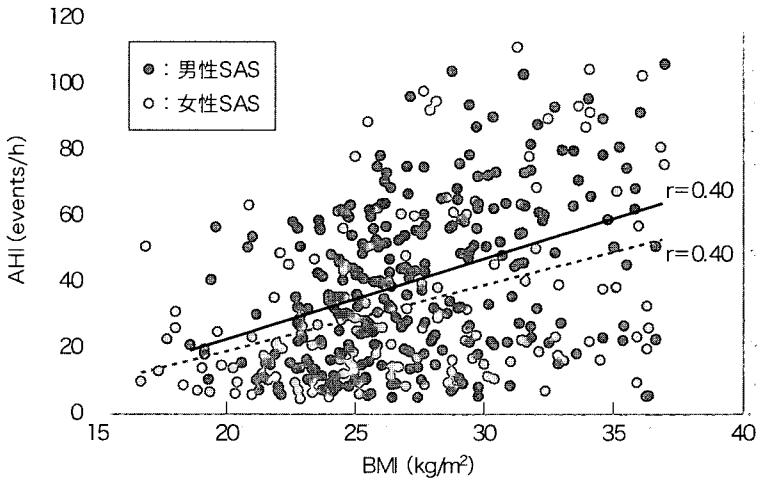

図4　BMIとAHIの関係に関する性差

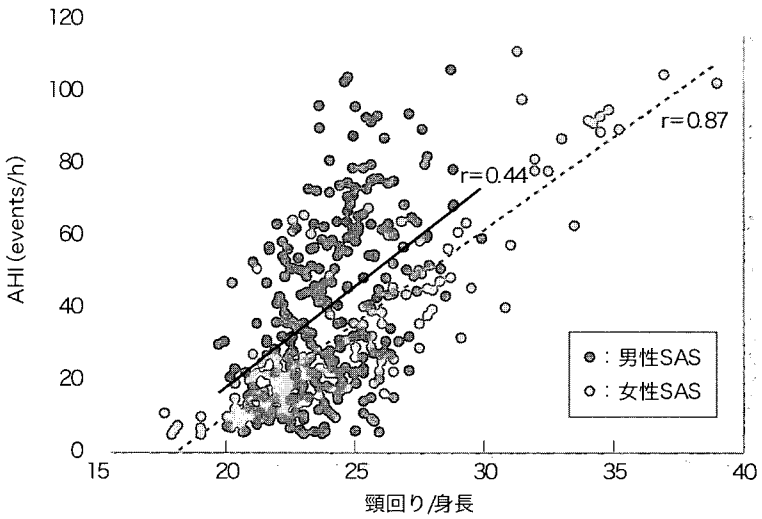

図5　頸周り/身長とAHIの関係に関する性差

択した場合、頸周り、腹囲は身長で補正するのが妥当である根拠になるかもしれない。BMIが同程度のとき、AHIで評価した睡眠時無呼吸症候群の重症度は男性のほうが強く、睡眠時無呼吸症候群の程度は男性優位ということが示唆された　逆に考えると、女性であることは、睡眠時無呼吸症候群に対して防御的に働いているのかもしれない。しかし、睡眠時無呼吸症候群の別の重症度指標である睡眠時のSpO_2の最低値には性差は認められなかった。

男女間でBMIに有意差がない対象例において、AHIが男性のほうが高値であったことより予想されるごとく、肥満の程度をBMIで評価したとき、同じBMIでは男性のほうが女性よりもAHIは高値であった（共分散分析にて$p<0.01$）（図4）。BMIの値はそのまま局所肥満の程度を反映するわけではないので、AHIの値に影響することが予想される頸部周囲径と腹部周囲径の値の性差を検討した。頸周り/身長と腹囲/身長には男女間で有意差は認めなかったが、同じ頸周り/身長と腹囲/身長に対するAHIの値は、男性のほうが女性よりも高値であった（共分散分

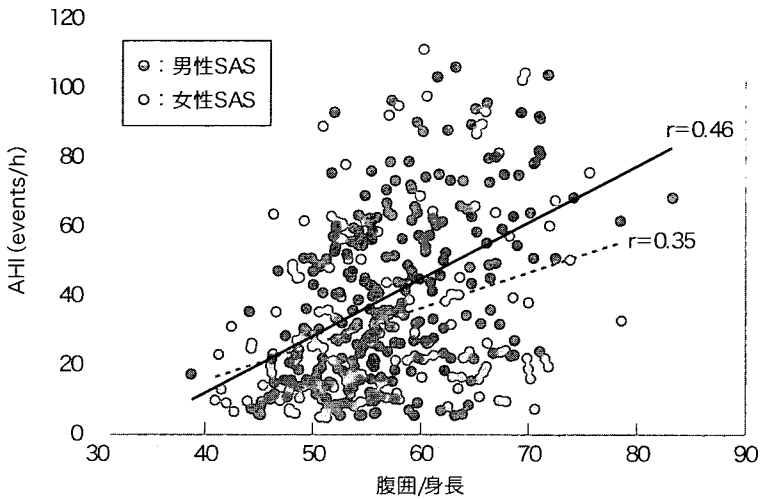

図6　腹囲/身長とAHIの関係に関する性差

	更年期前(n=79)	更年期後(n=79)	
年齢(年)	45.8± 1.1	64.9± 0.7	p<0.01
身長(m)	1.56± 0.01	1.53± 0.01	p<0.05
体重(kg)	66.1± 1.5	60.2± 1.2	p<0.01
BMI (kg/m^2)	27.3± 0.6	25.8± 0.5	p<0.01
頸周り(cm)	37.9± 0.8	37.1± 0.7	p=ns
頸周り/身長(cm/m)	24.4± 0.5	24.3± 0.5	p=ns
腹囲(cm)	83.2± 1.9	84.1± 1.4	p=ns
腹囲/身長(cm/m)	57.4± 1.0	55.1± 1.0	p<0.01
AHI (events/h)	31.8± 2.9	32.4± 2.8	p=ns
Low SpO_2 (%)	77.4± 1.2	78.3± 1.2	p=ns

表3　更年期前後における睡眠時無呼吸症候群症例の比較

析にてp＜0.01)(図5、6)。やはり、女性であることは、睡眠時無呼吸症候群に対して防御的に作用しているのかもしれない。この頸周り/身長と腹囲/身長の値が、そのまま局所肥満の程度を表していない可能性もあるが、睡眠時無呼吸症候群の性差には、局所肥満で表現される解剖学的性差以外の機能的要因が関与していることが推定される。

一般に、女性ホルモンは睡眠時無呼吸症候群に対して防御的に作用していると考えられている。女性ホルモンの存在は、上気道開大筋に対する神経活動を増強するとされている。われわれの経験した症例で、更年期前後で比較したとき、更年期前の症例のほうが体重・BMIが高値で肥満が強かった(表3)。しかし、AHIおよび睡眠時のSpO_2の最低値には、更年期前後で有意差は認められなかった。この現象は、女性ホルモンが睡眠時無呼吸症候群に対して防御的に作用しているということと矛盾していない。

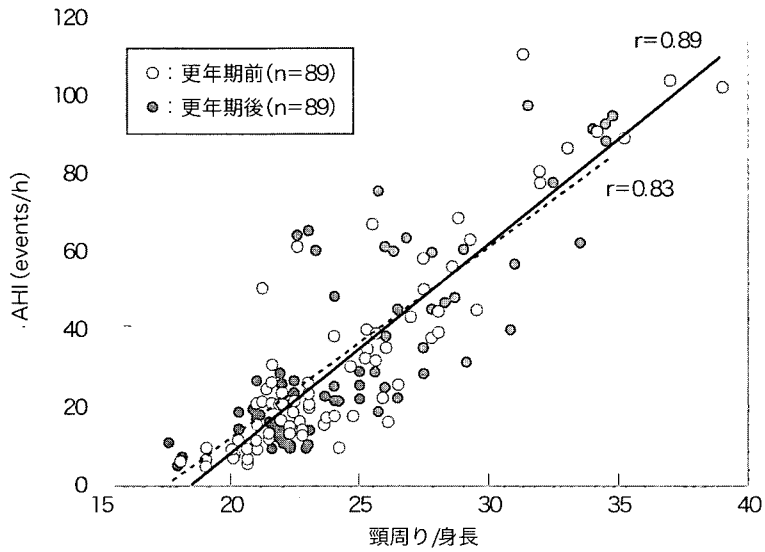

図7　更年期前後における頸周り/身長とAHIの関係

では、同様の局所肥満を呈している場合、更年期前の女性のほうが、更年期後の女性よりも無呼吸の程度は軽度である可能性が考えられる。そこで、頸周り/身長・腹囲/身長とAHIの関係を、女性の睡眠時無呼吸症候群症例において、更年期前後に分類して検討してみた。しかし、更年期前後において、頸周り/身長・腹囲/身長とAHIの関係には変化が認められなかった(図7)。女性ホルモンの存在は、局所肥満の程度を代償していないのかもしれない。睡眠時無呼吸症候群における更年期前の女性の肥満には、無呼吸の増悪と関係ない部分が含まれているのかもしれない。

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メタボリックシンドロームにおける内臓脂肪蓄積と独立した危険因子としての睡眠時無呼吸症候群

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緒　言

肥満者において，閉塞型睡眠時無呼吸症候群(OSAS)と高血圧症・脂質代謝異常・耐糖能異常の合併はしばしば認められる。近年になり心・脳血管疾患の要因として，肥満とりわけ内臓脂肪蓄積に由来するインスリン抵抗性を背景とするメタボリックシンドローム(MS)の概念が提唱された。一方OSASは肥満と独立した心・脳血管疾患の危険因子であることが指摘され，特に脳血管疾患発症において最大の危険因子である可能性が指摘されている[1]。本邦のMS診断基準によれば，必須項目となる内臓脂肪蓄積に加え，血圧高値・高血糖・血清脂質異常の3項目のうち2つ以上を有する場合にMSと診断される[2]。しかしながら本邦のOSAS患者の1/4は非肥満患者であり，多くは内臓脂肪蓄積を有さず，本邦の診断基準ではMSと診断されない。インスリン抵抗性の亢進においてOSASがBMIと独立した危険因子であることや[3]，前向き研究にてOSASが高血圧の発症において独立した因子であることがすでに示されているが[4]，内臓脂肪蓄積の影響を除外して検討した研究は行われていない。そこでわれわれは肥満や内臓脂肪蓄積を有さないOSAS患者における，MSに含まれるその他の異常，すなわち血圧高値・血清脂質異常・高血糖に加えて耐糖能異常の発症率について，これらの異常においてOSASが内臓脂肪蓄積と独立した危険因子となるかを検討した。また心・脳血管疾患の危険因子となるとされる，これらの異常を複数合併する者の割合についても検討した。

表1　対象症例の臨床的特徴

	OSAS (n=42)	non-OSAS (n=52)	P value
Gender (M/F)	42／0	52／0	NS
Age (yr)	51.8±2.4	46.5±2.2	NS
BMI (kg/m^2)	22.7±0.6	23.9±0.4	NS
VFA (cm^2)	62.0±3.2	58.4±3.8	NS
SFA (cm^2)	82.4±7.0	92.8±8.8	NS
V/S	0.89±0.05	0.76±0.05	<0.05
AHI (events/hour)	32.2±3.1	2.4±0.2	<0.01
Average SaO_2 (%)	94.4±0.4	96.3±0.2	<0.01
Lowest SaO_2 (%)	81.9±1.3	87.4±0.7	<0.01
%VC (%)	107.9±3.3	104.3±2.7	NS
$FEV_{1.0}$% (%)	83.1±1.4	85.2±1.2	NS
PaO_2 (mmHg)	88.2±1.5	88.6±1.7	NS
$PaCO_2$ (mmHg)	43.0±0.6	42.9±0.5	NS

対象および方法

睡眠障害外来を受診した男性患者において，肥満および内臓脂肪蓄積を伴わず，かつ年齢・BMI・内臓脂肪面積において有意差を認めないOSAS群42名と非OSAS群52名を抽出した(表1)。OSASの診断はポリソムノグラフィー(PSG)にてAHI≧5かつ他の睡眠障害をもたらす疾患が否定されたものとした。内臓脂肪量の判定は，本邦のMS診断

Key words：閉塞型睡眠時無呼吸症候群，耐糖能異常，高血圧症

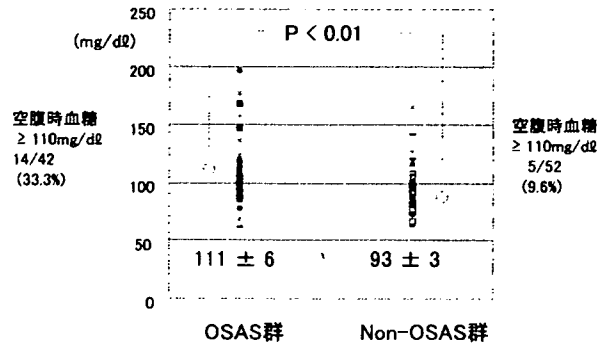

図1　空腹時血糖の比較

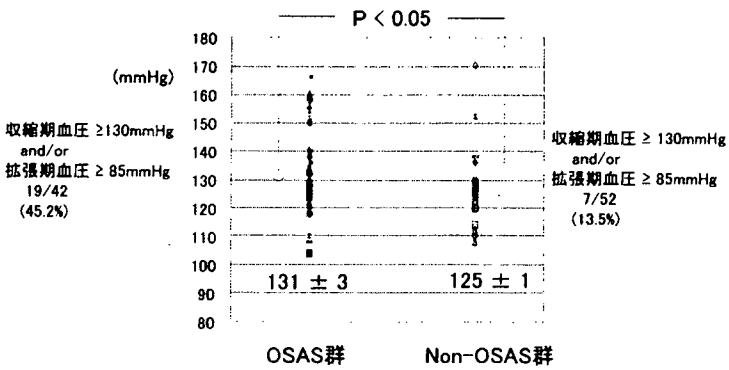

図2　収縮期血圧の比較

基準[2]に準じた。すなわち腹部CTによる計測で内臓脂肪面積≦100cm²であるものを，内臓脂肪蓄積がないものとした。PSG目的の入院時に起床時血圧および早朝採血による空腹時血糖(FBS)・中性脂肪・HDL-C・インスリン(IRI)を測定し，HOMA-RをIRI (U/mℓ) × FBS (mg/dℓ) ÷ 405として求めた。各項目の測定値および本邦のMS診断基準における内臓脂肪蓄積以外，すなわち血圧高値・血清脂質異常・高血糖のうち2つ以上の項目の異常を認めるものの割合について両群間における比較を行った。

結　果

OSAS群と非OSAS群において，FBSと収縮期血圧およびHOMA-Rにおいて有意にOSAS群が高値であった(p<0.01, p<0.05, p<0.05)(図1，図2，図3)。その他の拡張期血圧・中性脂肪・HDL-Cにおいては統計学的に差は認められなかった。また血圧高値・血清脂質異常・高血糖のうち2つ以上の項目のMS診断基準による異常値を認めた者の割合においても，OSAS群が有意に高かった(p<0.05)(図4)。このことは高血圧および耐糖能異常の発症と，さらに血圧高値・血清脂質異常・高血糖のうち複数の発症に，OSASが肥満や内臓脂肪蓄積と独立してかかわる可能性を示唆している。

考　察

MSについてはいくつかの診断基準が存在するが，本邦の基準では内臓脂肪蓄積の存在が必要条件とされている[2]。従来BMIが肥満度を評価する指標として使われてきたが，その心血管疾患の予測指標としての信頼性について疑問が呈されてきていることもその背景にあると考えられる[5]。心・脳血管疾患の危険因子の本態がインスリン抵抗性にあるという仮説がMSの概念に取り入れられてきており，当研究の結果はOSASがMSの構成要素になるか否かを検討する意義があることを示唆し

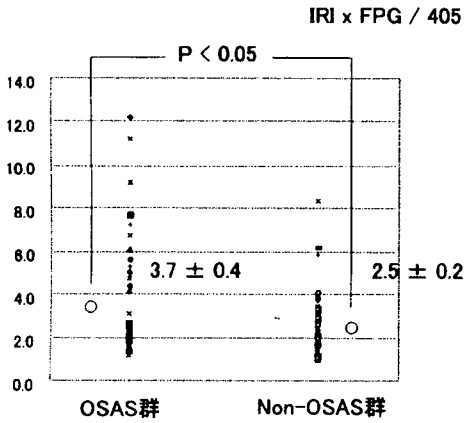

図3　HOMA-Rの比較

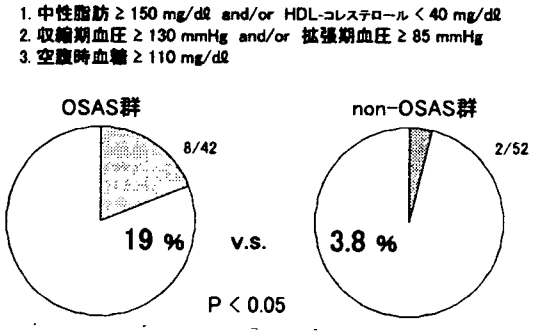

図4　血圧高値・血清脂質異常・高血糖のうち2つ以上の項目の異常を認めるものの割合

ている。OSASと特に脳血管疾患の関係を考えるうえで，諸外国と比較し本邦の脳血管障害による死亡率の高さは心血管障害による死亡率の低さと対照的である[6]。その傾向は高血圧治療の普及した現在も存在し，久山町研究によれば心血管疾患および脳梗塞の最大の危険因子は1960年代には高血圧であったのが90年代には糖尿病となっている[7]。また脳卒中の発症者の半数は高血圧治療中に発症しており[8]，心・脳血管疾患の予防においてはより一層の研究と介入が必要となっている。すでにOSASを有する脳梗塞患者において，CPAPによる脳梗塞の二次予防効果が示されている[9]。本邦での内臓脂肪蓄積と独立した危険因子としての心・脳血管疾患の発症および予後におけるOSASの研究は，MSの概念にさらに新しい知見を加える可能性があると考える。

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38. 夜間呼吸が止まっている，どうしよう？

巽 浩一郎

閉塞型睡眠時無呼吸症候群は，高血圧症，虚血性心疾患，脳血管障害という循環器系疾患発症の危険因子になることが知られているが，糖尿病の悪化要因でもある（Ip M, et al. Am J Respir Crit Care Med. 2002; 165: 670, Harsch IA, et al. Am J Respir Crit Care Med. 2004; 169: 156）．糖尿病も閉塞型睡眠時無呼吸症候群も，ともに肥満がその発症要因として関与しているが，糖尿病（耐糖能異常，インスリン抵抗性）発症に関しては，睡眠時無呼吸症候群の存在よりも肥満の関与が大きいことは認められている．本項では，糖尿病の合併症として問題になる閉塞型睡眠時無呼吸症候群の診断と治療に関して概説する．

A．閉塞型睡眠時無呼吸症候群：診断へのアプローチ

最初に，本項の結論を記載する（表1）．もう少し付け加えるならば，睡眠時無呼吸症候群を疑う徴候は以下のとおりである．1．習慣性いびき，2．他人に睡眠時の無呼吸を指摘された，3．昼間の傾眠，4．肥満，高血圧症．

B．睡眠時無呼吸症候群の診断はスクリーニングだけでは不十分

睡眠時無呼吸症候群診断のための睡眠検査には，スクリーニング検査と polysomnography（PSG）がある（表2）．スクリーニング検査として酸素飽和度（SpO_2）の測定を用いる場合には，基準値から4%以上の低下を有意とする．

表1 睡眠時無呼吸症候群：診断へのアプローチ

太っている糖尿病の患者
特に，高血圧症を合併している患者には，
1）いびきがうるさいといわれているかどうか
2）昼間に眠くて困ることはないかどうか
を問診しよう．

表2 睡眠時無呼吸症候群の診断手段

1）スクリーニング検査
　PSG検査から脳波測定のための検査を除いたもの
　パルスオキシメータ（SpO_2モニター）
　呼吸イベント，いびき，心電図
2）ポリソムノグラフィー polysomnography（PSG）

JCLS 498-12316

表3　閉塞型睡眠時無呼吸症候群（OSAS）の本来の定義

American Academy of Sleep Medicine Task Force（Sleep. 1999; 22: 667）による定義は以下のとおりである.
定義: A or B+C
A．日中の過度の眠気（OSAS以外の要因では説明できない）
B．下記の症状が2項目以上（OSAS以外の要因では説明できない）
　睡眠中の窒息感またはあえぎ
　睡眠からの頻回の覚醒
　熟眠後の爽快感の欠如
　日中の疲労感
　集中力の障害
C．睡眠検査にて5回/時以上の閉塞型呼吸イベント
　（閉塞型無呼吸/低呼吸，呼吸努力関連覚醒）

スクリーニング検査を施行した場合，personal computer（PC）で計算した値だけをみるのではなく，実測のSpO_2波形を参照して，4%以上のSpO_2低下（ODI）が5以上のときは，睡眠時無呼吸症候群疑いといえる．では，4% ODIが5以下であれば，まったく問題はないのであろうか？　睡眠時無呼吸症候群は否定されるのであろうか？　ここに大きな問題点がある（underdiagnosis）.

C．睡眠時無呼吸症候群とは

睡眠時無呼吸とは，呼吸の停止ではなく，呼吸による鼻または口での気流が10秒以上停止した状態のことを指している．そして睡眠時無呼吸症候群とは，その無呼吸に起因する何らかの自他覚症状がある場合に診断される.

しかし一般には，自覚症状・他覚所見（高血圧症など）がなくても，睡眠時無呼吸を1時間あたり5回以上認める場合に，閉塞型睡眠時無呼吸症候群（表3）と診断している．自覚症状・他覚所見のない場合は，本来は予備群である.

この定義の中の，閉塞型呼吸イベント（表3）の呼吸努力関連覚醒が，前項の「睡眠時無呼吸症候群の診断はスクリーニングだけでは不十分」と関係してくる．呼吸努力関連覚醒は，強いいびきによる睡眠中の覚醒反応を起こすという点で病的意義を有している．これが睡眠の質の低下，そして日中の眠気に関係してくる．このような場合には，睡眠時無呼吸症候群に準じた治療が必要になる.

D．睡眠呼吸障害の際の治療選択

睡眠時無呼吸症候群の重症度は，PSGによる無呼吸・低呼吸指数（apnea-hypopnea index: AHI）により分類されている（表4）．この客観的指標と，主観的な自覚症状である眠気などには，ある程度の相関関係はあるが，必ずしも自他覚所見が一致するとは限らない.

睡眠時無呼吸症候群に対する治療はCPAP療法のみではない（表5）．睡眠時無呼吸症候群では，気道は閉塞するが呼吸努力は続くため，上気道には陰圧がかかることになる．CPAP治療は，気道に陽圧をかける治療であるため，閉塞部位がどこでも関係なく治療可能である（図1）．耳鼻科的治療は，上気道の余分な軟部組織を削り取ろうというものである．軟部組織を取り除くことにより，気道にかかる圧力が低下するようであれば成功であり，気道にかかる圧力が低下しなければ失敗に

表 4　睡眠時無呼吸症候群の重症度分類

軽症	5≦AHI＜15
中等症	15≦AHI＜30
重症	30≦AHI

AHI：1 時間あたりの無呼吸・低呼吸の数

表 5　睡眠時無呼吸症候群の治療手段

1）減量療法	他の治療と並行指導
2）CPAP	1998 年 4 月より医療保険適応
3）耳鼻科的治療	耳鼻科で適応を考慮
4）口腔内装具	2005 年 4 月より医療保険適応

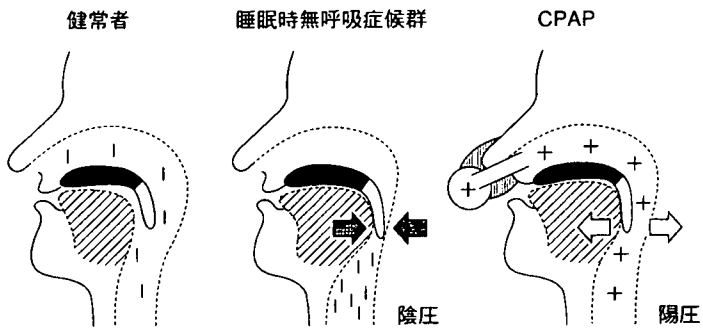

図 1　CPAP 治療
上気道に陽圧をかけるのが CPAP 治療であり，閉塞部位がどこでも治療可能となる．

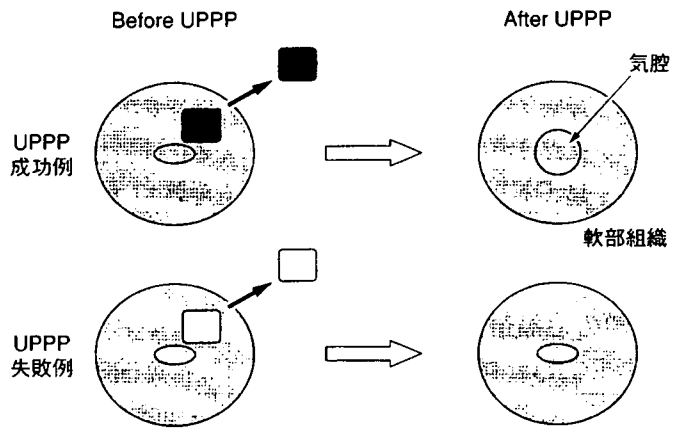

図 2　耳鼻科治療（UPPP）の成功例と失敗例

なる（図 2）．

口腔内装具が 2005 年度より保険適応になっている．口腔内装具は，下顎を前方に移動させ固定させることによって舌全体を前方に動かし，気道を拡大する下顎前方固定式マウスピース（PMA）（図 3）が主流である．口腔内装具の作用機序は，解剖学的是正と，神経筋活動の変化の双方が関与

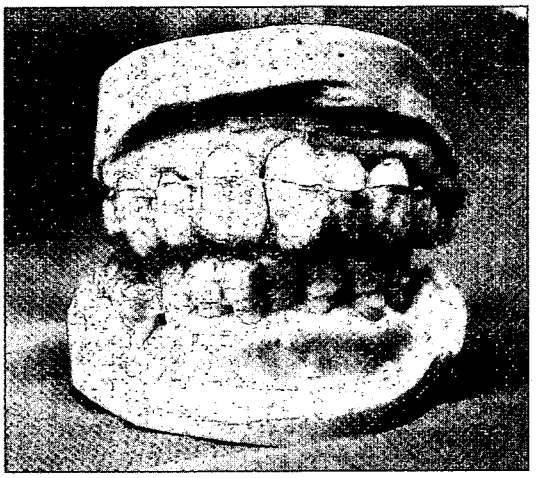

図3　下顎前方固定式マウスピース

表6　口腔内装具の作用機序

1．下顎を前方移動することで，舌が前方に牽引され，気道が拡大する．
2．下顎が固定されて，頤舌骨筋が緊張し，気道が拡大する．

表7　口腔内装具の適応

1．習慣性いびき
2．軽症の睡眠時無呼吸症候群
3．中等症～重症の睡眠時無呼吸症候群で，CPAP が施行できない症例，または耳鼻科的治療が不適切な症例

している と考えられる（表 6）．その適応は，従来は軽症の睡眠時無呼吸症候群と考えられていたが，重症でも効果が認められる症例もあることが判明している（表 7）．PMA は，下顎骨をどのくらい前方へ移動するかにより，効果が大きく異なる症例もあるので，PMA の作成は試行錯誤的な要素がどうしても伴う．

睡眠時無呼吸症候群で要治療と診断したときには，まず重症度にかかわらず，CPAP 治療を選択してみるという手がある．CPAP 治療が無理であれば，他の治療選択肢に変更可能だからである．CPAP 治療を継続することが無理そうであれば，耳鼻科的治療ないしは歯科口腔内装具の作成を考慮することになる．

CPAP 治療で，自覚症状の改善が得られた場合，上気道の解剖学的問題点を，耳鼻科治療・減量療法で改善できるのであれば，CPAP 療法からの離脱は可能である．軽症～中等症の睡眠時無呼吸症候群では，最初 CPAP 療法にて自覚症状が改善した後，口腔内装具で加療を続けるという場合もある．

CPAP 治療で，自覚症状の改善が得られ，上気道の解剖学的問題がほとんどないのであれば，CPAP 治療を可能な限り継続することになる．ただし，このような場合でも，口腔内装具にて効果があることもある（図 4）．

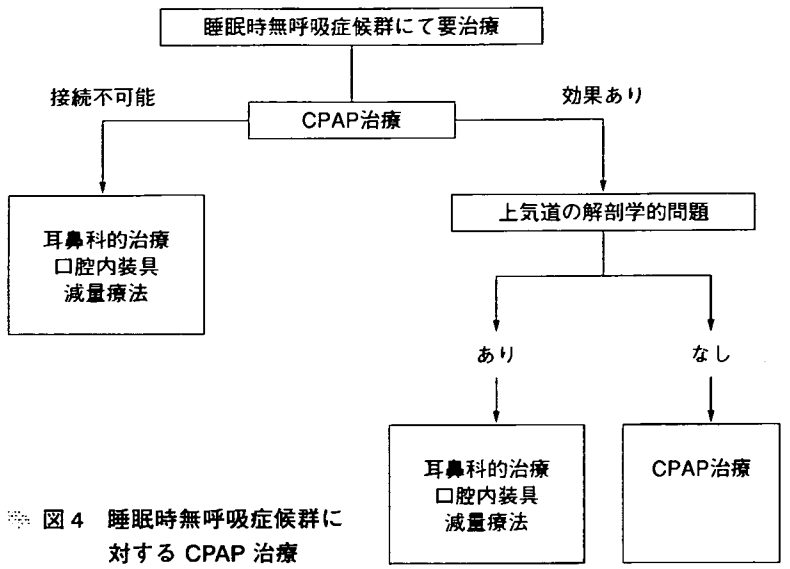

図4　睡眠時無呼吸症候群に対する CPAP 治療

表 8　睡眠時無呼吸症候群における肥満治療の目標

内臓脂肪の減少
→上気道周囲脂肪の減少
→上気道閉塞の程度の改善による自覚症状の改善
→CPAP からの離脱

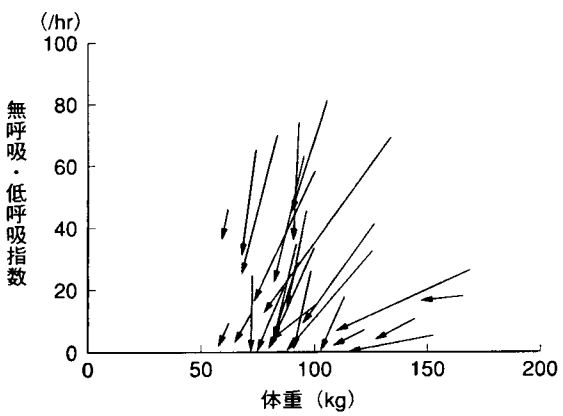

図5　体重減少の無呼吸指数への影響

睡眠時無呼吸症候群の根本的治療ではあるが，達成が困難であるのが，減量療法である．睡眠時無呼吸症候群における減量療法の目標は，内臓脂肪の減少に伴う上気道周囲脂肪組織の減少である．それが達成されれば，上気道の開存性が保て，自覚症状は改善，CPAP 療法から離脱というサクセスストーリーがみえてくる（表 8）．減量療法の目標は，標準体重に戻すことではない．まず，5%の体重減少を目標に減量療法をすることが肝要である．それだけでも無呼吸の程度の改善が得られ，場合により自覚症状が改善することもある（図 5）．

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Forum Original Research Communication

Plasma Thioredoxin, a Novel Oxidative Stress Marker, in Patients with Obstructive Sleep Apnea Before and After Nasal Continuous Positive Airway Pressure

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ABSTRACT

Obstructive sleep apnea (OSA) is associated with increased cardiovascular mortality, and oxidative stress was suggested to play an important role. We hypothesized that the plasma TRX level, a novel oxidative stress marker, is elevated in OSA patients. Plasma TRX and adiponectin levels, which are significantly associated with cardiovascular mortality, were measured in 41 patients with severe OSA before (*n* 41) and after (*n* 27) nasal continuous positive airway pressure therapy (nCPAP) for 1 month and in 12 subjects without OSA (non-OSA group). The TRX level was significantly higher (*p* 0.02) and the adiponectin level was significantly lower (*p* 0.02) in the OSA group than in the non-OSA group. After 1 month of nCPAP (*n* 27), the TRX level significantly decreased (*p* 0.03), and the adiponectin level significantly increased (*p* 0.03). Among the 14 patients with untreated OSA, the TRX and adiponectin levels did not significantly change over a 1-month interval. Among the 53 (41 OSA 12 non-OSA) subjects, the TRX level was positively correlated with the respiratory disturbance index (*p* 0.001) and percentage of time with Sao_2 90% (*p* 0.0002). The adiponectin level, but not the TRX level, was correlated with the BMI (*n* 53; *p* 0.02). Plasma TRX may be a unique marker for evaluating oxidative stress and monitoring the effectiveness of nCPAP in OSA patients. *Antioxid. Redox Signal.* 10, 0000–0000.

INTRODUCTION

THIOREDOXIN (TRX) is a small protein that contains a redox-active site and has a variety of biologic functions including cytoprotection against oxidative stress (23). Recent experimental studies showed that TRX is released from cells in response to oxidative stress (31) and plays a protective role against oxidant injury (13). In our previous studies, we found that the plasma/serum level of TRX is elevated in patients with oxidative stress–associated acute and chronic disorders such as viral infection (36), ischemia–reperfusion (21), myocardial infarction (22), chronic heart failure (12), and nonalcoholic steatohepatitis (35). Obstructive sleep apnea (OSA) has been reported to have significant effects on myocardial infarction (17), chronic heart failure (30), and nonalcoholic steatohepatitis (38). However, the blood levels of TRX in patients with OSA have not been investigated.

The mortality rate is increased in untreated patients with OSA, who are at increased risk for cerebrocardiovascular diseases (17). In addition, the prevalence of significant OSA is high (43). Recently, OSA has been associated with inflammation, endothelial dysfunction, and increased oxidative stress

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(34), which are generated by repetitive nocturnal hypoxemia and reoxygenation (Fig. 1). Oxidative damage is involved in the pathogenesis of atherosclerosis and cardiovascular diseases (6), as well as of inflammation (14).

To elucidate the involvement of oxidative stress in OSA, two types of oxidative stress markers have been studied: (a) products of oxidation such as reactive oxygen species, oxidized proteins, lipid oxidation, and DNA degeneration as the end products of oxidative stress; and (b) antioxidant proteins whose gene expression is induced by oxidative stress. An antioxidant protein such as TRX (13, 31) not only has a role as an oxidative stress marker, but also may potentially be protective against oxidative stress. Recently, oxidative stress has been investigated in patients with OSA by measuring the levels of various products of oxidation (3, 5, 15, 32, 41). However, no antioxidant protein has been measured in those reports.

Therefore, it is important and promising to investigate oxidative stress in patients with OSA with a sensitive antioxidant marker, such as plasma TRX, because the plasma TRX level is easy to measure and reflects the cellular response to oxidative stress (12, 22). We hypothesized that the plasma TRX level in OSA patients is elevated and that it is reduced by treatment. We also hypothesized that the plasma TRX level in patients with OSA is associated with inflammation and the pathogenesis of cardiovascular diseases.

Adiponectin is a cytokine produced exclusively by white adipose tissue and appears to play a central role in metabolic syndrome (19) in addition to having antiatherogenic and antiinflammatory effects (39). Adiponectin may play an important role in cardiovascular disorders (28). Therefore, we also measured the plasma adiponectin level in addition to plasma interleukin-6 (IL-6) and serum C-reactive protein (CRP) levels, which are known to be inflammatory markers predictive of cardiovascular diseases (16) and have been reported to be elevated in OSA patients (33, 42). We compared these parameters between the OSA patients and subjects without OSA and investigated the effect of nasal continuous positive airway pressure (nasal CPAP) therapy on these parameters in OSA patients.

METHODS

Subjects

OSA patient group. We enrolled 50 consecutive patients with OSA who were determined to be candidates for nasal CPAP treatment by polysomnography and clinical symptoms. The diagnosis of OSA was established on the basis of clinical symptoms such as excessive daytime sleepiness, unexplained daytime fatigue, choking or gasping during sleep, and an apnea hypopnea index (AHI) of 5 events per hour on polysomnography. Five patients were excluded because they had a history of myocardial infarction, brain infarction, chronic cardiac failure, or colon cancer or had a common cold at the time of the study. Polysomnography was performed in the hospital before CPAP treatment. Patients with an AHI of 20 events per hour were candidates for nasal CPAP.

Hypertension was defined as a diastolic pressure 90 mm Hg, a systolic pressure 140 mm Hg, or the use of antihypertensive medication. Diabetes mellitus was defined as a fasting blood glucose level of 126 mg/dl, increased blood glucose level of 200 mg/dl 2 h after a 75-g oral glucose load, or the use of antidiabetic medication. Hyperlipidemia was defined as a total blood cholesterol level of 220 mg/dl, triglyceride level of 150 mg/dl, or the use of lipid-lowering medication. The OSA patients in this study received the same medical regimen beginning 1 month before the start of this study and throughout the study.

OSA untreated group. When a patient is diagnosed with severe OSA at our hospital, nasal CPAP therapy is started about 1 month later. To investigate whether significant changes in the plasma TRX level occur in OSA patients who have not received CPAP treatment, 15 OSA patients were randomly selected from the 45 patients, and we planned to obtain blood samples from them in the morning twice at about a 1-month interval before nasal CPAP treatment was started. One patient did not return to our clinic for follow-up. Therefore, 14 patients [13

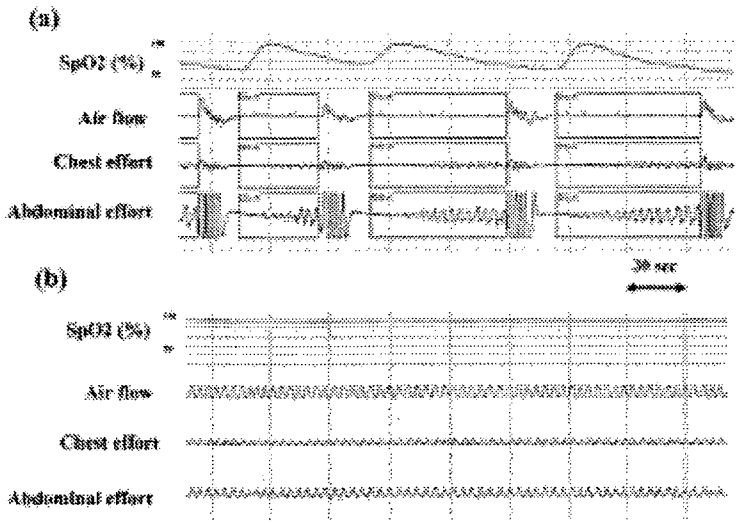

FIG. 1. Polysomnographic data of one of the OSA patients in this study who underwent nasal CPAP therapy (man, 53 years old; body mass index, 29.3 kg/m^2). (**a**) Polysomnographic data of the OSA patient before nasal CPAP treatment. After cessations of nasal and oral air flow with paradoxic chest and abdominal motions, periodical desaturations were observed. (**b**) Polysomnographic data of the same OSA patient after nasal CPAP treatment for 3 days. The periodic cessations of air flow and desaturations disappeared. Spo_2, Oxygen saturation measured with pulse oximetry; Ob A., obstructive sleep apnea.

TABLE 1. BASELINE CHARACTERISTICS OF THE OSA SUBJECTS AND NON-OSA SUBJECTS

Variable	*OSA*	*Non-OSA*	p	p*
Number	41	12		
Male/Female (no.)	38/3	11/1	0.96	
Age (yr)	49.8 10.0	46.7 11.2	0.22	
Body mass index (kg/m^2)	29.4 4.2	25.7 4.1	**0.004**	
Respiratory disturbance index (events/h)	48.5 18.2	2.80 1.7	**0.0001**	
Lowest SaO_2 (%)	65.4 15.3	86.3 6.1	**0.0001**	
% of time SaO_2 90% (%)	25.9 2.4	0.50 0.73	**0.0001**	
Current smoking (no.)	11	3	0.92	
Hypertension (no.)	27	6	0.41	
Diabetes mellitus (no.)	10	3	0.97	
Hyperlipidemia (no.)	16	4	0.77	
Thioredoxin (ng/ml)	41.0 24.4	23.9 14.7	**0.02**	**0.04**
Adiponectin (g/ml)	3.84 1.66	5.82 3.09	**0.02**	**0.03**
IL-6 (pg/ml)	1.56 2.49	0.99 0.94	0.77	0.92
CRP (mg/dl)	0.172 0.147	0.087 0.096	**0.02**	0.07

Data are expressed as mean SD.
*p**, *p* value after adjustment for BMI; OSA, obstructive sleep apnea.

men, one woman; age, 52.7 8.3 years; AHI, 49.1 24.1 events/hour; body mass index (BMI), 28.2 3.2 kg/m^2] were included in the OSA-untreated group.

OSA treatment group. To investigate the effect of nasal CPAP treatment, the remaining 30 patients with OSA underwent CPAP titration manually, received CPAP treatment [pressure (mean SD), 9.6 3.1 cm H_2O], and underwent polysomnography on the third night of CPAP therapy. Thereafter, they received nasal CPAP therapy for 1 month at home before revisiting the outpatient clinic. Three patients refused to use nasal CPAP continuously. We checked the use time by reading the time counter in each CPAP machine, and the remaining 27 patients used nasal CPAP for 4 h per night. These 27 patients (25 men, two women; age, 48.3 10.7 years; AHI, 48.2 14.8 events/hour; BMI, 30.1 4.6 kg /m^2) were included in the OSA treatment group. Blood samples were collected in the morning before and 1 month after beginning CPAP use. The BMI after 1 month of nasal CPAP did not significantly differ from that before CPAP therapy was started (p 0.26). Forty-one (14 untreated and 27 treatment) OSA patients were studied (Tables 1 and 2).

Non-OSA volunteer group. Twelve volunteers (11 men, one woman; age, 46.7 11.2 years; BMI, 25.7 4.1 kg/m^2) who did not have OSA were enrolled in the non-OSA group. They were not heavy snorers. In all of the volunteers, the arterial oxygen saturation was continuously monitored during sleep with a pulse oximeter (Pulsox-24; Minolta, Osaka, Japan) over two consecutive nights. The severity of sleep ap-

TABLE 2. BASELINE CHARACTERISTICS OF THE OSA TREATMENT GROUP AND OSA UNTREATED GROUP

Variable	*OSA treatment*	*OSA untreated*	p
Number	27	14	
Male/Female (no.)	25/2	13/1	0.99
Age (yr)	48.3 10.7	52.7 8.29	0.21
Body mass index (kg/m^2)	30.1 4.6	28.2 3.16	0.25
Apnea–hypopnea index (events/h)	48.2 14.8	49.1 24.1	0.83
Lowest arterial O_2 saturation (%)	65.2 16.5	65.8 13.4	0.67
Arterial O_2 90% (% of time)	29.3 22.9	19.3 20.6	0.21
Thioredoxin (ng/ml)	43.6 23.0	35.9 27.1	0.15
Adiponectin (g/ml)	3.55 1.37	4.40 2.04	0.20
IL-6 (pg/ml)	1.68 2.87	1.33 1.59	0.70
CRP (mg/dl)	0.178 0.156	0.161 0.130	0.46
Hypertension (no.)	18	9	0.90
Diabetes mellitus (no.)	6	4	0.74
Hyperlipidemia (no.)	10	6	0.76
Current smoking (no.)	8	3	0.67

Data are expressed as mean SD.
OSA, obstructive sleep apnea.

nea in the volunteers was quantified by the 3% oxygen desaturation index (3%ODI), which was the number of oxygen desaturations of 3% or more below the baseline level per hour during sleep. This index correlates well with the conventional AHI (26). Subjects who had a 3%ODI of 5 were diagnosed as not having OSA. The 3%ODI of the 12 volunteers was 2.8 1.7 (range, 1.74–3.86).

The rates of hypertension, diabetes mellitus, hyperlipidemia, and current smoking habit among the non-OSA group were not significantly different from those among the 41 OSA patients (see Table 1). The BMI was significantly lower in the non-OSA group than in the OSA group. Therefore, the BMI was adjusted in the data analysis afterward. Blood samples were obtained from the non-OSA subjects at 8:00 in the morning after fasting beginning at 20:00 on the previous night.

This study was approved by the medical ethics committee of our university and was in accordance with the recommendations found in the Helsinki Declaration of 1975. All patients and subjects in the study groups provided written informed consent for participation in this study.

Polysomnography

Polysomnography was started at 21:00 and ended at 7:30 the following morning (see Fig. 1). Polysomnography was performed as previously described (4). Surface electrodes were attached by using standard techniques to obtain an electrooculogram, electromyogram of the chin, and 12-lead electroencephalograph. Sleep stages were defined according to the criteria of Rechtschaffen and Kales (29). Ventilation was monitored by inductive plethysmography (Respitrace: Ambulatory Monitoring; Ardsley, NY). Airflow was monitored by thermistors (Nihon Kohden, Tokyo, Japan) that were placed at the nose and the mouth. Arterial oxygen saturation (Sao_2) was monitored continuously with a pulse oximeter (Pulsox-24; Minolta, Osaka, Japan) (see Fig. 1).

Apnea was defined as a complete cessation of airflow at the nose and mouth that lasts for 10s. Hypopnea was defined as a decrease in thoracoabdominal motion of 50% that lasts for 10 sec and associated with a decrease in the baseline Sao_2 of 3% (1). All AHI values were expressed as the number of episodes of apnea and hypopnea per hour over the total sleep time. Lowest Sao_2 during sleep and percentage of time of Sao_2 90% during sleep also were calculated in each patient.

Respiratory disturbance index

The respiratory disturbance index (RDI) (27) was defined as (a) AHI in OSA patients and (b) 3% ODI in the volunteers.

Measurement of plasma/serum factors

Blood samples were drawn at 8:00 in the morning after the subjects had fasted beginning at 20:00 the previous night. Blood samples were centrifuged immediately at 3,000 rpm at 4°C for 10 min. The separated samples were stored at 80°C until assay. The plasma levels of TRX (Redox Bioscience, Kyoto, Japan; intra- and interassay coefficients of variation were 3.7% and 4.8%, respectively) and adiponectin (Otsuka Pharmaceuticals, Tokyo, Japan; intra- and interassay coefficients of variation were 4.1% and 4.7%, respectively) were measured with enzyme-linked immunosorbent assay. The plasma level of IL-6 (R&D Systems, Minneapolis, MN; intra- and interassay coefficients of variation were 7.8 and 4.6%, respectively) was measured with the chemiluminescent enzyme immunoassay. The serum levels of high-sensitivity CRP (Dade Behring, Liederbach, Germany; intra- and interassay coefficients of variation were 1.7% and 4.9%, respectively) were measured by nephelometry.

Data analysis

Data were expressed as mean SD. The data for each parameter did not show a normal distribution. The Mann–Whitney *U* test was used to compare two groups. Differences between two intervals were compared with the Wilcoxon signed-rank test. Correlation analyses were performed with Spearman's correlation coefficients (*Rs*). The BMI was significantly lower in the non-OSA group than in the OSA group. Therefore, multiple linear regression analysis was performed, with plasma TRX level as the dependent variable. Logarithmic transformation was performed on the plasma TRX levels to correct for the abnormal distribution of the values. This transformed variable was used in the model. The independent variables that were entered were BMI and OSA (presence or absence of OSA). Similarly, we performed multiple linear regression analysis with adiponectin, IL-6, and CRP levels as the dependent variables. Statistical analyses were performed by using StatView software for Windows (Version 5.0; Abacus Concepts, Berkeley, CA). A p value of 0.05 was considered to be significant.

RESULTS

Effect of OSA on biomarkers

The plasma TRX level was significantly higher in the 41 OSA subjects before nasal CPAP therapy than in the 12 non-OSA subjects (41.0 24.4 ng/ml *vs.* 23.9 14.7 ng/ml; p 0.02). Conversely, the plasma adiponectin level was significantly lower in the OSA subjects than in the non-OSA subjects (3.84 1.66 g/ml *vs.* 5.82 3.09 g/ml; p 0.02) (see Table 1 and Fig. 2). The serum CRP level was significantly higher in the OSA subjects than in the non-OSA subjects (0.172 0.147 mg/dl *vs.* 0.087 0.096 mg/dl; p 0.02), whereas the plasma IL-6 level did not significantly differ between the two groups (1.56 2.49 pg/ml *vs.* 0.99 0.94 pg/ml; p 0.77) (see Table 1 and Fig. 2).

We divided the 53 subjects into the RDI 40 not-severe OSA group (NS-OSA: n 26) and the 40 RDI very severe OSA group (VS-OSA: n 27). The plasma TRX level was significantly higher in the VS-OSA subjects before nasal CPAP therapy than in the NS-OSA subjects (p 0.002). The serum CRP and plasma IL-6 levels were also significantly higher in the VS-OSA subjects than in the NS-OSA subjects (p 0.05 and p 0.006). Conversely, the plasma adiponectin level was significantly lower in the VS-OSA subjects than in the NS-OSA subjects (p 0.03).

We also divided the subjects into the RDI 20 non-OSA (N-OSA: n 12), 20 RDI 40 moderate OSA (M-OSA: n 14),

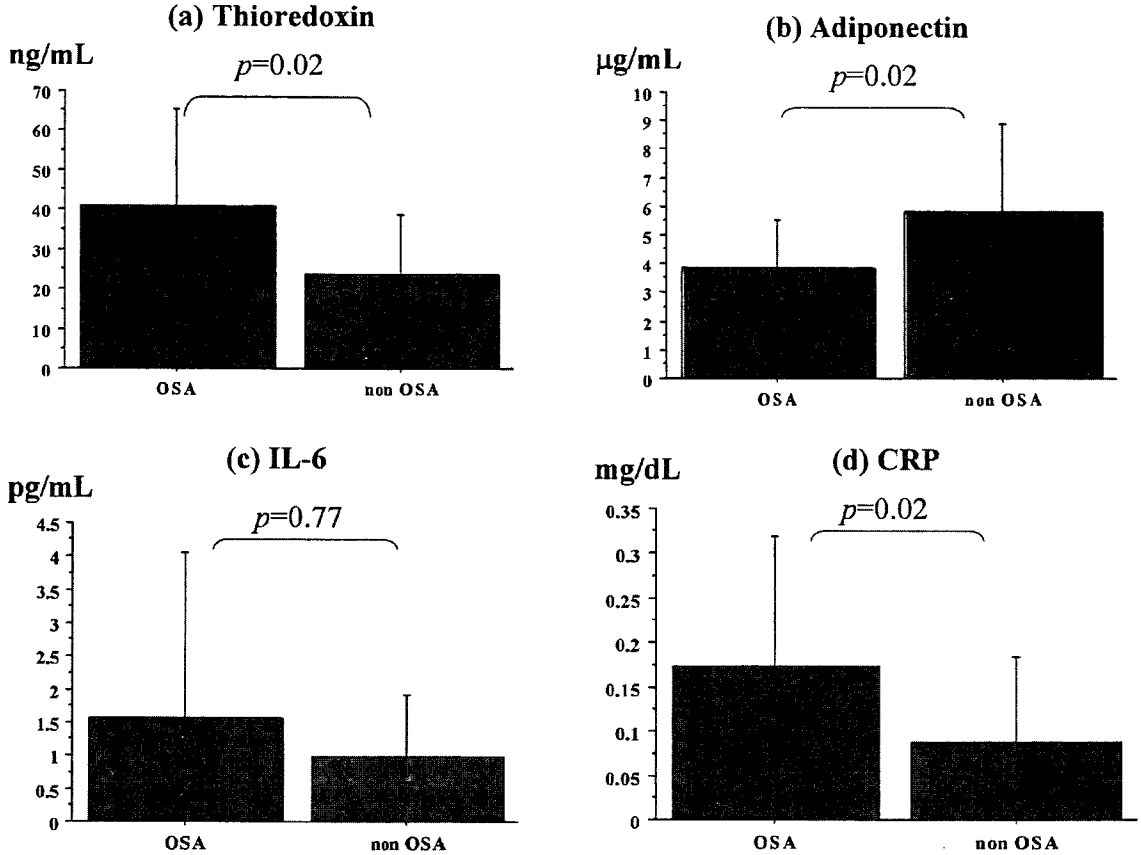

FIG. 2. Comparison of the plasma thioredoxin, adiponectin, IL-6, and serum CRP levels between the OSA group before nasal CPAP therapy and the non-OSA group. The plasma TRX level was significantly greater in the OSA group (n 41) than in the non-OSA group (p 0.02). Conversely, the plasma adiponectin level was significantly lower in the OSA group than in the non-OSA group (p 0.02). The serum CRP level was significantly greater in the OSA group than in the non-OSA group (p 0.02). The plasma IL-6 level did not differ significantly between the OSA and the non-OSA group (p 0.77). OSA, obstructive sleep apnea; IL-6, interleukin 6; CRP, C-reactive protein.

and 40 RDI severe OSA (S-OSA: n 27) groups. The plasma TRX level was significantly higher in the S-OSA subjects before nasal CPAP therapy than in the N-OSA subjects (p 0.004) and in the M-OSA subjects (p 0.02). The plasma TRX level was not significantly different between the M-OSA subjects before nasal CPAP therapy and the N-OSA subjects (p 0.5).

Relations between various parameters before nasal CPAP treatment and plasma TRX

The following correlation analyses were performed by using the baseline laboratory data of the 41 OSA subjects and the laboratory data of the 12 non-OSA subjects. The plasma TRX level was positively correlated with RDI (p 0.001; Rs 0.45) and the percentage of time with Sao_2 90% (p 0.0002; Rs 0.52) (Fig. 3). In addition, the plasma TRX level was positively correlated with the plasma IL-6 (p 0.009; Rs 0.36) and serum CRP levels (p 0.0002; Rs 0.51), and negatively correlated with the plasma adiponectin level (p 0.02; Rs 0.32) (Fig. 4). The adiponectin level was negatively correlated with RDI (p 0.01; Rs 0.35) and with the percentage of time with Sao_2 90% (p 0.04; Rs 0.29) (see Fig. 3). The plasma TRX level was not correlated with BMI (p 0.09; Rs 0.23), whereas the plasma adiponectin level (p 0.02; Rs 0.32) and the serum CRP level (p 0.0009; Rs 0.46) were significantly correlated with BMI (Fig. 5).

Multiple linear regression analysis was performed on the 53 subjects, with plasma TRX level as the dependent variable and BMI and OSA as the independent variables. BMI was not significantly associated with the plasma TRX level (p 0.45). Conversely, OSA was significantly associated with the plasma TRX level (p 0.04). The adjusted correlation coefficient (R) for the model was 0.36. After adjustment for BMI, age, and current smoking habit, the difference in plasma TRX levels between the OSA patients and non-OSA subjects was significant (p 0.04; R 0.38). The RDI was more significantly associated with the TRX level (p 0.02) than with the adiponectin level (p 0.13) independent of BMI (R 0.43). Moreover, after adjustment for BMI, age, current smoking habit, and co-

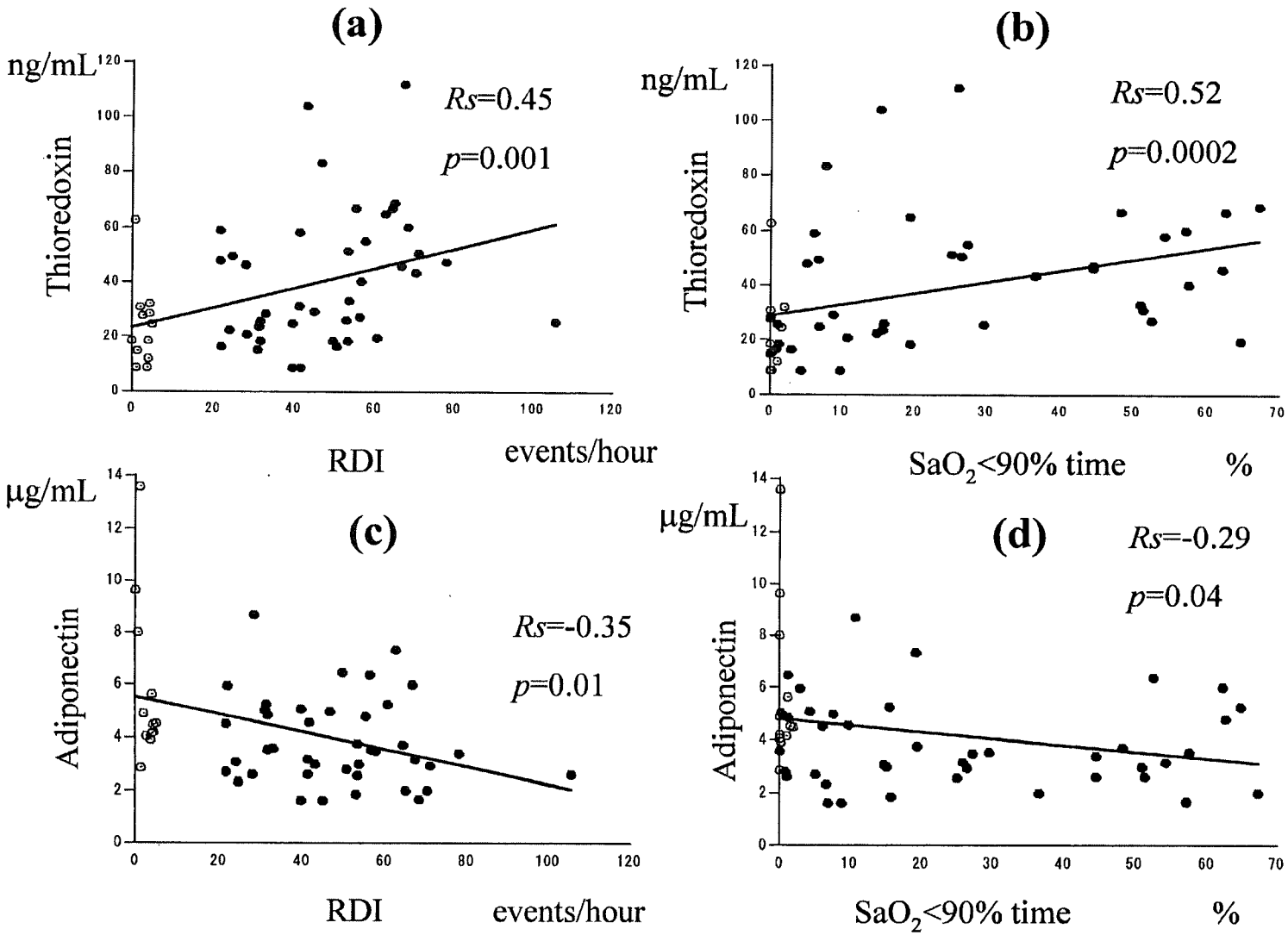

FIG. 3. Correlation analyses between the plasma thioredoxin or adiponectin level and RDI or Sao_2 90% of the time. The correlation analyses included the baseline laboratory data of the OSA subjects (*n* 41) and the laboratory data of the non-OSA subjects (*n* 12). The plasma thioredoxin level was positively correlated with RDI and with Sao_2 90% of the time. The plasma adiponectin level was negatively correlated with RDI and with Sao_2 90% of the time. *Solid circles*, OSA subjects, *n* 41; *open circles*, subjects in the non-OSA group, *n* 12. RDI, respiratory disturbance index; Sao_2, arterial O_2 saturation.

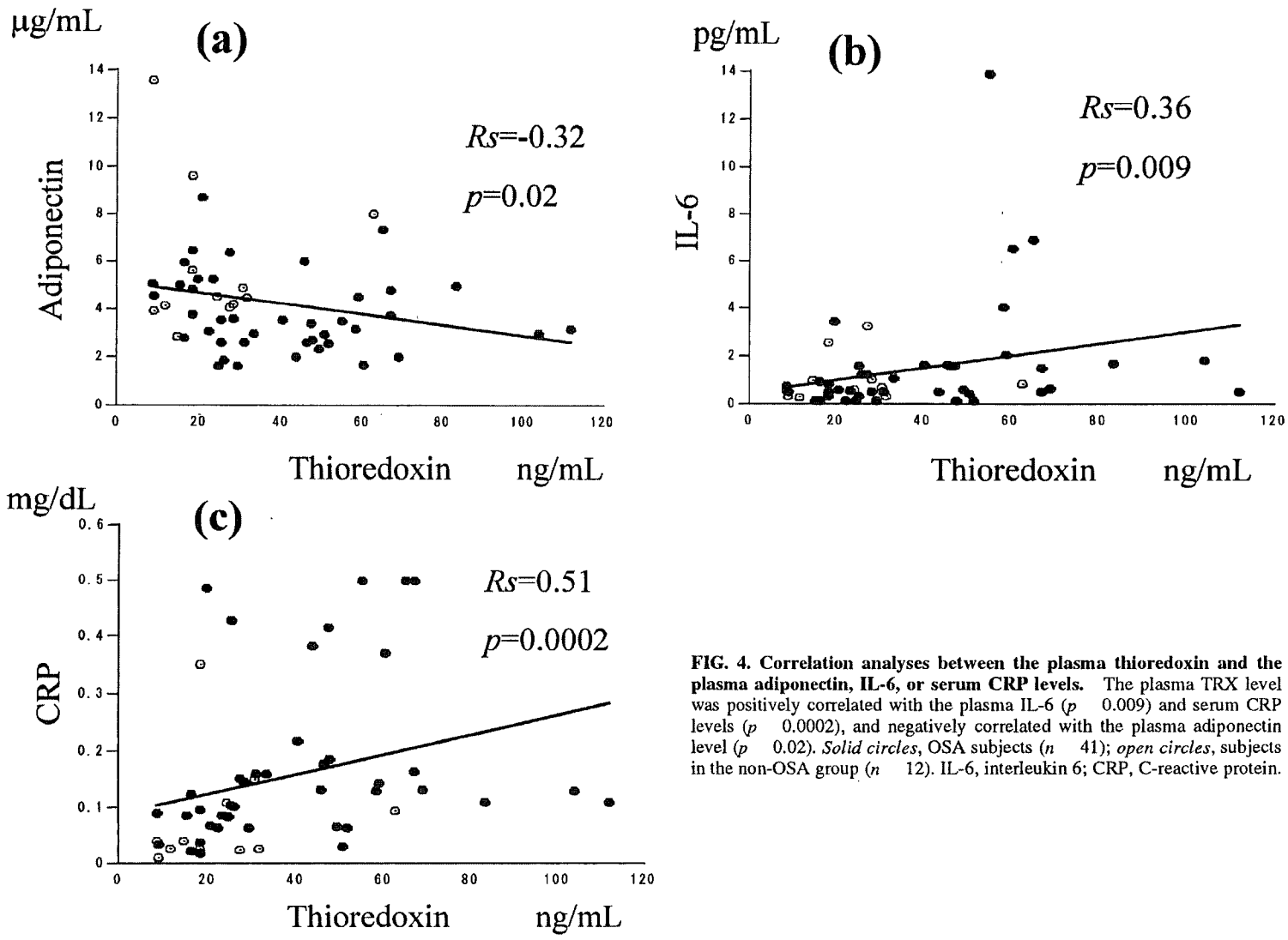

FIG. 4. Correlation analyses between the plasma thioredoxin and the plasma adiponectin, IL-6, or serum CRP levels. The plasma TRX level was positively correlated with the plasma IL-6 (p 0.009) and serum CRP levels (p 0.0002), and negatively correlated with the plasma adiponectin level (p 0.02). *Solid circles*, OSA subjects (n 41); *open circles*, subjects in the non-OSA group (n 12). IL-6, interleukin 6; CRP, C-reactive protein.

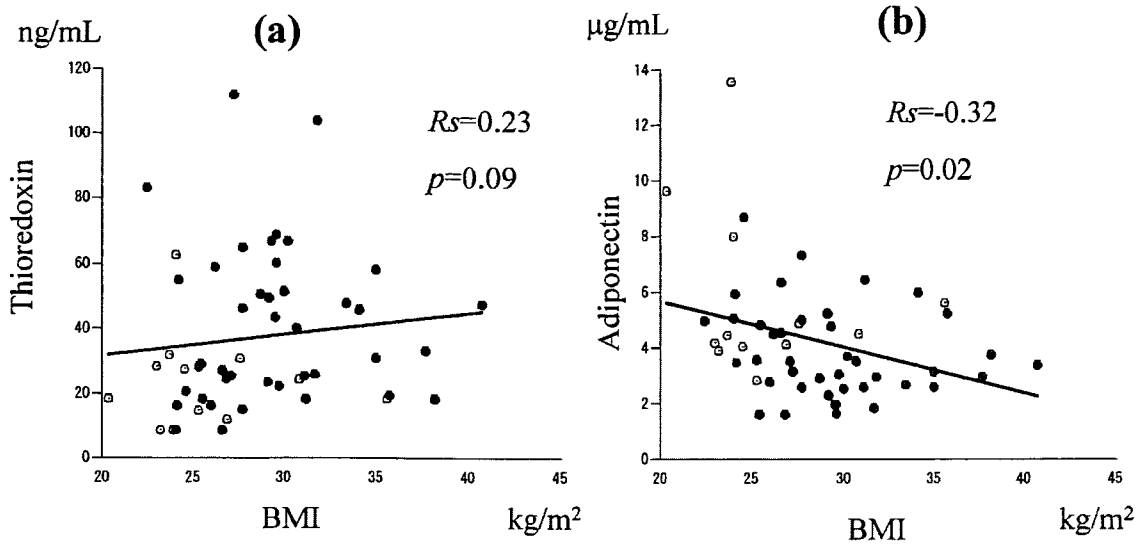

FIG. 5. Correlation analyses between BMI and the plasma thioredoxin or adiponectin level. The plasma adiponectin level, but not the plasma thioredoxin level, was negatively correlated with BMI. *Solid circles*, OSA subjects (*n* 41); *open circles*, subjects in the non-OSA group (*n* 12). BMI, body mass index.

morbidities, the difference in plasma TRX level between the OSA patients and non-OSA subjects was still significant (*p* 0.02; *R* 0.48). The plasma TRX level was not significantly associated with BMI (*p* 0.15), whereas it was significantly associated with RDI. (*p* 0.004; *R* 0.53).

Effect of nasal CPAP treatment on the biomarkers

In the OSA-treatment group, nasal CPAP for 1 month significantly improved nocturnal hypoxemia/reoxygenation parameters including the RDI (48.2 14.8 events/h to 1.81 1.21 events/h; *p* 0.0001), lowest nocturnal Sao_2 (65.2 16.5% to 88.1 4.04%; *p* 0.0001) and the percentage of time with Sao_2 90% (29.3 22.9% to 0.37 0.45% of time; *p* 0.0001). Although the BMI did not significantly change, the TRX, IL-6, CRP, and adiponectin levels changed significantly after 1 month of nasal CPAP use. The plasma TRX level (43.6 23.0 ng/ml to 33.3 20.8 ng/ml; *n* 27; *p* 0.03) significantly decreased after 1 month of nasal CPAP treatment. Conversely, the plasma adiponectin level (3.55 1.37 g/ml to 3.79 1.14 g/ml; *p* 0.03) significantly increased (Table 3, Fig. 6). The plasma IL-6 (1.68 2.87 pg/ml to 0.634 0.619 pg/ml; *p* 0.0008) and serum CRP levels (0.178 0.156 mg/dl to 0.120 0.120 mg/dl; *p* 0.01) also significantly decreased (see Table 3 and Fig. 6).

We performed correlation analyses between the "basal" serum TRX level before nasal CPAP treatment and the therapeutic response, such as the change in RDI or Pao_2. The TRX level was not correlated with the change in RDI (*p* 0.13; *Rs* 0.30), the change in lowest Sao_2 (*p* 0.99; *Rs* 0.003), or the change in the percentage of time with Sao_2 90% (*p* 0.11; *Rs* 0.31).

In the OSA-untreated group, the TRX, IL-6, CRP, and adiponectin levels did not significantly differ (all the *p* values

TABLE 3. CHANGES IN THE LEVELS OF MEDIATORS DURING THE MEASUREMENT INTERVAL IN THE OSA TREATMENT GROUP AND OSA UNTREATED GROUP

Variable		*First blood sample*		*Second blood sample*		p
Thioredoxin (ng/ml)	OSA treated	43.6	23.0	33.3	20.8	**0.03**
	OSA untreated	35.9	27.1	32.5	15.8	0.64
Adiponectin (g/ml)	OSA treated	3.55	1.37	3.79	1.14	**0.03**
	OSA untreated	4.40	2.04	4.30	2.06	0.29
IL-6 (pg/ml)	OSA treated	1.68	2.87	0.63	0.62	**0.0008**
	OSA untreated	1.33	1.59	0.94	0.58	0.78
CRP (mg/dl)	OSA treated	0.178	0.156	0.120	0.117	**0.01**
	OSA untreated	0.161	0.130	0.119	0.091	0.27

Data are expressed as mean SD.
OSA, obstructive sleep apnea.