臨床応用されている.

3. PDE5 阻害薬の肺高血圧に対する効果

PDE5 阻害薬の旗手としてED治療薬として臨床的に用いられたsildenafilは2005年にWHO機能分類II～IVの肺高血圧症(原発性肺高血圧症, 膠原病および先天性心疾患に伴う肺高血圧症)278例を対象に行われた無作為化二重盲検試験(RCT)で臨床症状, 運動耐容能, 肺血行動態の改善効果が認められ, 有用性が示された[6]. わが国では2008年1月に承認されている(レバチオ™). タダラフィルについてもRCTでの有用性が認められ[7], わが国でも2009年10月承認されている(アドシルカ™).

肺高血圧症診療の進歩には, 定期的に世界各地から国際的な研究者が集合し, up-to-dateな検討を重ね, 何らかの結論を出し, ガイドラインとして公表しているWHO公認の国際的な専門家会議の貢献が大きい. 最新の会議は2008年に米国カリフォルニア州ダナ/ポイントで開催され, 期待通りの成果を得ている. 改訂された新しいガイドライン[8]では, 重症度WHO機能分類II, IIIでSildenafilは推奨度A (強く推奨), TadarafilはB(通常の推奨), WHO機能分類IVではともにE/C(専門家の意見のみに基づいてやや推奨)とされており, 本特集他項のエンドセリン受容体拮抗薬と同様に重要な位置づけがなされている. 図2に肺動脈性肺高血圧症のエビデンスに基づく治療アルゴリズムを示す.

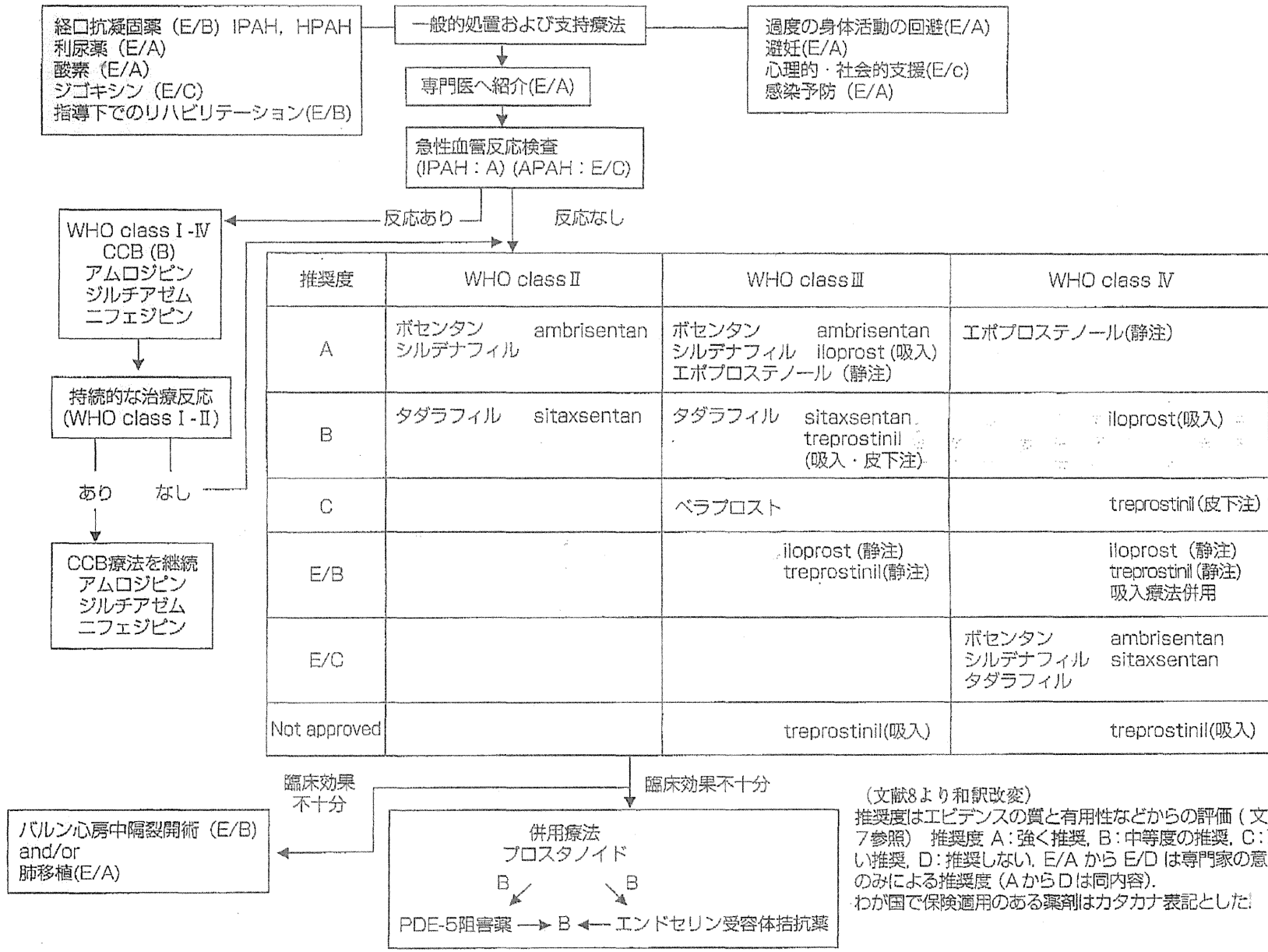
4. PDE5 阻害薬の臨床使用上の注意

PDE5 阻害薬はED治療薬としての臨床応用が先行しており, 症例の年齢などの背景から亜硝酸製剤との併用による心血管イベントの発症が強調された. NO産生を促すニトログリセリン, 亜硝酸アミル, 硝酸イソソルビド等との併用が過度の血管拡張作用を呈し血圧低下を招くことが機序となっている. PDE5 阻害薬の作用機序からみて理解しやすい副作用といえるが, シルデナフィル承認前後の副作用調査での頻度は不明である. 肺高血圧症では基礎に心疾患を合併している症例が多く, また症例によっては十分な監視の上でPDE5 阻害薬とNO吸入療法を併用することもある. シルデナフィルの場合, 一般的には潮紅, ほてりや動悸など1から5% 前後の頻度で認められ, 筋痛や頭痛も同等とされる. 特徴的なものはPDE6 阻害作用による霧視, 羞明などの眼症状で0.25% にみられる. このことはシルデナフィルのPDE5 阻害作用の選択特異性が低いことを示している. 2007年12月にシルデナフィルの使用による聴力の低下や喪失の危険性が米国で警告されているが, この機序は明らかではない.

PDE5 阻害薬は肝代謝で, CYP3A4 を誘導するリファンピシンやカルバマゼピンとの併用により効果が減弱し, CYP3A4 を阻害するイトラコナゾールやクラリスロマイシンとの併用による濃度上昇が認められる. したがって, グレープフルーツジュースの摂取には注意が必要である. また肺高血圧症治療薬のエンドセリン受容体拮抗薬ボセンタンはCYP3A4 を誘導するため, シルデナフィルとの併用ではシルデナフィルの血中濃度を低下させるが, ボセンタンの代謝に対してシルデナフィルは影響しないとされている.

シルデナフィルは内服後約1時間で血中濃度は最高となり, 約4時間効果が持続する. 一方, タダラフィルはその効果が30～36時間持続する. このため投与回数が1日1回ですみ, また, 食事の影響を受けないという利点がある. またPDE6 阻害作用はシルデナフィルの1/100と眼に対する危険性は低い. しかしタダラフィルは承認前の臨床試験において頭痛 (11.3%), 潮紅・ほてり (8.6%) など副作用の発現率が高く, また消化不良 (2.3%) なども目立ち, 慎重に両薬の使い分けをする必要がある.

PDE5阻害薬の保険適用としては, シルデナフィ



（文献8より和訳改変）
推奨度はエビデンスの質と有用性などからの評価（文献7参照） 推奨度 A：強く推奨，B：中等度の推奨，C：弱い推奨，D：推奨しない，E/A から E/D は専門家の意見のみによる推奨度（A から D は同内容）．
わが国で保険適用のある薬剤はカタカナ表記とした．

図 2. 肺動脈性肺高血圧治療アルゴリズム

ル，タダラフィルともに肺動脈性肺高血圧症とされている．前者は20 mg製剤を1日3回服用，後者は40 mg製剤を1日1回服用する．現在では，従来の原発性肺高血圧症の名称でなくより現実に則した分類がなされており，膠原病に合併する肺高血圧症も包含されている．肝疾患に伴う肺高血圧症も適応となるが，ボセンタンと異なりPDE5阻害薬は肝障害でも禁忌とはされていない．

5. 併用療法について

特発性肺動脈性肺高血圧症に対するプロスタグランジンI_2製剤，エポプロステノール持続静注法の有用性は，極めて予後の悪い本症の治療現場に光明を与えた．しかし簡便な治療法とはいえず，また効果の不十分な場合も少なくない．プロスタグランジンI_2のアナログであるベラプロストはRCTによる有効性の評価を得ている経口製剤であり，先述の新しいガイドラインでもWHO機能分類IIIの症例に対して推奨度C（弱い推奨）とされているが，長期連用により効果が消失するとされている[9]．

血管拡張薬として（体）高血圧症に頻用され安全性の面で保証されているカルシウム拮抗薬は，肺高血圧症に対して急性応答のみられない場合もあり，また長期連用で効果が消失することも多い．これに対して新規治療薬として大きな期待の中で次々と登場してきたエンドセリン受容体拮抗薬（ボセンタン，ambrisentan（治験中））や本項のPDE6阻害薬（シルデナフィル，タダラフィル）はそれぞれ単独でも有効性が認められ，またエポプロステノールやベラプロストなどのprostanoidとERA，prostanoidとPDE5阻害薬の併用効果についても期待されている．このうちPDE5阻害薬に関してわれわれはシルデナフィルとベラプロストの併用による相乗効果を実験的に認めている[10]が，臨床的にもシルデナフィルとエポプロステノールの併用のRCTで生存率向上を認めている[11]．ERAとPDE5阻害薬との併用は，先述のごとく代謝に影響するが，臨床上意味のある相互作用と確定されているわけではない．実際ボセンタン治療にタダラフィルを併用するRCTでは有用性が認められている．相互作用も含めた臨床上の有用性について最適の組み合わせは現時点では明らかではないが，経口薬で，十分な効果が持続的に得られることが望ましく，やはり有効な薬剤の開発とその併用療法の開発が期待される．

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全身性疾患としてのCOPD

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キーワード　慢性閉塞性肺疾患　全身性疾患　併存症

はじめに

慢性閉塞性肺疾患（COPD）は長期の喫煙歴をもつ中・高年者に発症する疾患であるために，喫煙や加齢に伴う種々の併存症をもっている場合が多い．また，COPD自体が肺以外への影響，いわゆる“systemic effect”をもたらし，種々の併存症を誘発することから全身性疾患として捉えられるようになった[1,2]．このことはGlobal Initiative for Chronic Obstructive Lung Disease（GOLD）[3]では，すでに2006年の改訂において，新たなCOPDの疾患概念として追記されており，肺以外の症状も個々の患者の重症度や生活の質（QOL）に影響を及ぼすため，併存症も含めた包括的重症度評価を行う必要があると記載されている．2009年に改訂された日本呼吸器学会の『COPD（慢性閉塞性肺疾患）診断と治療のためのガイドライン　第3版』[4]においても，病態生理の項目として，COPDの全身的影響が列記されている（表1）．本稿では，これらのCOPDの併存症について概説し，その対策についても言及する．

表1　COPDの全身的影響

- 全身性炎症：炎症性サイトカインの上昇，CRPの上昇
- 栄養障害：脂肪量，除脂肪量の減少
- 骨格筋機能障害：筋量・筋力の低下
- 心血管疾患：心筋梗塞，狭心症，脳血管障害
- 骨粗鬆症：脊椎圧迫骨折
- 抑うつ
- 糖尿病
- 睡眠障害
- 貧血

［日本呼吸器学会COPDガイドライン第3版作成委員会：COPD（慢性閉塞性肺疾患）診断と治療のためのガイドライン．第3版，メディカルレビュー社，東京，2009より引用］

Ⅰ．全身性炎症

COPD患者では肺の炎症のみならず全身性炎症が存在し，tumor necrosis factor-α（TNF-α）やinterleukin-6（IL-6）などの炎症性メディエーターやC反応性蛋白（CRP）の血中濃度の上昇が認められる[5]．全身性炎症は併存症としての栄養障害，骨粗鬆症，骨格筋機能障害，心血管疾患，代謝性疾患などの基盤病態として重視されている（図1）．全身性炎症を基盤とした複数の併存症がみられるという観点から，COPDを慢性全身性炎症症候群（chronic systemic inflammatory syndrome）と呼ぶことも提唱されている[6]．したがって，COPDを全身性疾患として治療する場合，全身性炎症の制御を目的とした治療の確立が必要となる．全身性炎症の発症機序として，肺で産生された炎症性サイトカインの“spillover”が想定されている[1]．肺においてのみTNF-αを過剰発現するトランスジェニックマウスにおいて，血中TNF-αレベルの著明な上昇と筋肉量の減少が認められている．

Systemic Effects in COPD
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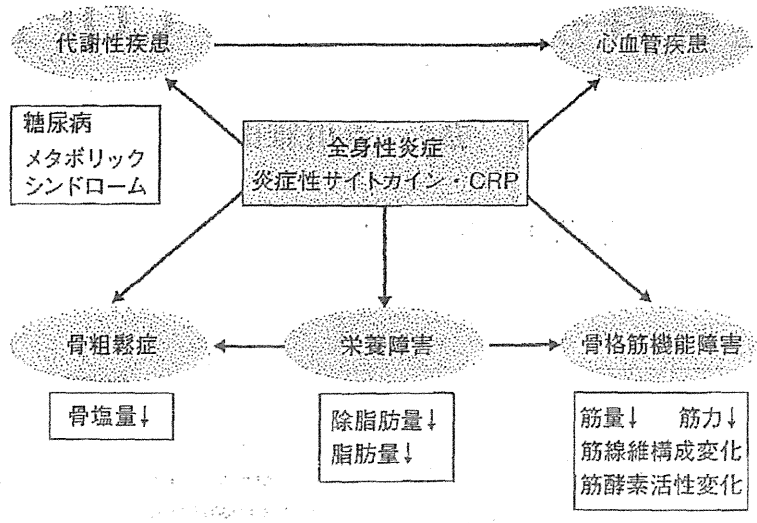

図1　COPDの全身性炎症とsystemic effect

一方，臨床的には誘発喀痰中のsoluble TNF receptor（sTNF-R55，sTNF-R75）およびIL-8濃度はこれらの血漿中濃度とは相関せず，肺局所と全身での炎症は異なった制御を受けている可能性も報告されている[7]．また，低酸素血症がTNF-α systemを活性化する機序も想定されており，現時点では全身性炎症の発症メカニズムは明確にされていない．コルチコステロイドの吸入や内服による血清CRPの低下，抗TNF-α薬であるインフリキシマブの投与，酸化ストレスに対するN-アセチルシステイン（NAC）の投与なども報告されているが，全身性炎症の発症メカニズムの解明とその対策は今後さらに検討されるべき課題である．

Ⅱ．栄養障害

COPD患者では栄養障害が高頻度に認められ，特に重症の気腫型COPDでは高度なことが多く，栄養学的介入の必要性が高い．わが国では気腫型COPD患者の約70%と，欧米に比較して高頻度に体重減少が認められる．また，体重減少は肺機能とは独立した予後因子となることが明らかにされている[3]．安定期のCOPD患者における軽度の体重減少では脂肪量（fat mass；FM）の減少が主体であり，中等度以上の体重減少患者では除脂肪体重（lean body mass；LBM）の減少も加わるマラスムス型の蛋白・エネルギー栄養障害を呈する[8]．栄養障害を示唆する体重，身体組成の変化はCOPD患者の肺機能や呼吸筋力，運動耐容能などの基本的な病態生理と密接に関連しており，QOL（生活の質）の低下や急性増悪，再入院のリスクとの関連も指摘されている．

また，体重減少は骨塩量の減少とも関連している[8]．栄養障害の原因として安静時エネルギー消費量の増大，全身性炎症，レプチンやグレリンなどの摂食調節ホルモンの異常などが関与している[8]．

近年，さまざまな経腸栄養剤や補助栄養食品が使用可能となっており，病態に応じた選択が必要となる．換気能からみた場合，換気不全による高炭酸ガス血症を伴えば，呼吸商の小さい脂質を主体とする栄養剤を考慮すべきである．一方，著しい換気障害がなければ炭水化物主体，脂質主体にかかわらず十分なカロリー補給を最優先する．抗炎症作用をもつω3系脂肪酸やコエンザイムQ_{10}の含有率の高い栄養剤の投与も推奨される[9]．蛋白合成促進と異化抑制作用のある分岐鎖アミノ酸（BCAA）の含有率の高い栄

養剤の有用性も報告されている．

呼吸リハビリテーションにおいて運動療法を実施する場合は，栄養治療も同時に行う必要がある．また，GOLDでも栄養補給療法単独では不十分であり，非特異的な蛋白同化作用を有する運動療法を併用すべきであると提言している．呼吸リハビリテーション中の栄養補給療法として，BCAA含有率が高い栄養剤の有用性が示唆されている．しかし，米国胸部専門医学会(ACCP)/米国心血管・呼吸リハビリテーション協会(AACVPR)やGOLD，および欧州静脈経腸栄養学会（ESPEN）などによるガイドラインでは，栄養補給療法の有効性や蛋白同化ホルモンの併用を支持するエビデンスはないとされており，randomized controlled trialの集積が必要と考えられる．

Ⅲ．骨粗鬆症

骨粗鬆症は骨量の減少と骨組織の微細構造の破綻により骨の脆弱性や骨折の危険性が高まる病態である．脊椎の圧迫骨折や腰痛などを来し，ADL（日常生活活動）やQOLが著しく低下する原因となる．COPD患者では喫煙，低酸素血症，低栄養，骨格筋量の減少，ビタミンDやカルシウム不足などが骨粗鬆症の合併要因となる．従来，副腎皮質ステロイド投与との関連が重視されていたが，投与されていない患者でも高率に脊椎圧迫骨折を合併することが報告されている．

気流閉塞は骨粗鬆症のリスクであり，重症の気流閉塞ではオッズ比が2.4倍に高まると報告されている[10]．また，CT画像における肺気腫の指標である低吸収領域（low attenuation area；LAA）の肺野全体に対する面積比（LAA%）がCT像から計測した椎体の骨密度の規定因子となることも報告されている[11]．TNF-α，IL-1，IL-6などの炎症性サイトカインは骨におけるコラーゲン産生を抑制し，骨吸収を促進することが知られており，COPDでみられる全身性炎症が骨粗鬆症を誘導する可能性も考えられる．以上のことから，COPD患者では骨粗鬆症の早期診断と骨量の維持や骨折の予防に留意すべきであり，活性型ビタミンD製剤やビスホスホネート製剤などによる薬物治療に加えて栄養治療や運動療法による包括的アプローチが必要と考えられる．

Ⅳ．骨格筋機能障害

COPD患者では骨格筋量の減少や質的変化に基づく骨格筋機能障害が認められる．下肢筋力の低下[12]や下肢筋量の減少[13]は運動耐容能の規定因子として重要である．また，筋線維の構成としては，健常人ではⅠ型筋線維（遅筋線維）の比率が高いのに比べ，COPD患者ではⅠ型筋線維の低下と，Ⅱ型筋線維（速筋線維）の増加，特にⅡb型筋線維の増加が認められる．また，重症になるほどⅠ型筋線維の低下が進行し，筋断面積も減少する．さらに，骨格筋での好気的エネルギー産生に必要な酸化酵素活性が低下しており，これが運動早期における動脈血中の乳酸の上昇や運動能の低下と関連している[14]．

また，炎症性メディエーターであるTNF-αは骨格筋細胞のアポトーシスを誘導することによって筋肉量の減少をもたらす．また，体重減少患者では下肢運動筋における誘導型一酸化窒素合成酵素（iNOS）やnuclear factor kappa B（NF-κB）の発現が亢進しているため，筋蛋白合成の減少やアポトーシスの亢進がみられ，筋肉量の減少が進行する[15]．血中IL-6の上昇やCRPの上昇が筋力低下や運動能の低下と関連することや，IL-8が大腿筋力と負の相関を示すことも報告されている．さらに，全身性炎症の程度が呼吸リハビリテーションの効果を規定する要因であることも示唆されている[16]．以上から，COPD患者の骨格筋では質的変化に加えて，全身性炎症が機能障害の原因となり，運動能の低下にも関与していると考えられる．

V. 心血管疾患

COPDは虚血性心疾患の独立した危険因子の1つとして挙げられている．また，不整脈の合併が多く，対標準1秒量（%FEV_1）の低下は心房細動の発症を増加させるとの報告もある．さらに，脳血管障害の発症リスクと%FEV_1の低下との関連も報告されている．CRPの上昇が心血管疾患の合併や死亡と関連することから，全身性炎症がその原因として重視されている．欧米のCOPD患者では心血管疾患による死亡が多く，死亡原因の20～30%を占めている[17]．特に軽症，中等症でその傾向が顕著に認められる．一方，わが国では呼吸不全死が65～70%を占めている．わが国で心血管疾患による死亡が少ない機序として，気腫型COPDが高率であり，肺過膨張と関連して抗動脈硬化作用や抗炎症作用をもつアディポネクチンの血中濃度が上昇していることが示唆されている[18]．

VI. 代謝性疾患

COPDは糖尿病発症の危険因子であり，相対危険率が1.8倍との報告がみられる[19]．また，半数近いCOPD患者が複数のメタボリックシンドローム（metabolic syndrome；MS）の要素をもつことも指摘されている[20]．一般的に全身性炎症は糖代謝異常やインスリン抵抗性を惹起しMS発症につながるメカニズムとして重視されている．TNF-αの上昇とNF-κBの活性化は相互に炎症や酸化ストレスを増幅し，結果的にインスリン抵抗性を生じる．さらにインスリンや遊離脂肪酸もNF-κBを活性化する．それに対し，脂肪細胞から分泌されるアディポネクチンはインスリン感受性を改善することにより抑制的に作用する．これらの炎症過程はMSと共に動脈硬化を促進し，心血管イベントの発症要因となる．

わが国におけるCOPD患者では欧米と比較して過体重が低頻度であり，しかもアディポネクチンの高値が想定されることから，糖尿病やMSの合併も欧米よりも低率であると推測されるが，phenotypeの違いも含めた詳細な疫学的検討が必要である．

COPD患者では全身性炎症を基盤とする心血管疾患や代謝性疾患を合併するという観点から，抗炎症効果を有する薬物治療の有効性が期待される．最近，スタチンの抗炎症効果が注目されており，COPD患者の心血管イベントを抑制し，予後を改善することが報告されている．吸入ステロイドと長時間作用型β_2刺激薬の併用が心血管疾患に対して有効であることも報告されている．

VII. 消化器疾患

COPD患者では消化性潰瘍の合併頻度が20～40%と高率であり，発症機序として低酸素血症，高炭酸ガス血症，喫煙，低栄養，治療薬剤（メチルキサンチン，β_2刺激薬，ステロイド薬）などの関与が想定されている．また，肺過膨張による横隔膜の平定化や胸郭拡大，横隔膜筋量の減少などにより下部食道括約筋の機能が低下するため，胃食道逆流症（gastroesophageal reflux disease；GERD）を合併することがある．COPD患者ではGERDの合併率が高く，急性増悪のリスクになる可能性が報告されている[21]．

VIII. 抑うつ

COPD患者では高率に不安や抑うつなどの精神症状を合併する[22]．その原因として疾患の進行に伴う機能的障害や呼吸困難による日常生活の制限，さらに社会的な孤立感や疎外感などが挙げられている．不安と抑うつは患者の訴えの増加につながりQOLを低下させるとともに，過剰な医療機関受診や薬剤使用とも関連する．また，急性増悪や死亡率との関連も報告されてい

る．

おわりに

COPDは全身性炎症，栄養障害，骨粗鬆症，骨格筋機能障害，心血管疾患，糖尿病，消化器疾患，抑うつなどさまざまな併存症を伴う全身性疾患である．呼吸機能障害に対する薬物治療のみならず，全身性疾患としての観点から病態や重症度を評価し，包括的な治療戦略を構築することがQOLや予後の改善に重要である．

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所在の変わる皮膚および関節の疼痛を訴えた肺トキソカラ症の1例

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Key Words：toxocariasis，皮下疼痛，関節痛，幼虫ES抗原

はじめに

今回，われわれは所在の変わる皮膚および関節の疼痛を訴えた肺トキソカラ症（肺T症）と考えられる1例を経験したので報告する。

症　例

42歳，女性，主訴は関節痛。既往歴は20歳時片頭痛，家族歴は姉が関節リウマチ，父が糖尿病。15本/日×23年間の喫煙歴あり。飲酒歴は機会飲酒。2000年にハワイ渡航歴あり。室内犬（チワワ）を飼育し2008年4月に自宅で出産。7月上旬から右膝痛が出現，左腋窩部痛および左手関節腫脹を伴うようになり近医を受診。膠原病を疑われた。経過観察中に関節腫脹は軽快したが，皮下疼痛は持続，左腋窩部から左肘関節内側へ移動した。さらに，右肘

A Case of Pulmonary Toxocariasis with Migrating Dermal Pains and Arthralgia

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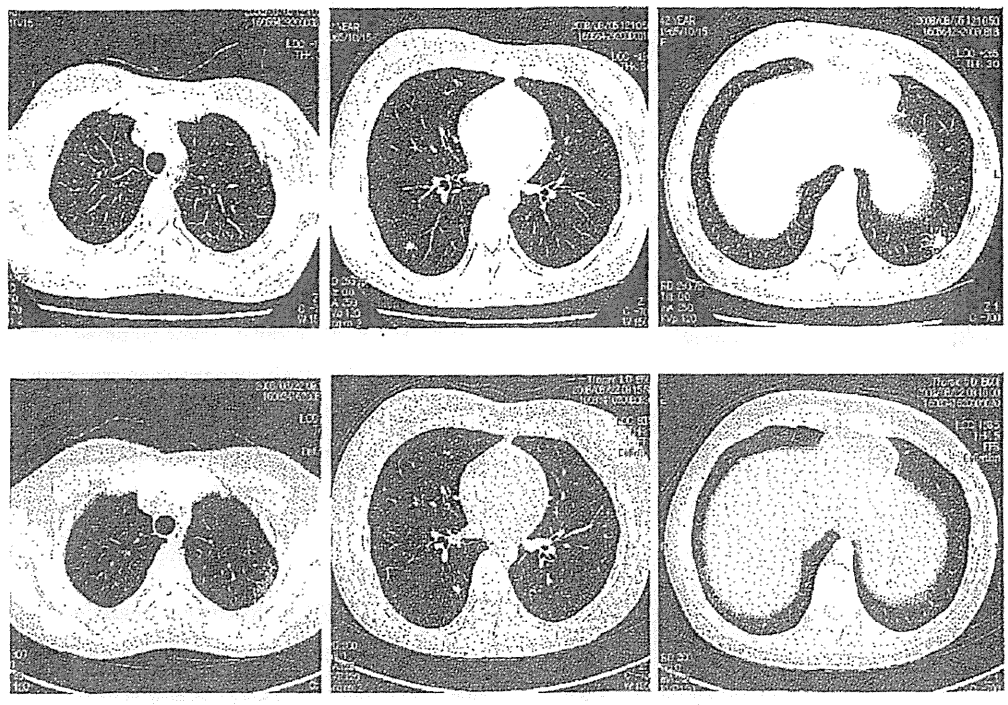

上段　2008/8/5　前医での胸部 CT　スリガラス影を伴う結節影が散在
下段　2008/8/22　当院での胸部 CT　前回の陰影は消失し，新たな陰影の出現を認める

図1　胸部 CT 像

関節内側皮下や腰や頚部皮下にも所在の変わる疼痛も自覚した。血液検査では好酸球増多，抗核抗体陽性（リウマチ因子は陰性），IgE 高値，胸部 XP・CT では両肺に多発結節影を認め，8 月 19 日当院へ入院となった。入院時には，皮下疼痛および関節痛は持続していたが，皮膚病変は認めず，関節腫脹もすでに消失し，身体理学所見では明らかな異常は認めなかった。血液検査では末梢血白血球数 12,200/μl（好酸球分画 33％），IgE 6,809U/ml，抗核抗体＞2,560 倍。胸部 CT（図 1）では肺野に周辺にスリガラス影を伴う多発性小結節影を認めた。

入院後の胸部 CT では，当初認めた結節影は消失し，新たに結節影およびスリガラス陰影の出現を認めた。8 月 29 日気管支鏡検査を行い肺胞洗浄液採集，肺生検を施行したが特異的所見は得られなかった。一方，寄生虫抗体スクリーニング dot-ELISA（SRL）では，イヌ回虫とブタ回虫に陽性を示した。イヌ回虫幼虫排泄（TcLES）抗原を用いた 3 試験（toxocaraCHECK，寒天ゲル内二重拡散法，plate-ELISA 法）はいずれも陽性で，リコンビナント TcLES 抗原を用いた plate-ELISA も陽性であった。特徴的胸部画像所見，血清検査成績，仔犬飼育歴の存在より肺 T 症と診断した。

診断後アルベンダゾール（ABZ，エスカゾール）600mg/ 日投与を開始。2 週間の ABZ 治療にて関節や皮膚の症状は速やかに改善したが，胸部病変は完全には消失せず，消退および新出現を繰り返した。初回 ABZ 終了後の 4 ヵ月間に，さらに 3 週間および 2 週間の追加投与を間欠的に行い，肺病変は消失し，徐々に好酸球数，IgE 値も低下した。3 回の ABZ 治療中に軽度のトランスアミナーゼ値上昇を認めたが，いずれも投与終了とともに速やかに正常値に復した。

考　察

Beaver らは，ヒトを固有宿主としない線虫の幼虫が，ヒト体内に幼虫のまま生存し諸臓器を移行して生じる様々な症状を示す病態を総称して内臓幼虫移行症（Visceral larva migrans，VLM）とした[1]。T 症（Toxocariasis）は，イヌ回虫（*Toxocara canis*）あ

るいはネコ回虫（*Toxocara cati*）の幼虫による内臓幼虫移行症であるが，本症例は，室内飼育犬の出産2～3月後より体調の不具合を感じていることから，イヌ回虫幼虫感染によるT症と考えられた。飼育犬の糞便からは親犬，仔犬（検査時5ヵ月齢）のいずれからもイヌ回虫虫卵を検出しなかったが，すでに消化管内に成虫は存在しなかったためと考えられた。

肺や肝臓が侵される内臓型T症の典型例では，発熱，倦怠感，咳嗽などの諸症状を伴うが，多くは潜在例で自覚症状は軽微あるいは無症状であることが多い[2]。本肺T症例でも，呼吸器関連症状はなく，むしろ皮膚および関節症状が医家受診に至る契機となった。T症における関節痛の頻度は，Paludoらの Toxocara IgG 抗体陽性小児の 118 例の検討によると 1.7%と高いものではないが[3]，免疫機能（Th1/h2 バランス）に影響する蠕虫感染では，潜在する免疫異常を修飾して関節リウマチ類似関節炎症状を呈する可能性も十分あると思われる[4][5]。本症例では，ABZ 治療により抗核抗体価が低下傾向を示した。また，所在の変わる皮下疼痛の訴えも極めて稀で，所在が変わって移動したこと，および ABZ 治療に反応して消失したことより原疾患関連症状であろうと考えている。

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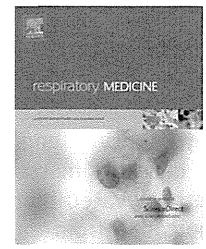

Associations between alcohol consumption and sleep-disordered breathing among Japanese women

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KEYWORDS
Alcohol consumption;
Women;
Sleep-disordered breathing;
Epidemiology

Summary
Background: The associations between alcohol consumption and sleep-disordered breathing in women are uncertain.
Methods: We conducted a cross-sectional study of 3113 women aged 30–69 years. The 3% oxygen desaturation index (3%ODI), based on overnight pulse oximetry findings, was selected as an indicator of sleep-disordered breathing.
Results: 3%ODI frequencies of ≥5 were higher for drinking women with ethanol intakes of ≥23.0 g/d than for never drinkers: the respective multivariable odds ratios and 95% confidence intervals was 1.8(1.0–3.4). The corresponding odds ratio was 3.0(1.6–5.8) for habitual snoring. The associations of ethanol intakes of ≥23.0 g/d with 3%ODI ≥ 5 was more evident among women with BMI <23.0 kg/m^2 (median) than those with higher BMI but did not vary by habitual snoring. The multivariable odds ratios of 3%ODI ≥ 5 for women with ethanol intakes of ≥23.0 g/d versus never drinkers were 2.7(1.0–6.7) for lower BMI and 1.5(0.6–3.3) for higher BMI and the corresponding odds ratio were 2.8(1.6–7.2) and 3.2(1.3–7.9) for habitual snoring, respectively.
Conclusion: Alcohol consumption was associated with higher prevalence of sleep-disordered breathing among Japanese women.

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Introduction

Sleep-disordered breathing (SDB) is associated with risk of hypertension[1] and cardiovascular disease[2] as well as with all causes of mortality.[2,3] Alcohol consumption is associated with elevated morning blood pressure levels[4] and risk of mortality from cardiovascular disease.[5] Previous clinical studies reported that alcohol consumption prior to bedtime was associated with an increase in the number and duration of hypopnea and apnea occurrences in snorers or sleep-disordered breathing patients,[6–8] and required higher levels of continuous positive airway pressure (CPAP) to prevent apnea and hypopnea.[9] However, it is not yet clear to what extent alcohol consumption by women is associated with risk of SDB. Several previous epidemiological studies found that alcohol consumption was associated with snoring for men[10,11] and for men and women combined.[12] However, such an association with SDB was observed only in men,[13–15] but not in women[15] or in men and women combined.[16,17] Further, a previous study of Japanese men showed that this association was more evident in men with low BMI than in those with high BMI.[14]

To examine the associations between alcohol consumption and sleep-disordered breathing specifically among Japanese women, we conducted a large community-based study.

Methods

Study population

The Circulatory Risk in Communities Study (CIRCS) is a dynamic community cohort study of Japanese covering five communities in Japan.[18] The CIRCS underwent sleep investigation in three communities: Yao City, Osaka Prefecture; Ikawa town, Akita Prefecture; and Kyowa town, Ibaraki Prefecture from 2001 to 2005. The participants of 981 women from the district of Yao (recruitment rate among the cardiovascular survey participants = 78% for women), 608 women from Ikawa (85%), and 1559 women from Kyowa (78%) were available for the present sleep study with satisfactory recording by a pulse-oximeter. Also, women with self-reported history of stroke or coronary heart disease (n = 35) were excluded because they were likely to change their lifestyles. The data for 3113 women aged 30–69 years were used for the analysis. The study protocol was approved by the Medical Ethics Committees of the University of Tsukuba, Osaka University and the Osaka Medical Center for Health Science and Promotion. Informed consent was obtained from the community representatives to conduct an epidemiological study based on guidelines of the Council for International Organizations of Medical Science.[19]

Measurement of cardiovascular risk factors

Height in stocking feet and weight in light clothing were also measured, and body mass index (BMI) was calculated as weight (kg)/height (m^2). Interviews were conducted to ascertain the frequency of snoring (often, sometimes, never, unknown), number of cigarettes smoked per day, ethanol intake per day, and past histories of sleep apnea, stroke and coronary heart disease.

Persons who replied "often" for snoring over the previous three months were labeled as suffering from habitual snoring. Persons who smoked one or more cigarettes per day were defined as current smokers and those who had not smoked for 3 months or more were defined as former smokers, while both never smokers and occasional smokers were regarded as non-smokers because the latter are very rare in Japan. The usual weekly alcohol intake was assessed in units of "*go*", a Japanese unit of volume corresponding to 23 g ethanol, which was then converted to grams of ethanol per day.[4,14] One "*go*" is equivalent to 180 ml of sake and corresponds to one bottle (633 ml) of beer, two single shots (75 ml) of whiskey, or two glasses (180 ml) of wine. Subjects who drank >8 g of ethanol per week were considered to be current drinkers and those who had not drunk for 3 months or more were defined as former drinkers.

Assessment of sleep-disordered breathing

Arterial oxygen saturation during one night of sleep at home was measured with a pulse-oximeter (PULSOX-3Si; Minolta Co., Osaka, Japan). The device stores values of peripheral blood oxygen saturation by performing a moving average for the last 5 s, updated every second. This sampling time was short enough to avoid the underestimation of oxygen desaturation.[20] The stored data were downloaded to a personal computer via an interface (PULSOX IF-3; Minolta) and analyzed using proprietary software supplied with the equipment (DS-3 version. 2.0a; Minolta) and the records reviewed by trained physicians. The oxygen desaturation index (ODI) was calculated based on frequency of ≥3% reductions in arterial oxygen saturation during sleep. The 3% ODI as an indicator of sleep-disordered breathing described in previous studies[14,21] was also used for this study. It represents the number of events per hour of adjusted measurement time in which blood oxygen decreases by ≥3%. The individuals filled out a sleep diary in order to exclude waking time from the analysis to minimize the potential overestimation of sleep duration. All data were reviewed by trained physicians and total recording time less than 4 h or the artifact likely due to frequent body movement or inadequate fitting of the probe were excluded. Overall 3%ODI was established as the mean value of 3%ODIs over at least a 4-h period of sleep as measured by pulse oximetry. The sleep-disordered breathing was defined in terms of 3%ODI level as ≥5 events per hour and the 3%ODI <5 was used as the reference category. A previous validity study reported that sensitivity was 80% and specificity 95% for 3%ODI ≥5 to detect an apnea-hypopnea index (AHI) of ≥5 by full polysomnography.[22]

Statistical analysis

Age-adjusted population characteristics according to categories of drinking status (never, former, and ethanol intakes of <23.0 and ≥23.0 g/day) were calculated by using analysis of covariance and the chi-square test. Logistic regression analysis was used to estimate the odds ratio of the

prevalence of 3%ODI $\geq$ 5 and habitual snoring according to categories of ethanol intake. The potentially confounding variables were age (year), BMI (kg/m^2), smoking status (never, ex- and current smoking), and communities (Yao, Ikawa, and Kyowa). The associations of alcohol consumption with 3%ODI $\geq$ 5 and habitual snoring were examined and stratified by using the median BMI (<23.0 and $\geq$23.0 kg/m^2). The significance for interactions by body mass index was tested by using the cross-product terms of ethanol intake and body mass index categories in multivariable models.

All statistical analyses were performed with SAS version 9.1.3 software (SAS Institute Inc., Cary, NC). All probability values for statistical tests were two-tailed, and values of $p < 0.05$ were regarded as statistically significant.

Results

The proportion of sleep-disordered breathing equivalent to 3%ODI $\geq$ 5 were 17.4% for total subjects aged 30–69 years, 17.5% for never drinkers, and 23.9% for women with ethanol intake of $\geq$23.0 g/d. The respective proportion of habitual snoring was 10.5%, 10.1% and 23.5%. Compared with never-drinking women, women with ethanol intake of $\geq$23.0 g/d were younger, showed higher mean values of 3%ODI and were more likely to smoke. Mean body mass index did not differ between women with ethanol intake of $\geq$23.0 g/d and never-drinking women (Table 1).

The proportions of sleep-disordered breathing and habitual snoring were higher for women with ethanol intake of $\geq$23.0 g/d compared with never drinkers (Table 2). The multivariable odds ratios of these outcomes were 1.8 (1.0–3.4) and 3.0(1.5–5.8), respectively.

We also examined the association of drinking status with sleep-disordered breathing and habitual snoring, stratified by median BMI (BMI <23.0 versus $\geq$23.0 kg/m^2) (Table 3). The association between ethanol intake and sleep-disordered breathing were more evident among women with lower BMI than those with higher BMI although the interaction by BMI did not reach the levels of statistical significance ($p = 0.23$).

The multivariable odds ratios of 3%ODI $\geq$ 5 for ethanol intakes of $\geq$23.0 g/d versus never drinking were 2.7 (1.0–6.7) for lower BMI and 1.5(0.6–3.3) for higher BMI. The association between ethanol intake and sleep-disordered breathing did not vary by habitual snoring.

Discussion

In our study of a general population of 3113 Japanese women, we found that ethanol intakes of $\geq$23.0 g/d were associated with approximately 2.0-fold higher prevalence of sleep-disordered breathing equivalent to 3%ODI $\geq$ 5.

To the best of our knowledge, this is the first study to show an association between alcohol consumption and higher prevalence of sleep-disordered breathing among a general population of Japanese women. Our findings are in agreement with the results of clinical experimental studies, which demonstrated an increase in mean AHI,[6] increased frequency of arterial oxygen desaturation[7,8] and the need for higher continuous positive airway pressure to eliminate snoring[9] after the ingestion of alcohol prior to bedtime. The adverse effects of alcohol on SDB are narrowing of the pharyngeal airways and an increase in nasal resistance,[23] selective reduction in hypoglossal motor nerve activities,[24] and diminished arousal response.[7]

Our study showed that the association of alcohol consumption with sleep-disordered breathing equivalent to 3%ODI $\geq$ 5 was more evident among women with lower BMI (<23.0 kg/m^2) than those with higher BMI. The Wisconsin Sleep Cohort Study found no association between alcohol consumption and SDB among 645 women.[15] In that study, however, they did not conduct a stratified analysis by BMI, whose mean BMI was much higher (31 kg/m^2) than that in our present population (23.0 kg/m^2). This suggests that the strong effect of excess weight on sleep-disordered breathing may mask a moderate effect of alcohol consumption. Further, compared with whites, Asians tend to have a lower position of the hyoid bone and shorter dimension of the posterior airway space,[25] Japanese may have a higher risk of sleep-disordered breathing than whites when they drink habitually. Moreover, the positional sleep apnea occurs more commonly in the less obese subjects.[26] In addition, we previously reported a positive association between alcohol consumption and sleep-disordered breathing among Japanese men: the multivariable OR of 3%ODI $\geq$ 5 was 1.95 (1.15–3.31) for ethanol intake $\geq$1.0 g/d per kg for men aged 40–69 years.[14]

Table 1 Age-adjusted mean and prevalence of selected cardiovascular risk factors among 3113 Japanese women aged 30–69 years.

	Total subjects	Never drinkers	Ex-drinkers	Ethanol intake, g/day	
				<23.0	≥23.0
No.	3113	2368	174	492	79
Age, years	55.5	56.1	54.3†	53.0‡	52.7‡
3%ODI, episodes/h	3.0	3.0	2.8	2.9	3.9*
Subjects with 3%ODI ≥ 5, %	17.4	17.5	17.7	16.0	23.9
Habitual snoring, %	10.5	10.1	10.4	10.7	23.5‡
Body mass index, kg/m^2	23.3	23.4	23.3	22.8†	23.1
Current smokers, %	5.8	3.5	19.2‡	7.6‡	34.6‡

*$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$, are compared with never drinkers. Habitual snoring: snoring "often" over the last three months.

Table 2 Multivariable odds ratios and 95% confidence intervals of sleep-disordered breathing and habitual snoring according to alcohol consumption.

	Never drinkers	Ex-drinkers	Ethanol intake, g/day	
			<23.0	≥23.0
Total number	2368	174	492	79
3%ODI ≥ 5, No.	428	29	68	17
Age-adjusted OR	1.0	1.0 (0.7–1.5)	0.9 (0.7–1.2)	1.6 (0.9–2.8)
Multivariable OR	1.0	1.0 (0.6–1.6)	1.0 (0.8–1.4)	1.8 (1.0–3.4)*
Habitual snoring, No.	205	15	46	15
Age-adjusted OR	1.0	1.0 (0.6–1.8)	1.1 (0.8–1.5)	2.7 (1.5–5.0)†
Multivariable OR	1.0	1.0 (0.5–1.7)	1.1 (0.8–1.6)	3.0 (1.6–5.8)*

*$p < 0.05$, †$p < 0.01$ compared with never drinkers.
Multivariable adjustment: age (year), body mass index (kg/m^2), smoking status (never, ex- and current smoking), and community.

Table 3 Multivariable odds ratios and 95% confidence intervals of 3%ODI ≥5 according to alcohol consumption by median BMI subgroups.

	Never drinkers	Ex-drinkers	Ethanol intake, g/day	
			<23.0	≥23.0
Total number	2368	174	492	79
BMI < 23.0 kg/m^2	1150	84	285	40
3%ODI ≥ 5, No.	118	7	18	7
Multivariable OR	1.0	0.9 (0.4–2.1)	0.7 (0.4–1.2)	2.7 (1.0–6.7)*
Habitual snoring, No.	62	5	15	7
Multivariable OR	1.0	1.0 (0.4–2.7)	0.9 (0.5–1.6)	2.8 (1.1–7.2)†
BMI ≥ 23.0 kg/m^2	1218	90	207	39
3%ODI ≥ 5, No.	310	22	50	10
Multivariable OR	1.0	1.0 (0.6–1.7)	1.2 (0.8–1.9)	1.5 (0.6–3.3)
Habitual snoring, No.	143	10	31	8
Multivariable OR	1.0	0.9 (0.5–1.9)	1.4 (0.9–2.1)	3.2 (1.3–7.9)†

*$p < 0.05$, †$p < 0.01$ compared with never drinkers.
Multivariable adjustment variables are similar as shown in Table 2.

A major strength of our study is the use of a large general population sample, which has the advantage of providing a more realistic estimation for the association between alcohol consumption and sleep-disordered breathing than can be attained with hospital or laboratory studies, because the subjects can maintain regular daily habits such as sleeping or alcohol consumption. Also, SDB[14] and cardiovascular risk factors[27–29] were measured with standardized methods with proven satisfactory reliability and precision.

The limitation of our study is that since we used pulse oximetry to evaluate sleep-disordered breathing, we could not accurately ascertain the severity of SDB, sleep architecture changes, relationships with REM sleep, sleep fragmentation and positional nature of hypoxia, while the sensitivity was 80% and specificity 95% for 3%ODI ≥ 5 to detect an AHI ≥ 5 by full PSG.[22] Second, pulse oximetry inherently underestimates respiratory disturbance events during sleep compared with measurements obtained with full PSG, particularly for non-obese subjects such as those studied here (mean BMI = 23.6 kg/m^2). In fact, one study found that, for the 3%ODI of ≥5 to screen for AHI ≥5/h by PSG, the sensitivity was 68% for subjects with BMI ≤ 27.0 kg/m^{2}and 94% for those with BMI > 27.0 kg/m^2.[22] Third, we conducted the multivariable analysis to examine relationships between alcohol consumption and sleep-disordered breathing, but we have no data on potential confounding factors such as income, pulmonary disease, psychiatric disease, allergies, and use of benzodiazepines, narcotics, antidepressants and illicit drugs. Fourth, the number of drinkers was still small due to the low prevalence in drinkers among Japanese women.[5] A larger study is of value to confirm our findings.

In conclusion, habitual alcohol consumption was found to be associated with higher prevalence of sleep-disordered breathing among Japanese women.

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Conflict of interest

None.

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Differences in relationships among sleep apnoea, glucose level, sleep duration and sleepiness between persons with and without type 2 diabetes

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Keywords
actigraph, diabetes, fasting plasma glucose, obstructive sleep apnoea, sleep duration, sleep fragmentation

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SUMMARY

Obstructive sleep apnoea is common in patients with diabetes. Recently, it was reported that short sleep duration and sleepiness had deleterious effects on glucose metabolism. Thereafter, several reports showed relationships between glucose metabolism and obstructive sleep apnoea, sleep duration or sleepiness. But the interrelationships among those factors based on recent epidemiological data have not been examined. We analysed data on 275 male employees (age, 44 ± 8 years; body mass index, 23.9 ± 3.1 kg m^{-2}) who underwent a cross-sectional health examination in Japan. We measured fasting plasma glucose, sleep duration using a sleep diary and an actigraph for 7 days, and respiratory disturbance index with a type 3 portable monitor for two nights. Fifty-four subjects (19.6%) had impaired glucose metabolism, with 21 having diabetes. Of those 21 (body mass index, 25.9 ± 3.8 kg m^{-2}), 17 (81.0%) had obstructive sleep apnoea (respiratory disturbance index ≥ 5). Regarding the severity of obstructive sleep apnoea, 10, four and three had mild, moderate and severe obstructive sleep apnoea, respectively. The prevalence of obstructive sleep apnoea was greater in those with than without diabetes ($P = 0.037$). Multiple regression analyses showed that the respiratory disturbance index independently related to fasting plasma glucose only in the diabetic subjects. In patients with diabetes, after adjustment for age, waist circumference, etc. sleep fragmentation had a greater correlation with fasting plasma glucose than sleep duration, but without significance ($P = 0.10$). Because the prevalence of obstructive sleep apnoea is extremely high in patients with diabetes, sufficient sleep duration with treatment for obstructive sleep apnoea, which ameliorates sleep fragmentation, might improve fasting plasma glucose.

INTRODUCTION

Sleep and glucose metabolism have long been known to have a complex interrelationship (Spiegel *et al.*, 2009). As the prevalence of obesity, diabetes, sleep apnoea and habitual sleep restriction continue to rise together, accumulating laboratory and epidemiological evidence suggests that sleep restriction and sleep apnoea may be partially responsible for the epidemic of obesity and diabetes (Spiegel *et al.*, 2009). In addition, sleepiness is said to be a marker of insulin resistance, independent of obesity (Barceló *et al.*, 2008).

Diabetes is now a global health priority, as the International Diabetes Federation (2010) estimates that 285 million people worldwide have diabetes and that this total will rise to 438 million in 20 years. However, the epidemiology and pathophysiology of diabetes are apparently different among races. A recent report indicated that diabetes in Asia is characterized by rapid rates of increase over short periods, onset at a relatively young age and a low body mass index (BMI), and that specific strategies for the prevention and control of diabetes in Asia are essential (Chan *et al.*, 2009).

Obstructive sleep apnoea (OSA) is a highly prevalent sleep disturbance, with its severity increasing with the degree of obesity. The prevalence of OSA among patients with diabetes reported in the four studies that used the gold standard method of full polysomnography (PSG) for OSA assessment and that defined OSA as an apnoea–hypopnoea index (AHI) >5 events h^{-1} was consistently higher than 50% (average 73%; Aronsohn *et al.*, 2010; Einhorn *et al.*, 2007; Foster *et al.*, 2009; Resnick *et al.*, 2003). Thus, studies in Western populations revealed very high rates of OSA among individuals with diabetes, but diabetic individuals in Asian populations have a lower average BMI than those in Western populations. Because obesity is a strong risk factor for OSA, it is important to examine whether there are similar associations between the respiratory disturbance index (RDI) and diabetes in Asian populations. However, there have been few reports of population-based studies from Asia, where the prevalence of diabetes as well as that of OSA is interestingly compatible to that in the West (Chan *et al.*, 2009; Ramachandran *et al.*, 2010).

In addition to the relationship between diabetes and OSA, the relationship between diabetes and sleep duration is gaining considerable attention. However, no previous studies have simultaneously examined the inter-relationship among diabetes, sleep duration and OSA using objective assessments of sleep duration rather than self-reported assessments. Thus, we hypothesized that the prevalence of diabetes was high in patients with OSA in Japan despite the lower BMI in Japan as well as in other East Asian countries. The hypothesis that sleep duration has a significant association with fasting plasma glucose (FPG) in patients with OSA was also considered. Moreover, we not only tested the impacts of sleep duration on FPG, but also those of sleep quality assessed by sleep fragmentation. To test these hypotheses, we used information from a cross-sectional epidemiological health survey of 275 middle-aged male employees in Japan (Chin *et al.*, 2010; Nakayama-Ashida *et al.*, 2008). Although most epidemiological studies used subjective self-reported sleep duration, such self-reports may be inaccurate and cause misclassification of sleep duration (Van Den Berg *et al.*, 2008). The actigraphic measurements used in this study would ensure greater accuracy of sleep duration and sleep quality than in previous reports.

MATERIALS AND METHODS

Subjects

We performed a cross-sectional epidemiological health examination of male employees of an urban wholesale company in Japan. Male subjects only were chosen for the study, as the number of female employees was very small. Of the 322 male employees who recorded their breathing during sleep using a home monitoring system (Nakayama-Ashida *et al.*, 2008), 275 were investigated further by determining their clinical characteristics and comorbidities (Chin *et al.*, 2010). Forty-seven of the 322 employees were excluded because blood parameters or waist circumferences were not measured. The relative proportions of the degrees of severity of OSA were similar in these 47 excluded subjects as in the 275 subjects. The study protocol was approved by the IRB Committee, which is associated with the Kyoto University Graduate School and Faculty of the Medicine Ethics Committee. The committee follows the principles of the Declaration of Helsinki. The study approval number was E-37. Written informed consent was obtained from all subjects.

Measurements of body weight and waist circumference, and diagnosis of diabetes

Trained research staff measured body weight and waist circumference. Fasting blood samples were taken in the morning after an overnight sleep. Measurements of FPG levels were obtained retrospectively from the company's periodic examination data (Chin *et al.*, 2010). For these measurements, all subjects were told not to eat and drink anything after 20:00 hours except water, and their blood was sampled the following morning after 09:00 hours. Thus, all subjects had undergone a more than 12-h fast. In accordance with guidelines of the American Diabetes Association and World Health Organization, diabetes was considered present when the FPG level was 126 mg dL^{-1} (7.0 mM) or greater, or hypoglycaemic medication (insulin or oral hypoglycaemic agent) was being administered. Impaired fasting glucose (IFG) was considered present when the FPG level was 110 mg dL^{-1} (6.1 mM) or greater but lower than 126 mg dL^{-1} (7.0 mM; Hayashino *et al.*, 2008).

Analysis of data from actigraph and a portable monitor

Each participant was asked to wear an actigraph (Morgenthaler *et al.*, 2007; Actiwatch AW-Light: Mini Mitter, Bend, OR,

USA) for seven consecutive days (five workdays and two weekend days) to estimate sleep/wake time and a type 3 portable monitor (PM; Morpheus; Teijin, Tokyo, Japan, which is the same as Somté; Compumedics, Vic., Australia; Chesson *et al.*, 2003), an alternative to PSG in the diagnosis of OSA (Kushida *et al.*, 2005), for two nights at home. The PM recorded chest and abdominal respiratory movements, nasal pressure, oxygen saturation, heart rate and body position.

We estimated sleep duration at night by analysing the actigraph tracings in conjunction with information from a sleep diary kept by the subjects (Nakayama-Ashida *et al.*, 2008). Sleep duration was assessed separately for an entire week, which included both workdays and weekend days. The RDI (number of apnoea and hypopnoea episodes per hour of the analysed time length) was calculated from PM data using the sleep durations obtained from the actigraph. PM records were visually inspected and scored by at least two medical doctors specialized in respiratory medicine. Apnoea is defined as cessation of breathing for at least 10 s, and hypopnoea as a more than 50% reduction in the amplitude of nasal pressure or respiratory effort associated with a more than 3% reduction in oxyhaemoglobin saturation for at least 10 s. Apnoea and hypopnoea were scored blinded to other information except for the sleep/wake time estimated by actigraphy. Data without oxygen saturation values, illegible recordings and data for <2 h were excluded from the analysis. When data from both recorded nights were available, PM records from the second night were analysed. Subjects with an RDI of 5–14.9, 15–29.9 and ≥30 were considered to have mild, moderate and severe OSA, respectively. We also assessed average sleep fragmentation from data obtained by the actigraph for seven consecutive nights. Sleep fragmentation, an index of restlessness during sleep expressed as a percentage, was calculated by summing two percentages: (i) the percentage of the sleep period spent moving (epoch with >2 activity counts is considered moving); and (ii) the percentage of immobile phases (consecutive epochs with no movement) that are only ≤1 min long (Knutson *et al.*, 2011).

Assessment of sleepiness

The modified Japanese version of the Epworth Sleepiness Scale (ESS) was used to assess subjective sleepiness (Takegami *et al.*, 2009). Subjects also filled out a sleep diary during the survey period.

Statistical analysis

Results are expressed as mean ± SD. Unpaired *t*-tests or exact chi-square tests were used to compare the backgrounds of participants. One-sample Kolmogorov–Smirnov tests were used to check whether the data had normal distribution. The relationships between two sets of data were analysed by Pearson correlation coefficient tests. *P*-values <0.05 were considered to be statistically significant. Stepwise multiple regression analyses were performed to identify those variables that could predict the FPG level and ESS scores. Specifically, age, waist circumference, RDI, average sleep fragmentation, ESS scores and sleep duration were analysed to identify those variables that could predict FPG independently. In the same way, age, waist circumference, RDI, average sleep fragmentation, sleep duration and FPG were analysed to identify those variables that could predict ESS scores independently. Statistical analyses were performed using Statview 5.0 (SAS Institute, Cary, NC, USA).

RESULTS

Characteristics of the subjects

Table 1 shows the characteristics of the subjects. Of the 275 subjects, 21 (7.6%) had diabetes; among these, six (2.2%) were being treated with hypoglycaemic medication. Further examination proved that all 21 had type 2 diabetes. Subjects with diabetes were older, more obese, had a larger waist circumference and waist-to-hip ratio, and were more likely to have OSA than those with normal fasting glucose ($P = 0.036$) and than those without diabetes ($P = 0.037$). Thirty-three subjects (12.0%) had IFG. Subjects with IFG were also older, more obese, and had a larger waist circumference and waist-to-hip ratio than those with normal fasting glucose. But the prevalence of OSA in those with IFG did not differ significantly from those with normal fasting glucose ($P = 0.71$).

Among the 21 subjects with diabetes, 17 (81.0%) had OSA (RDI ≥ 5). Regarding the severity of OSA, 10 (47.6%), four (19.0%) and three (14.3%) had mild, moderate and severe OSA, respectively. Among the 33 subjects with IFG, 20 (60.7%) had OSA, with nine (27.3%), nine (27.3%) and two (6.1%) having mild, moderate and severe OSA, respectively. When considering the 221 subjects with normal fasting glucose, 124 (56.1%) had OSA, with 84 (38.0%), 29 (13.1%), and 11 (5.0%) having mild, moderate and severe OSA, respectively.

Association between diabetes, sleep apnoea and sleep duration

Firstly, we analysed the relationships between FPG and OSA. There was a significant relationship between FPG and RDI in the entire subject population [correlation coefficient (r) = 0.19, $P = 0.0019$]. Then, when that population was divided into two groups, that is, those with and without diabetes, FPG and RDI had a significant relationship in both groups before adjustment; however, the relationship was only significant in subjects with diabetes after adjustment (subjects with diabetes: $r = 0.45$, $P = 0.042$, and $r = 0.49$, $P = 0.040$ after adjustment for age, waist circumference, which was a marker of visceral adiposity, average sleep fragmentation, ESS scores and sleep duration; subjects without diabetes: $r = 0.14$, $P = 0.030$ and $r = 0.009$, $P = 0.89$

Table 1 Characteristics of the subjects

	All subjects	*Subjects with diabetes*	*Subjects with NFG*	P-*value*	*Subjects with IFG*	*Subjects with NFG*	P-*value*
Number of subjects (%)	275 (100.0)	21 (7.6)	221 (80.4)		33 (12.0)	221 (80.4)	
Age (years)	44 ± 8	50 ± 5	43 ± 8	<0.001	47 ± 6	43 ± 8	0.0039
BMI (kg m^{-2})	23.9 ± 3.1	25.9 ± 3.8	23.5 ± 2.9	<0.001	25.5 ± 3.5	23.5 ± 2.9	<0.001
Waist circumference (cm)	83.6 ± 8.5	89.7 ± 8.8	82.4 ± 7.9	<0.001	88.3 ± 9.2	82.4 ± 7.9	<0.001
Waist-to-hip ratio	0.88 ± 0.05	0.92 ± 0.05	0.87 ± 0.05	<0.001	0.91 ± 0.06	0.87 ± 0.05	<0.001
RDI (h^{-1})	10.2 ± 10.7	13.9 ± 10.5	9.4 ± 10.2	0.054	12.8 ± 13.6	9.4 ± 10.2	0.090
OSA* *n*	161	17	124	0.036	20	124	0.71
Average sleep fragmentation (%)	32.0 ± 10.4	31.8 ± 9.4	32.3 ± 10.2	0.81	30.2 ± 11.9	32.3 ± 10.2	0.27
ESS score	8.2 ± 4.3	8.2 ± 4.9	8.0 ± 4.3	0.84	9.1 ± 3.7	8.0 ± 4.3	0.21
Average sleep duration (h)	6.0 ± 0.8	5.7 ± 0.9	6.0 ± 0.8	0.068	6.0 ± 0.7	6.0 ± 0.8	0.60
Workday sleep duration (h)	5.6 ± 0.9	5.4 ± 0.9	5.7 ± 0.9	0.26	5.7 ± 0.9	5.7 ± 0.9	0.85
Weekend sleep duration (h)	6.9 ± 1.5	6.2 ± 1.3	6.9 ± 1.5	0.040	6.8 ± 1.0	6.9 ± 1.5	0.55
FPG (mg dL^{-1})	103.7 ± 22.0	156.5 ± 48.1	96.8 ± 7.1	<0.001	116.0 ± 4.8	96.8 ± 7.1	<0.001

Values are presented as mean ± SD or *n* (%) unless stated otherwise.
*OSA was defined as having RDI of more than 5 h^{-1}.
BMI, body mass index; ESS, Epworth Sleepiness Scale; FPG, fasting plasma glucose; IFG, impaired fasting glucose; NFG, normal fasting glucose; OSA, obstructive sleep apnoea; RDI, respiratory disturbance index.

after adjustment for age, waist circumference, average sleep fragmentation, ESS scores and sleep duration; Fig. 1a,b). When we divided the subjects without diabetes into two groups, that is, those with IFG and those with normal fasting glucose, to analyse the relationship between FPG and RDI, we found no significant correlation (subjects with IFG: $r = 0.14$, $P = 0.45$; subjects with normal fasting glucose: $r = 0.10$, $P = 0.15$; Fig. 1c,d).

Secondly, as to the relationship between FPG and sleep duration, we found a significant inverse relationship between FPG and sleep duration in the entire subject group ($r = -0.13$, $P = 0.041$). However, when separately analysing subjects with and without diabetes, FPG was not related to sleep duration (subjects with diabetes: $r = -0.24$, $P = 0.30$; subjects without diabetes: $r = 0.005$, $P = 0.93$). After adjustment for age, waist circumference, RDI, average sleep

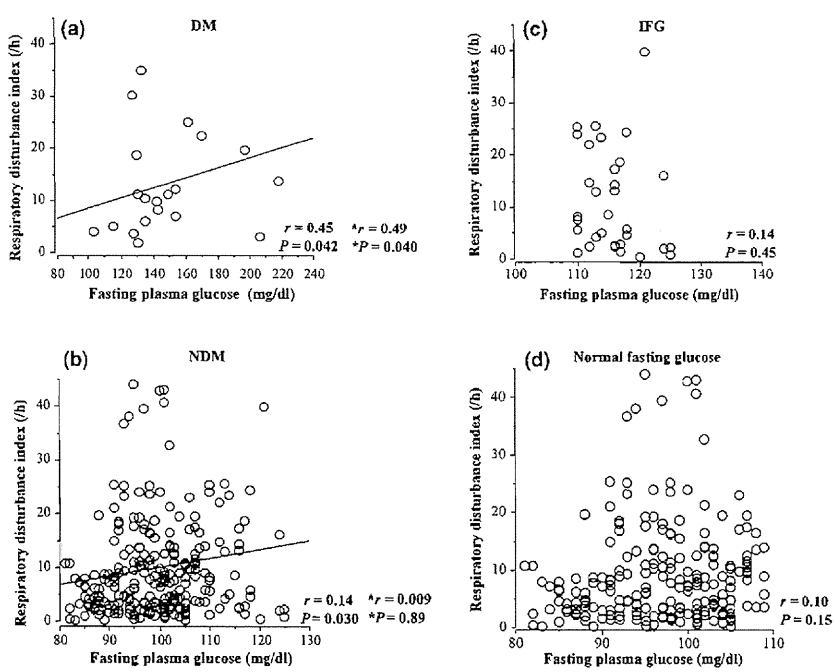

Figure 1. Relationship between FPG and RDI in the subjects with diabetes (DM) (a), those without diabetes (NDM) (b), those with impaired fasting glucose (IFG) (c) and those with normal fasting glucose (d). *r and *P were values after adjustment for age, waist circumference, average sleep fragmentation, ESS scores and sleep duration.