH/NAFLDではアディポネクチンの血中濃度は低下しており，肝の脂肪沈着を増悪させ，線維化の進展させる[17]．TNF-α (tumor necrosis factor alpha) も脂肪細胞から分泌され，インスリン抵抗性を悪化させる．肥満にともなって脂肪細胞でのTNF-α発現量が増し，血中TNF-α濃度が上昇する．レプチンも脂肪細胞で産生され，食欲抑制作用をもつほかにインスリン効果を増強する．NASH/NAFLDの患者では血中レプチン値が上昇しているにもかかわらず，食欲抑制がなく，インスリン

抵抗性とともにレプチン抵抗性にもなっている.

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トピックス

IV. 最近の話題
2. 鉄と発癌

大竹　孝明　　生田　克哉　　高後　　裕

要　旨

鉄は生体反応に必須の金属元素であるが，過剰状態では自由鉄分画が増加し活性酸素種産生を介して細胞毒性，DNA損傷ひいては発癌を誘導する．鉄は遺伝性ヘモクロマトーシスだけでなく，C型慢性肝炎の肝癌発生機序にも関与している．これに対し瀉血療法が発癌抑制効果をあげている．さらに鉄はアスベストによる胸膜中皮腫，子宮内膜症による卵巣癌の発症にも関与していることが示唆されてきている．

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Key words：酸化ストレス，活性酸素種（reactive oxygen species：ROS），Fenton反応，8-hydroxydeoxyguanosine（8-OHdG）

はじめに

生物は進化の過程で生体内での酸素運搬の担い手として環境に溢れて存在する鉄を選択した．しかし，鉄はしばしば諸刃の剣として働くことが解ってきた．炎症，放射線，紫外線などと同様に遷移金属である鉄の過剰状態は活性酸素種（reactive oxygen species：ROS）産生を介して発癌のリスク因子として働く．これはDNA（deoxyribonucleic acid）損傷，細胞内シグナル伝達系および遺伝子発現異常，細胞増殖およびアポトーシスなど多くのステップで関与している．このことからC型慢性肝炎では除鉄療法を行うことによって鉄過剰状態の細胞内酸化ストレスを軽減し，発癌抑制を目指した治療が行われている．

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1. 生体内の鉄

鉄は生体にとって必須金属のひとつで，最も多く存在する金属元素でもある．赤血球ヘモグロビン，筋細胞ミオグロビン，細胞内の多数の酵素においてヘム鉄は補因子として広く使用されている．循環血液中ではほとんどの鉄がトランスフェリン（Tf）に結合したトランスフェリン結合鉄の状態で存在するが，鉄過剰となり血清Tfが60％以上になり飽和してくるとアルブミン，クエン酸等とゆるく結合した非トランスフェリン結合鉄（non-transferrin bound iron，NTBI）が出現する．この一部分が不安定血清鉄（labile plasma iron，LPI）として細胞毒性が強い[1]．LPIは主に心筋障害の原因と言われている．同様に，細胞内では非ヘム鉄は通常フェリチンやヘモジデリンによって隔離貯蔵されているが，細胞内鉄過剰になってくると不安定鉄プール（labile iron

pool，LIP）という易利用性の自由鉄分画が増加してくる[2]．LIPの増加によって鉄毒性が増し，実質細胞が傷害され，主に肝障害，糖尿病，内分泌腺障害が起き，DNA損傷を介した発癌に関与してくる．

2．生体内鉄代謝

健常状態の鉄代謝において腸管粘膜や皮膚上皮細胞の脱落によってわずかに喪失するだけで，能動的な体外への排泄機構は存在しない．鉄の供給源のほとんどは網内皮系細胞が老廃赤血球を貪食し，ヘモグロビン鉄を再利用することによって得られている．わずか1～2 mgの鉄が上部小腸から吸収され，鉄の出納のバランスがとれている．吸収された食餌鉄は主にトランスフェリン結合鉄の形で血中を輸送された後，主に骨髄での赤血球造血で利用されるとともに，残りは肝臓や網内皮系細胞に蓄積される．中でも鉄の貯蔵臓器として重要な役割をしているのが肝臓である．貯蔵鉄は肝実質細胞内ではフェリチンにKupffer細胞内ではヘモジデリンに隔離貯蔵されており，必要に応じて血清中の再利用プールに汲み出される．このように生体の鉄代謝は半閉鎖系システムであり，正常状態では鉄の過剰や欠乏が起きないように厳密に調節されている．逆に鉄の排泄機構がないことから鉄過剰症という病態がいろんな原因で発生してくる．

3．鉄過剰と酸化ストレス

鉄は生体内に最も多く存在する金属元素である．鉄は細胞内ではフェリチン，ヘモジデリンなどの多くのキレート蛋白により隔離されている．このことは鉄がフリーラジカルを産生することを回避するために重要である．しかし，細胞内で鉄が過剰になってくると不安定鉄プール（LIP）が増加してくる．LIPの主体はクエン酸等と結合している遊離の3価鉄であるが，還移元

$$H_2O_2 + Fe^{2+} \rightarrow OH^- + \underline{OH^{\cdot}} + Fe^{3+}\ (\text{Fenton反応})$$

$$O_2^{\cdot -} + Fe^{3+} \rightarrow Fe^{2+} + O_2$$

$$H_2O_2 + O_2^{\cdot -} \rightarrow OH^- + \underline{OH^{\cdot}} + O_2\ (\text{Harber-Weiss反応})$$

図1．鉄を触媒としたラジカル産生

素である鉄イオンは一部2価鉄となり，酸素の存在下でFenton反応等によって容易に強力なフリーラジカルであるヒドロキシラジカルを産生し（図1），蛋白質，脂質，DNAと反応し，細胞障害をもたらし，肝線維化，発癌に関与する．例えば肝臓は主要な鉄の貯蔵庫でもあるが，もともと生体の代謝の中心臓器で様々な代謝活動が多数の酵素によって盛んに行われている．ミトコンドリアやマイクロゾームの電子伝達系では多量のROSが産生される．また，肝炎がある場合，浸潤炎症細胞内にも多量の活性酸素が産生されており，このような環境下において鉄過剰状態になるとフリーラジカル産生が促進され，肝炎がさらに悪化するものと考えられる．このような酸化ストレス状態がC型慢性肝炎，アルコール性肝障害，非アルコール性脂肪性肝炎の病態では起きている．

4．鉄過剰による発癌

疫学的検討では貯蔵鉄が多いほど発癌リスクが増大することが報告されている．特に有名であるのは遺伝性ヘモクロマトーシスにおける肝発癌のリスクが健常人の200倍になることである．また，本邦に多い疾患であるC型慢性肝炎の肝組織中にも鉄の過剰蓄積があり，フリーラジカル産生を介して，肝細胞障害や肝発癌に関与している[3]．さらに，この鉄による酸化ストレス状態はアルコール性肝障害[4]や非アルコール性脂肪性肝炎[5]でも起きている．Kato等はインターフェロン治療不適応例または無効例において瀉血療法と鉄制限食による厳密な除鉄治療によってコ

ントロール群に比べ有意に肝発癌を抑制することを報告している[6]．また，アスベスト暴露による胸膜中皮腫[7]や子宮内膜症による卵巣癌[8]の発癌リスクにおいても局所の鉄過剰が関与していることが指摘されている．アスベストでは特に鉄含量の多いcrocidoliteとamositeの線維成分に発癌性が高いことが分かってきた．また，子宮内膜症における高度の溶血がフリーのヘムおよび鉄のレベルを増加させ，これらの酸化ストレスによって細胞の脂質，蛋白質を変性し，DNA損傷，線維化に関与することが報告されている．また，欧米の報告では乳癌患者においてもヘモクロマトーシス遺伝子HFEのC282Yアレルの頻度が健常者や他の癌腫に比べて高いことから鉄過剰の関与が示唆されている[9]．さらに，鉄と前立腺癌のリスクも示唆されている[10]．

5. 除鉄治療による肝発癌抑制効果

瀉血は最も簡便に体内鉄を除去できる古典的手法である．生体には通常4～6 gの鉄が存在し，その65% が赤血球内ヘモグロビン鉄である．血液1 mlあたり平均1 mgの鉄が含まれ，一回200～400 mlの瀉血で0.2～0.4 gの鉄を除去できる．瀉血療法では人工的に一時的な貧血状態が起こり，これに対する反応として赤血球造血が亢進し，ヘモグロビン産生のために肝臓にある貯蔵鉄を骨髄へ動員，結果的に肝内鉄量が減少し，肝細胞内での鉄によるラジカル産生が低下し，肝細胞障害が改善すると考えられる．

実際に瀉血療法を行い血清ALT（alanine aminotransferase）値が改善した症例の治療前後での肝生検組織を用い，肝内鉄蓄積の評価としてPrussian blue鉄染色，フリーラジカル産物でありDNA障害の指標である8-hydroxydeoxyguanosine（8-OHdG）の免疫組織染色を行うと瀉血前に肝細胞に認められていたヘモジデリン鉄は瀉血後に消失し，強く発現していた8-OHdGも発現は低下または消失している（図2）．このことから瀉血療法によって過剰蓄積していた鉄が汲み出され，細胞内酸化ストレスが軽減したことがわかる．

Kato等は長期間除鉄治療を維持できたC型慢性肝炎症例では，有意に肝発癌率が低下したことを報告している[6]（図3）．これは，瀉血療法はフリーラジカル産生源である自由鉄を減少させることによって血清ALT値の改善効果だけでなく，酸化DNA損傷を軽減し，肝癌発生を予防する効果を持つことを示している．

6. 鉄誘導発癌モデル動物

過剰の鉄イオンが発癌に関与することは動物モデルを用いた基礎実験でも実証されている．肺癌，胸膜・腹膜中皮腫など多くのモデルが報告されているが[11]，本邦では初めにOkada等がラットに鉄ニトリロ三酢酸を腹腔内投与することによって腎癌を発症することを示した[12]．また，Wilson病はATP7B遺伝子変異が原因の銅排泄障害によって肝組織に銅が蓄積する病態であるが，しばしば溶血発作等によって鉄の過剰蓄積も認められる．我々はWilson病のモデルで肝炎肝癌自然発症モデルであるLECラットにおいて，鉄制限により肝癌の発生が有意に抑制されることを報告した[13]．これはWilson病においても鉄の過剰蓄積がフリーラジカルの産生を介して肝細胞障害と肝発癌に関与し，鉄制限食投与による鉄の過剰蓄積を抑制することによって酸化ストレスを軽減させうることを証明したものである．

7. 鉄酸化ストレスとDNA損傷

はじめに遺伝性ヘモクロマトーシスでは酸化ストレスによるDNA損傷の初期段階としてDNAにおけるetheno adductsが増加していることが報告され[14]，本病態において非癌部のp53遺伝子変異アレルの出現頻度が酸化ストレスからの発癌リスクのマーカーになることが報告された[15]．当

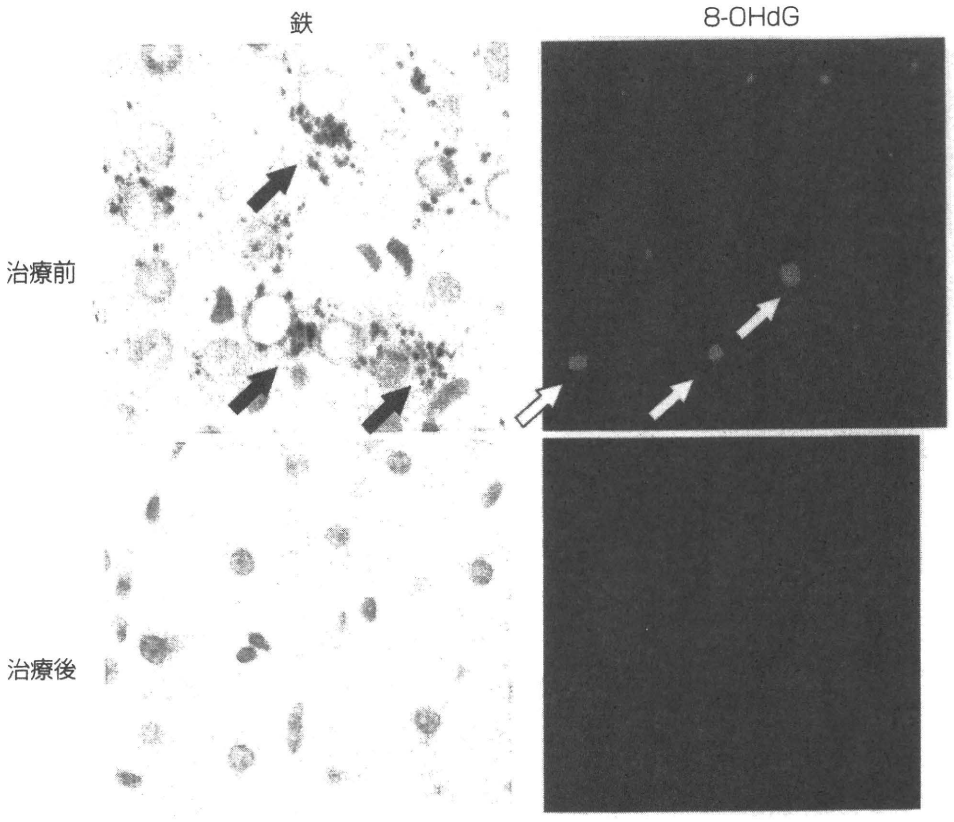

図 2. 瀉血療法前後における肝内鉄蓄積と肝細胞内 8-OHdG の発現の変化
瀉血前に肝細胞に認められていた過剰鉄は瀉血後に消失しており，強く発現していた 8-OHdG も発現低下，消失している．

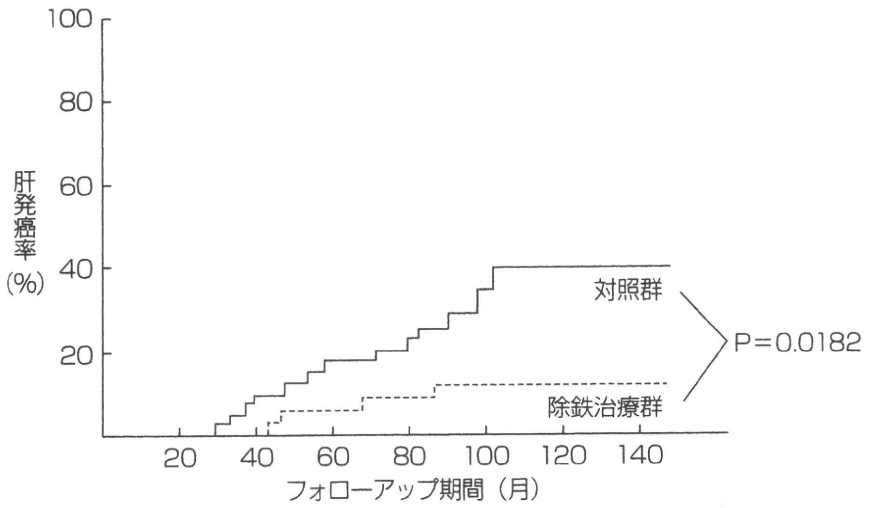

図 3. 除鉄治療の肝発癌抑制効果
除鉄治療は対照群に比べて肝発癌率が有意に抑制されている．
（文献 6 より引用）

初，これらの鉄誘導性発癌の酸化DNA損傷は細胞内でランダムに起きていると考えられていたが，最近の*in vivo*における知見では選択性がある可能性が示唆されている．Toyokuni等は鉄負荷のラット腎癌モデルにおいて酸化ストレスの主な標的遺伝子が癌抑制遺伝子のcyclin依存性キナーゼ抑制因子であるp16（INK4A）と報告している．p16遺伝子のアレル欠損は発癌の初期段階で起き，しかも他の癌抑制遺伝子に比べ特異的に起きている[16]．これはラジカルによる酸化DNA損傷の受けやすい部分が存在する可能性を示しており，鉄誘発性の発癌メカニズムの解明のため，今後さらなる検討が期待される．

まとめ

鉄負荷は酸化ストレスによる組織障害に引き続き，発癌を誘導する．特に遺伝性ヘモクロマトーシスの研究を通して，鉄代謝，鉄酸化ストレスのメカニズムが解明されてきている．さらに，鉄誘発性の発癌メカニズムはC型慢性肝炎における肝癌，アスベスト暴露による胸膜中皮腫，子宮内膜症による卵巣癌など他の癌腫発生にも関与しており，今後の発癌研究において重要なテーマと考えられる．

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Relationship between Alcohol Consumption and Serum Adiponectin Levels: The Takahata Study—A Cross-Sectional Study of a Healthy Japanese Population

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Context: The relationship between alcohol consumption and serum adiponectin levels has not been fully explored in an Asian population.

Objective: Our goal was to determine whether alcohol consumption is associated with a change in adiponectin levels in a healthy Japanese population.

Design: This was a cross-sectional study.

Setting: Subjects were recruited from participants in a health check-up program.

Participants: This study included 2932 subjects (1306 men and 1626 women).

Main Outcome Measures: The effects of total weekly or daily volume of ethanol intake on serum adiponectin levels were evaluated. In addition, the correlation of clinical traits with serum adiponectin levels was examined. A multivariate regression model was used to control for possible confounding factors.

Results: Alcohol consumption was weakly correlated with decreased serum adiponectin levels in men [Spearman's ordered correlation coefficient (r_s) = −0.141; $P < 0.001$]; an even weaker correlation was seen in women (r_s = −0.055; P = 0.025). Multivariate analysis demonstrated that alcohol consumption was independently associated with hypoadiponectinemia.

Conclusion: In contrast to reports from the United States and Europe among White and Black subjects, our study demonstrated an inverse association between alcohol intake and serum adiponectin levels in Asian subjects, suggesting ethnic differences in the effects of alcohol consumption on serum adiponectin levels. (***J Clin Endocrinol Metab* 95: 3828–3835, 2010**)

Adiponectin, predominantly synthesized in adipose tissue, is a major modulator of insulin action and resistance (1). It is also related to lipid metabolism, particularly higher levels of high-density lipoprotein cholesterol (HDL-C) and lower levels of triglycerides (2). Higher adiponectin levels are associated with a lower risk of coronary heart disease (3, 4) and type 2 diabetes (5).

Light to moderate alcohol intake is associated with lower risk for coronary heart disease, potentially by increasing HDL-C levels (6) or enhancing fibrinolysis (7).

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Abbreviations: ADH, Alcohol dehydrogenase; ALDH2, acetaldehyde dehydrogenase type 2; ALT, alanine aminotransferase; BMI, body mass index; FBG, fasting blood glucose; γ-GTP, γ-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HMW, high molecular weight; LDL-C, low-density lipoprotein cholesterol; r_s, Spearman's ordered correlation coefficient.

Several previous studies performed in White and Black populations investigated the association between adiponectin concentrations and the risk of developing cardiovascular disease or type 2 diabetes and showed that alcohol intake was associated with elevated serum adiponectin levels (3). In contrast, recent studies in mice and rats have demonstrated that chronic ethanol feeding decreases circulating adiponectin concentrations (8, 9).

As previously described, there are ethnic differences both in serum adiponectin levels (10) and in the risk of type 2 diabetes and cardiovascular disease between Asian and White individuals that are not explained by conventional risk factors (11). In light of these findings, we hypothesized that alcohol consumption may have a different effect on modulation of adiponectin levels in individuals of Asian descent. This relationship has not been fully elucidated on a large scale because of the limited number of subjects. Given the sample size available to us, we chose to evaluate the relationship between alcohol consumption and serum adiponectin levels among a Japanese general population while adjusting for potential confounding factors.

Subjects and Methods

Study population

This study is a part of the Japanese prospective, population-based study held in an agricultural area located about 350 km north of Tokyo. The design and methods of these studies have been reported elsewhere (12–14). Briefly, the study was designed to evaluate the role of lifestyle, diet, and genetic factors in the subsequent development of many common diseases. The study cohort consists of subjects recruited from participants in the regular health check-up program for residents. Since 2004, the baseline survey and subsequent follow-up surveys have been conducted annually. The survey collects information on lifestyle and anthropometric measurements and collects blood and urine specimens from participants on the morning of the survey. The study protocols were approved by the ethics committee at Yamagata University.

Of 3826 participants in the health check-up program from June 1, 2004, through November 30, 2005, the present study population started with 3166 subjects aged 40 yr or older who agreed to participate (83%). Written informed consent was obtained from all subjects. For this analysis, we restricted subjects to those with available information on drinking status and adiponectin levels (n = 3130). We also excluded those who ate breakfast before blood was drawn or those with missing information regarding biomedical variables, anthropometrical variables, or blood pressure. Thus, data from 2932 subjects (1306 men and 1626 women) who met all eligibility criteria were analyzed.

Data collection and measurements

Height, weight, and blood pressure were measured with the subject in light clothes and without shoes, and the body mass index (BMI) (kilograms per square meter) was calculated. After blood samples were drawn, they were frozen in aliquots at −70 C within 4 h and stored frozen until measurements. Biochemical variables evaluated in this study included levels of total adiponectin, total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C, triglycerides, fasting blood glucose (FBG), fasting serum insulin, alanine aminotransferase (ALT), and γ-glutamyltransferase (γ-GTP). Plasma glucose, serum lipids, and liver enzymes were assayed by routine automated laboratory methods in a single laboratory (BML Inc., Tokyo, Japan). Serum insulin concentrations were measured using a chemiluminescent immunoassay kit (Kyowa Medics, Tokyo, Japan), with intra- and interassay coefficients of variation of 2.0–3.0 and 0.9–4.7%, respectively. Plasma total adiponectin levels were determined by a human adiponectin ELISA (Otsuka Pharmaceutical Co., Tokyo, Japan). Intra- and inter-assay coefficients of variation were 3.3–3.6 and 3.2–7.3%, respectively. All biochemical measurements were performed using plasma samples collected after an overnight fast. The estimate of insulin resistance was done using the homeostasis model assessment of insulin resistance (HOMA-IR), which was calculated from FBG and fasting insulin levels using the following formula: FBG (milligrams per deciliter) × fasting plasma insulin (microunits per milliliter)/405.

Assessment of alcohol consumption and smoking history

Information on alcohol consumption and smoking habits of each individual was obtained in face-to-face interviews. Alcohol consumption was calculated on the basis of ethanol volume, and each drinker's status was defined according to the total weekly volume of ethanol intake. The amounts of alcoholic beverages, including beer, wine, and whisky, were converted to an equivalent amount of sake (rice wine). One hundred eighty milliliters of sake contains 20 g ethanol; 180 ml sake equals 500 ml beer, 180 ml wine, or 60 ml whisky in alcohol content. Information on smoking habits was categorized as current use, past use, or never. To assess the reliability of the amount of alcohol consumption, we compared the volume of ethanol intake in the present study with the information on similar items in the survey conducted using a self-administered questionnaire during May 16 through May 29, 2005. Among 1457 subjects who completed the lifestyle questionnaire, Spearman's ordered correlation coefficient (r_s) between the two variables was 0.71.

Statistical analysis

Because alcohol habits are gender related (15), the analysis was conducted according to gender. Variables are given as means ± SD for variables with a normal distribution, median (25th–75th percentile) for skewed variables or n (percent) for numerical or categorized variables. The skewed variables (adiponectin, glucose, insulin, and triglyceride levels) were log transformed before statistical analysis.

Alcohol consumption was treated both as a continuous variable and as a categorical variable: abstainer, less than 120 g/wk, 120–239 g/wk, and 240 g/wk or more. BMI (<22.0, 22.0–24.9, and ≥25.0) and HOMA-IR (<2.0, 2.0–3.9, and ≥4.0) were categorized before statistical analysis. One-way ANOVA was used for testing between multiple groups, and Dunnett's test was used for subsequent comparison of abstainers with other groups. An unpaired t test was used to compare continuous data, and the χ^2 test was used for the analysis of proportions between groups. Pearson's correlation coefficient or r_s was calculated to evaluate

TABLE 1. Characteristics of study participants

	Men (n = 1306)	Women (n = 1626)	*P* value[a]
Age (yr)			
40–49	142 (10.9)	188 (11.6)	0.351
50–59	312 (23.9)	426 (26.2)	
60–69	447 (34.2)	546 (33.6)	
≥70	405 (31.0)	466 (28.7)	
Adiponectin (μg/ml)	7.0 (5.1–9.9)	10.4 (7.4–14.9)	<0.001
BMI (kg/m^2)			
<22.0	424 (32.5)	550 (33.8)	0.731
22.0–24.9	485 (37.1)	588 (36.2)	
≥25.0	397 (30.4)	488 (30.0)	
Blood pressure (mm Hg)			
Systolic	136.1 ± 15.7	133.1 ± 16.1	<0.001
Diastolic	81.9 ± 9.9	77.5 ± 9.8	<0.001
Serum lipids (mg/dl)			
Total cholesterol	193.4 ± 31.0	207.3 ± 0.9	<0.001
HDL-C	56.3 ± 14.4	61.6 ± 14.2	<0.001
LDL-C	119.1 ± 28.9	128.9 ± 29.6	<0.001
Triglycerides	95 (69–136)	88 (65–118)	<0.001
Glucose tolerance			
Glucose (mg/dl)	96.9 ± 19.5	92.3 ± 13.3	<0.001
Insulin (μU/ml)	4.2 (3.0–7.0)	5.0 (3.9–8.0)	<0.001
HOMA-IR			
<2.0	1084 (83.0)	1292 (79.5)	0.001
2.0–3.9	184 (14.1)	303 (18.6)	
≥4.0	38 (2.9)	31 (1.9)	
Liver enzymes			
ALT (IU)	21 (17–29)	18 (15–24)	<0.001
γ-GTP (IU)	32 (21–52)	19 (14–26)	<0.001
Alcohol consumption (g/wk)			
None	351 (26.9)	1384 (85.1)	<0.001
<120	366 (28.0)	207 (12.7)	
120–239	285 (21.8)	28 (1.7)	
≥240	304 (23.3)	7 (0.4)	
Smoking habit			
Never	506 (38.7)	1495 (91.9)	<0.001
Current	445 (34.1)	88 (5.4)	
Former	355 (27.2)	43 (2.6)	

χ^2 test, unpaired *t* test, or Mann-Whitney *U* test was used for analyses. Data are n (%) unless otherwise indicated: mean ± SD for blood pressure, total cholesterol, HDL-C, LDL-C, and glucose; median (25th–75th percentile) for adiponectin, triglycerides, insulin, ALT, and γ-GTP.

[a] Men *vs.* women.

the relationship between two continuous or ordered variables. Multiple regression analysis was used with covariance analyses, and log-transformed adiponectin was used as the independent variable. In multivariable analyses, the impact of the effect of 10 g/d alcohol consumption was assessed. The SPSS 15.0 program for Windows (SPSS Inc., Chicago, IL) was used for the statistical analyses. $P < 0.05$ (two sided) was considered statistically significant.

Results

Characteristics of the 2136 subjects are shown in Table 1. There were significant differences in adiponectin levels, lipid levels, glucose, insulin, HOMA-IR, and both systolic and diastolic blood pressure between men and women. Levels of all these variables, except for HDL-C and triglycerides, were significantly higher in women than in men. Only 15% of female subjects were drinkers compared with 73% of men ($P < 0.001$).

The relationship between adiponectin concentrations and potentially confounding factors and alcohol intake are shown in Table 2. Using correlation analysis, we found a small and significant negative correlation for adiponectin concentrations and alcohol consumption in men (r_s) = −0.141; $P < 0.001$) and a weaker negative correlation in women ($r_s = -0.055$; $P = 0.025$). Significant negative correlations with adiponectin concentrations were observed in total cholesterol, LDL-C, triglyceride, BMI, blood glucose, insulin, HOMA-IR, ALT, γ-GTP, systolic and diastolic blood pressure, and smoking habits in both in men and women. A positive correlation was observed in HDL-C levels in both genders.

In the next analysis, we used categorized data on alcohol consumption to investigate the relationship between alcohol intake and serum adiponectin levels. As shown in Fig. 1, adiponectin levels significantly decreased in a dose-

TABLE 2. Relationship between serum adiponectin concentrations and other factors studied

	Men (n = 1306)		Women (n = 1626)	
	Adiponectin levels or correlation coefficient[a]	*P* value	Adiponectin levels or correlation coefficient[a]	*P* value
BMI (kg/m^2)				
<22.0	8.4 (6.2–12.1)	<0.001	12.9 (9.2–17.6)	<0.001
22.0–24.9	6.9 (5.1–9.4)		10.0 (7.3–14.4)	
≥25.0	6.0 (4.4–8.1)		9.0 (6.4–12.7)	
Blood pressure (mm Hg)				
Systolic	−0.009	0.749	−0.029	0.242
Diastolic	−0.100	<0.001	−0.027	0.275
Serum lipids (mg/dl)				
Total cholesterol	−0.113	<0.001	−0.029	0.245
HDL-C	0.329	<0.001	0.355	<0.001
LDL-C	−0.103	<0.001	−0.097	<0.001
Triglyceride	−0.390	<0.001	−0.307	<0.001
Glucose tolerance				
Glucose (mg/dl)	−0.091	0.001	−0.183	<0.001
Insulin (μU/ml)	−0.341	<0.001	−0.441	<0.001
HOMA-IR				
<2.0	7.6 (5.4–10.3)	<0.001	11.4 (8.3–15.9)	<0.001
2.0–3.9	5.3 (3.8–6.7)		7.5 (5.7–10.7)	
≥4.0	4.9 (3.4–7.0)		5.6 (4.3–7.7)	
Liver enzymes				
ALT (IU)	−0.264	<0.001	−0.185	<0.001
γ–GTP (IU)	−0.300	<0.001	−0.223	<0.001
Alcohol consumption (g/wk)	−0.141	<0.001	−0.055	0.025
Smoking habit				
Never	7.5 (5.4–10.4)	<0.001	10.5 (7.5–15.0)	0.002
Current	6.7 (4.7–9.3)		9.1 (5.9–13.9)	
Former	7.2 (5.0–10.0)		9.8 (6.6–14.7)	

ANOVA, Pearson's correlation coefficient, or Spearman's correlation coefficient was used for analyses.

[a] Data are median (25th–75th percentile) of serum adiponectin levels, Pearson's correlation coefficient, or Spearman's correlation coefficient.

dependent manner in men ($P < 0.001$). A similar trend was noted in women ($P = 0.029$), although the relationship was not as clear as that seen in men. In women, a borderline significant decrease of serum adiponectin levels was observed among drinkers who consumed less than 120 g/wk of ethanol compared with abstainers ($P = 0.053$). A decrease in serum adiponectin levels was not noted in those who consumed 120 g/wk or more of ethanol compared with abstainers.

We also examined the established relationship between alcohol consumption and HDL-C levels. Significant positive correlations were demonstrated ($r_s = 0.165$, $P < 0.001$ for men; and $r_s = 0.118$, $P < 0.001$ for women), indicating that these relationships were consistent with previous studies.

Subsequently, we conducted a multiple regression analysis to assess the effect of 10 g/d alcohol intake on adiponectin concentrations, controlling for potential confounding factors. We included age, sex, BMI, systolic blood pressure, LDL-C, HDL-C, triglycerides, glucose, HOMA-IR, ALT, and smoking habits as covariates. Alcohol consumption was independently associated with hypoadiponectinemia: 10 g/d ethanol intake was associated with a 0.028 (95% confidence interval = −0.040 to −0.016; $P < 0.001$) μg/ml decrease of log-transformed adiponectin concentrations (Table 3).

Discussion

In this population-based cross-sectional study, we found that alcohol intake and serum adiponectin levels were significantly inversely associated in men. A suggested inverse association was demonstrated in women who consumed less than 120 g/wk alcohol. The weak inverse association between alcohol consumption and serum adiponectin concentrations was found even after adjustment for possible confounding factors. These are contradictory observations when compared with several previous epidemiological and experimental reports performed in White and Black populations (4, 16), but they are consistent with experimental studies in animal models (8, 9). Recently, Kawamoto *et al.* (17) reported an inverse relationship between high molecular weight (HMW) adiponectin and alcohol consumption among healthy Japanese men in a cross-sectional study. HMW complex is the most active

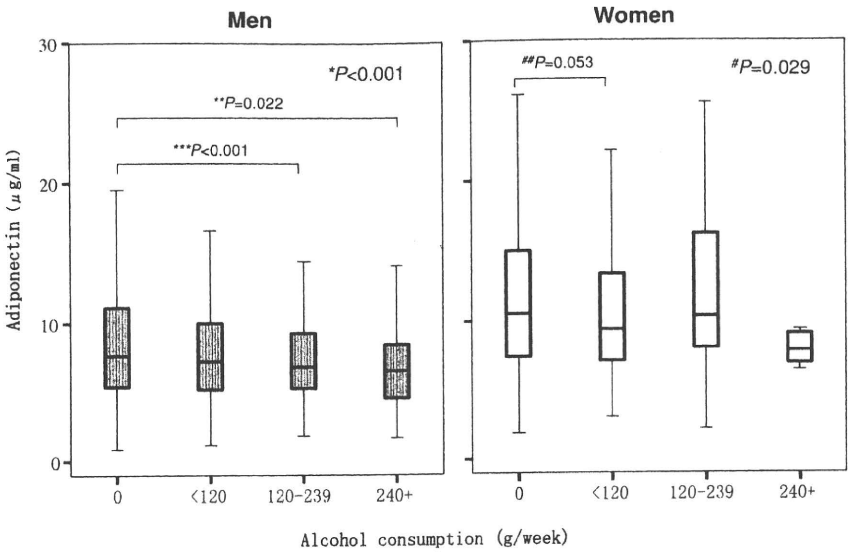

FIG. 1. Box plots illustrating serum plasma adiponectin concentrations for each level of alcohol consumption by gender. *Horizontal lines inside each box* represent medians, and the *top and bottom of the boxes* are the 25th and 75th quartiles, respectively. The *error bars* indicate 95% confidence intervals. *, $P < 0.001$ in men, and #, $P = 0.029$ in women for comparisons by ANOVA; **, $P = 0.022$, and ***, $P < 0.001$ in men, and ##, $P = 0.053$ in women for comparisons with abstainers in each group (Dunnett's test).

form of adiponectin and was closely associated with the type 2 diabetes when compared with total adiponectin (18). Moreover, it was shown that moderate alcohol consumption had different effects on HMW adiponectin, medium molecular weight adiponectin, and low molecular weight adiponectin (19). Further study is necessary to evaluate the effect of HMW on the association between serum adiponectin levels and alcohol consumption in a Japanese population.

Multiple regression analysis demonstrated that serum adiponectin levels were significantly related to sex, age, BMI, HDL-C, triglyceride, HOMA-IR, and ALT. All of the results are in good agreement with previous reports (3, 4, 10, 20, 21). Schulze *et al.* (4) observed an inverse relationship between plasma adiponectin levels and BMI and triglyceride but a positive relationship between plasma adiponectin levels and HDL-C and age in diabetic men. Ferris *et al.* (10) reported that serum adiponectin levels inversely correlated HOMA-IR in White subjects. A sex-based difference in plasma adiponectin levels was supported by previous studies (21, 22) and could be partly explained by differences in body fat distributions (22).

The consistent findings regarding the relationship between serum adiponectin levels and BMI, serum lipids, and insulin resistance and between alcohol consumption and HDL-C levels imply that factors related to ethnic differences, alcohol metabolism, and dietary intake may explain the discrepancies between our results and those of previous studies conducted in humans.

Alcohol is initially oxidized to acetaldehyde, mainly by the alcohol dehydrogenase (ADH) enzyme, and acetaldehyde is subsequently oxidized into acetate by the acetaldehyde dehydrogenase type 2 (ALDH2) enzyme (23). The gene that encodes these two representative alcohol-metabolizing enzymes displays polymorphisms that modulate individual differences in alcohol- and acetaldehyde-oxidizing capacity. Several ethnic differences in distribution of the ADH and ALDH2 genotypes, and in subsequent ethanol metabolism, have been demonstrated. First, the ADH class IV isozyme (σ-ADH), which is present predominantly in the upper gastrointestinal tract but not in the liver and which contributes to gastric ethanol oxidation, is absent or markedly decreased in 80% of Japanese people (24, 25). Second, about 85% of Japanese subjects are carriers of the ADH2*2 allele compared with only 5% or less of European and White American subjects (26). The ADH2*2 encodes an active enzyme and may be expected to generate more acetaldehyde because of this higher activity. Third, the ADH3*1 allele, coding for the rapidly acting ADH3, is more predominant (~95%) in Japanese subjects, whereas it is present in only 40–50% of White subjects (27). Finally, the ALDH2*2 allele, which encodes a catalytically inactive subunit, is present in about 45% of Japanese subjects, although it is extremely rare in White subjects (26). The latter three features indicate a failure to rapidly metabolize acetaldehyde, leading to excessive accumulation of acetaldehyde and higher susceptibility to acetaldehyde among a considerable number of Japanese subjects compared with White subjects. Ethanol and its metabolites, especially acetaldehyde, have been shown to have a toxic influence (23). Acetaldehyde is not only a highly toxic metabolite with extraordinary reactivity but was also shown to induce proinflammatory cytokines, TNF-α, and IL-1β in HepG2 cells (28), whereas TNF-α decreased the levels of adiponectin in human differentiated adipocytes (29). We assume that acetaldehyde and/or acetaldehyde adducts produced through oxidation of ethanol potentially modulate, in part, the association between alcohol intake and serum adiponectin concentrations in the Japanese population. Adjustments for polymorphisms in alcohol-metabolizing genes may explain the differences noted in ethnic groups.

Dietary factors play an important role in the development of type 2 diabetes and ischemic heart disease, because excess caloric intake contributes to the development of obesity, a major risk factor for both diseases. Studies on

TABLE 3. Multivariate-adjusted associations between serum adiponectin concentrations and alcohol consumption in 2932 subjects

Variables	Partial correlation coefficient	SE	Standardized partial correlation coefficient	95% confidence interval		*P* value
				Lower limit	Upper limit	
Sex (men,[a] women)	0.267	0.022	0.244	0.223	0.310	<0.001
Age (yr)	0.106	0.009	0.192	0.089	0.124	<0.001
BMI (<22,[a] 22–24.9, ≥25) (mm Hg)	−0.068	0.012	−0.099	−0.090	−0.045	<0.001
Systolic blood pressure (mm Hg)	0.000	0.001	−0.002	−0.001	0.001	0.902
LDL-C (mg/dl)	−0.001	0.000	−0.029	−0.001	0.000	0.058
HDL-C (mg/dl)	0.008	0.001	0.222	0.007	0.010	<0.001
Triglyceride (mg/dl)	−0.001	0.000	−0.081	−0.001	0.000	<0.001
Glucose (mg/dl)	−0.001	0.001	−0.025	−0.002	0.000	0.144
HOMA-IR (<2.0,[a] 2.1–3.9, ≥4.0)	−0.200	0.021	−0.170	−0.241	−0.158	<0.001
ALT (IU/liter)	−0.002	0.001	−0.060	−0.004	−0.001	<0.001
Smoking status (never,[a] current/former)	−0.031	0.022	−0.027	−0.074	0.011	0.147
Alcohol consumptions (10 g/d)	−0.028	0.006	−0.083	−0.040	−0.016	<0.001

Multiple regression analysis was used in covariance analyses for serum adiponectin concentrations after log transformation as independent variable.

[a] Reference category.

the dietary predictor of plasma adiponectin concentrations in animal models demonstrated that a high-fat diet is related to decreased serum adiponectin levels, just as it related to an increase in insulin resistance (30). Several controversial observations regarding fat intake have been reported when alcohol consumption accompanied this intake. High-fat, ethanol-containing food decreased serum adiponectin concentrations in mice (8) and rats (31). Decreases in serum adiponectin concentrations after ethanol feeding were dependent on the type of fat in the diet. Ethanol-containing diets high in unsaturated fats contributed to ethanol-induced decreases in adiponectin levels, whereas inclusion of saturated fats in the ethanol-feeding protocol prevented decreased adiponectin levels (9). A diet enriched in saturated fatty acids effectively reversed alcohol-induced necrosis, inflammation, and fibrosis despite continued alcohol consumption (32). The precise mechanism through which dietary fatty acids plus ethanol affect adiponectin expression and its secretion has yet to be determined. The protective action of saturated fatty acids is suggested to be partly caused by down-regulation of TNF-α (30, 33), which suppresses an adiponectin expression (29). In the Japanese population, both intake of total fat and that of saturated fats are lower than in the U.S. population (16, 34). The lower intake of saturated fat in the Japanese population may contribute to the different influence of alcohol consumption on adiponectin concentrations between Japanese and White subjects. However, it was not helpful to compare the effect of the intake of saturated fats with that of unsaturated fats in our study, because intake of these two fats was highly correlated ($r_s = 0.87$) among 1457 subjects who had completed the nutritional survey conducted in the same district using a self-administered questionnaire (unpublished data).

Carbohydrate intake may also be a factor that modulates the relationship between alcohol intake and adiponectin concentrations. In epidemiological studies, high glycemic loads, which were calculated by multiplying the carbohydrate content of each food by its glycemic index, were significantly associated with lower adiponectin concentrations in healthy men (16). For Japanese people, rice is the primary food that contributes to total carbohydrate and energy intake, which is seldom the case in Western populations. Data from the nutritional survey conducted in the same district (unpublished data) have shown that carbohydrate intake accounted for about 59% of total energy intake, and the mean glycemic load was about 206 among subjects aged 40 yr or over. Both parameters were higher than those of White adults (16). Although the effect of the dietary glycemic intake on the relationship between alcohol intake and adiponectin concentrations has not been fully elucidated, the higher intake of carbohydrate in the Japanese population may contribute to the different influence of alcohol consumption on adiponectin concentrations between Japanese and White subjects.

Our study demonstrated an inverse association between alcohol intake with serum adiponectin levels in men, with less clear findings in women. This discrepancy might be explained, in part, by the gender difference in ethanol metabolism. Women differ from men in several factors associated with alcohol metabolism (35), including 1) a lower gastric σ-ADH activity, which mediates the first-pass mechanism of ethanol in women, and 2) a decreased volume of ethanol distribution (body size and distribution space for alcohol, with water space being smaller

in women). However, these properties are not sufficient to explain the gender difference of the effect of alcohol intake on serum adiponectin concentrations. The small number of drinkers among our female subjects (15%) might cause difficulty in evaluating this result. Further study, including increasing the number female drinkers enrolled, is necessary to examine this inference.

There are potential limitations to this study. Because of its cross-sectional nature, this study did not provide a causal inference regarding the association between alcohol intake and serum adiponectin levels. However, information on the drinking habits of subjects was determined before the measurement of adiponectin concentrations; thus, an incorrect finding of an inverse association is unlikely. Data on drinking habits was based on face-to-face interviews, which leads to the possibility of misclassification of exposure (*e.g.* underreporting). However, it is also unlikely that this type of misclassification is directly dependent on adiponectin levels, which could be a nondifferential misclassification. Because our study subjects were recruited from participants in a health screening program, any generalization of these results to the normal population should be made with caution.

In conclusion, alcohol consumption was weakly associated with decreased serum adiponectin concentrations in apparently healthy Japanese subjects. Further investigations in Japanese subjects on alcohol metabolism and nutrition intake are necessary to clarify the factors that modulate this inverse effect, which differs from that seen in White subjects.

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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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