答したものは3,893人（76.2%）であった。各項目の欠側値の割合は9.5～19.2%であった。回転なしの主因子分析により，一因子性であることを確認した。因子寄与率は40.1%であった。また，各項目の因子負荷量は0.55～0.68であり，各項目で大きな差はなかった。各項目と合計得点との相関係数は0.46～0.69であった。クロンバック α の値は，0.78（男性0.79，女性0.78）であった。

ESSの合計得点の度数分布を図1，性・年齢階級別合計得点の平均値と標準偏差を表2に示す。全体での合計得点は5.18±3.82（平均値±標準偏差），男性では5.25±3.89，女性では5.12±3.75であった。性別の平均得点に差はなかった。年齢階級別の平均得点については，男性および女性とも有意な差があった（$P=0.015$ および $P<0.001$）。年齢階級別の合計得点は，男女とも20代，50代および70代以上が高くなるW型を示していた。男性については，合計得点が80代以上で最も高く，次いで50代，20代であった。女性についても，最も合計得点が高いのは80代以上で，次いで70代，20代，50代であった。

全項目回答者のみの合計得点は5.03±3.73であり，男性では5.13±3.80，女性では4.95±3.67であった。全項目回答者と欠側補正対象者における合計得点の平均値は有意な差があり（$P<0.001$），欠側補正対象者の方が高かった。全項目回答者と欠側補正対象者の性別，年齢階級における χ^2 検定では，性別および年齢階級とも有意な差があった（$P<0.001$ および $P<0.001$）。欠側補正対象者は，男性が7.8%，女性が14.5%と女性が多く，年齢では20代で2.3%，30代で2.4%，40代で3.6%であるのに対し，50代では8.8%，60代では12.2%，70代では16.5%，80代以上では12.6%と高齢になるほど，欠側補正対象者の割合が増加していた。

3. EDSの有症割合について

ESSの合計得点11点以上をカットオフ値としたEDSの有症割合は9.2%（男性は9.6%，女性は8.8%）であった。ESS合計得点と同様に性別では有意差はみられなかったが，年齢階級では男性および女性でそれぞれ有意な差がみられた（P

図1　The Epworth Sleepiness Scale（ESS）合計得点の度数分布

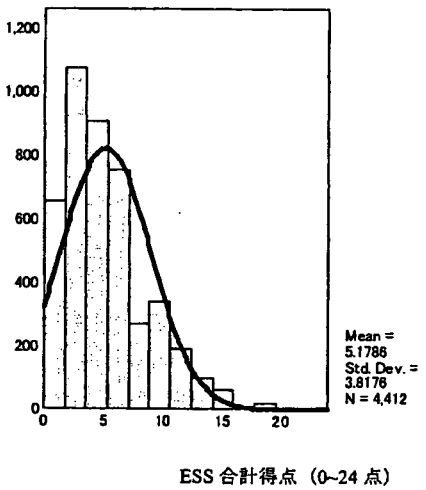

表2　性・年齢階級別ESS合計得点

	男性（n=2,025）		女性（n=2,387）	
	n	ESS 合計得点†	n	ESS 合計得点‡
年齢（歳）				
20–29	251	5.38±4.00	296	5.65±3.92
30–39	271	4.75±3.69	334	4.64±3.34
40–49	354	5.13±3.64	414	4.95±3.33
50–59	405	5.51±4.09	481	5.00±3.41
60–69	416	5.39±3.62	439	4.53±3.36
70–79	248	4.83±3.99	310	5.53±4.40
80–	80	6.28±4.88	113	7.38±5.44

注）分散分析，平均値±標準偏差
† P 値＝0.015
‡ P 値＜0.001

表3　日中の過度の眠気（EDS）有病割合

	男性†（n=2,025）	女性‡（n=2,387）
	n（%）	n（%）
年齢（歳）		
20–29	27(10.8)	34(11.5)
30–39	19(7.0)	19(5.7)
40–49	28(7.9)	28(6.8)
50–59	47(11.6)	38(7.9)
60–69	33(7.9)	25(5.7)
70–79	24(9.7)	41(13.2)
80–	16(20.0)	26(23)
合計	194(9.6)	211(8.8)

注）EDS：ESS合計得点≧11
† χ^2 検定，P 値＝0.05
‡ χ^2 検定，P 値＜0.001

＝0.01および$P<0.001$)。年齢階級別のEDS有症割合は男女ともW型を示しており，合計得点と同様の結果であった（表3)。また，EDSの有無を従属変数としたロジスティック回帰分析では，性，年齢，睡眠時間の不足（6時間未満の睡眠)，睡眠薬の服用，BMI，飲酒のうち，EDSは年齢（$P=0.002$)，6時間未満の睡眠（$P=0.008$)，飲酒（$P<0.001$）と関連があった。

カットオフ値を9から12の範囲に変化させて，EDS有症割合を推定したところ，男性では9以上では17.4%，10以上では12.4%，12以上では7.5%，女性では9以上では16.5%，10以上では11.7%，12以上では5.9%であった（図2，図3)。

2000年の人口を用いて標準化されたEDSの有症割合と95%信頼区間は9.33%（9.32–9.34）であり，男性は9.57%（9.54–9.59)，女性は9.20%（9.18–9.22）であった。

Ⅳ 考　　察

本研究では，ある自治体の20歳以上の全住民を対象としてESSの性・年齢階級別得点分布を記述するとともに，日中の過度の眠気の有症割合を推定した。これまで国内外ともに，性・年齢階級別のESSの標準値を明らかにしているものは皆無であるが，一般集団におけるESS得点，EDS有症割合は報告されている（表4)。表4に示したとおり，それぞれのESS得点やEDS有症割合には大きなばらつきがある。これらの先行研究の結果を本研究の結果と直接比較することはできない。その理由としてはEDSの評価方法が異なっていること，対象としている集団および規模が異なっていること，文化的な差異や主観的尺度の特

図2　日中の過度の眠気有症割合（男性)：
ESS合計得点による変化（≧9, 10, 11, 12)

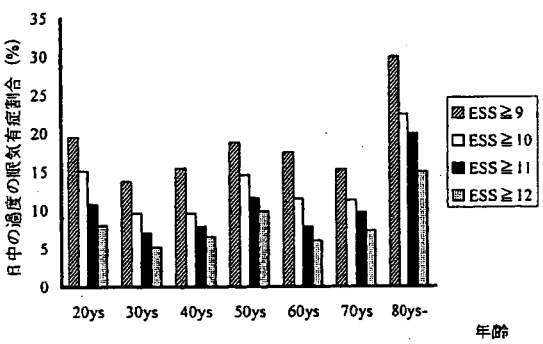

図3　日中の過度の眠気有症割合（女性)：
ESS合計得点による変化（≧9, 10, 11, 12)

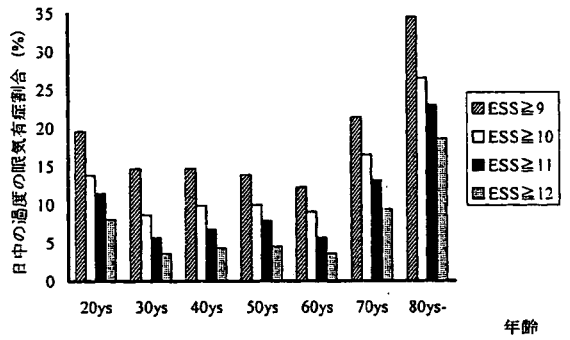

表4　ESS合計得点と日中の過度の眠気（EDS）有症割合に関する他の文献検討

著　者	国	対象人数	対象年齢	男性(%)	ESS score	EDS(%)
J Zielinski et al[15]	ポーランド	1,186	38–67	49.6	8.5±0.1	26.1
KF Chung et al[13]	中国†	61	21–65	33.3	7.5±3.0	
Johns MW et al[14]	オーストラリア†	331	22–59	80.7	5.8±4.1	10.9‡
Doi Y et al[17]	日本†	4,722	20–59	82.6		13.3(男性)，7.2(女性)‡
Ohayon MM et al[18]	イギリス	4,972	15–	52.3		5.5(severe)，15.2(moderate)
Lavie P[19]	イスラエル†	1,502		84		4.9
Hublin C et al[20]	フィンランド	11,354	33–60	45.6		6.7(男性)，11.0(女性)
Martikainen N et al[21]	フィンランド	1,190	36–	69		7.0(男性)，12.0(女性)
Ohayon MM et al[22]	フランス	1,026	60–	40.2		13.6
Souza JC et al[23]	ブラジル	408	18–			18.9‡
Liu X et al[24]	日本	3,030	20–	48.9		14.9

注）† 職業集団を対象としたもの
‡ ESSから推計されたEDS有病割合

性である回答バイアス等が挙げられる。

日本人を対象とし，本研究と同様にESSを用いてEDS有症割合を推定した研究には，Doi Yらの研究がある[17]。Doi Yらの結果は，本研究の結果より男性が非常に高い結果となっている。この研究では対象集団が職域（非交代勤務ホワイトカラー勤労者）に限定されたものであることが本研究の結果と異なった要因と推測される。また，Liu XらによるEDS有症割合[24]が，本研究の結果より高いことについては，EDSの定義が異なっていることが考えられる。本研究では，ESS 11点以上をEDSと定義したが，彼らの調査では本研究と比べて，軽度の日中の眠気をEDSと定義している可能性がある。本研究でもESS 10点以上をEDSと定義した場合は，男性12.4%および女性11.7%であった。

平成12年度厚生労働省保健福祉動向調査（心身の健康）では，睡眠に関する全国調査が行われており，眠気についても調査されている[29]。「眠ってはいけないときに起きていられない（車の運転など）」という問題を抱えている人は3.2%であった。ESSの問8はほぼ同様の質問項目であることから比較したところ，「しばしば眠ってしまう」「よく眠ってしまう」と答えたのは4.7%であった。保健福祉動向調査が10代および20代において眠気が強く，その後低下しているのに対し，本調査での結果では，60代より高齢になるにつれて眠気が強くなっていた。これについては，質問内容の違いや地域の違いなどが考えられるが今後の検討が必要である。

同様に，Liu Xら[24]，Doi Yら[17]による調査でも，年齢において差がみられている。本研究の新たな知見は，男性，女性ともEDS有症割合がW型を示し，20代，50代および80代で眠気が強い傾向がみられたことである。本研究では，年齢以外に6時間未満の睡眠と鼾の有無でEDSと有意な関連があった。これらの要因はそれぞれ年齢と有意な関連を示しているが，このようなW型にはならない。年齢により，それぞれ異なった生物医学的および社会医学的な諸要因が関係していると考えられる。定量的な分析ではデータが限られるため，原因を十分に追求することは困難であり，今後，質的な研究と定量的な研究を取り入れて原因を追求する必要がある。

本研究の限界としては，EDSを評価するために主観的な尺度（ESS）を用いたことである。ESSがEDSのゴールドスタンダードとされているMSLTと相関していない可能性が示されている[30~33]。また，客観的にEDSを評価する方法と主観的に評価する方法では，眠気の違った側面を測定しているとも推測されている[30,31]。本研究では，EDSを評価する上で対象者の主観的な評価が重要であると考え，EDSの評価に主観的尺度であるESSを採用したが，客観的尺度による評価との整合性については課題として残された。

ESS質問票の問題点として，ESSは日常のある状況下での眠気を評価するものであり，回答者本人にとっては想定されない状況についての質問項目が含まれる場合が考えられた（運転免許証を持っていない人など）。また，欠側補正対象者が女性に多く，また高齢になるにつれ増加しており，欠側補正対象者は全項目回答者に比べ眠気が強かったことを考慮すると，今回使用したESS質問票には改善の余地があると考えられる。今回の調査で用いた日本語版ESSについて妥当性，信頼性の計量心理学的な評価を行った結果，構成概念妥当性，信頼性は，原版である英語版ESSとほぼ同様の結果であった。しかし，今回の調査では内容的妥当性の検討ができておらず，欠側が生じる理由を十分に検討することはできなかった。これらのことから，今後，順翻訳・逆翻訳，パイロットテストといった尺度開発の過程を踏んだ日本語版ESSの開発が必要であると考える。また，質問項目の再考も必要である可能性がある。

今後，我々は日本呼吸器学会からの委託を受け，ESSの原版開発者であるJohns MW博士とともに日本語版ESSを開発する予定である。

ESS質問票の特徴として，ESS質問票は日中の眠気を測定するものであり，眠気が問題となる疾患群においては正規分布に従うが健常人を対象とした場合は得点が底うちになることが報告されている[25]。本研究の結果においても，ESSの性・年齢階級別の合計得点は正規分布に従っておらず，中央値が平均値を下回っていた。このことから，本調査のESS合計得点の分布は点数の低い方に傾いており，平均値を基準として考えるときに注意が必要である。

今回の調査は，地方自治体の住民を対象とした

ものであるため，日本人を代表した値であるとはいえない。今後，日本国民を代表する集団において，ESSの国民標準値を求める調査が行われる必要がある。平成14年，道路交通法が改正され，「免許の拒否又は保留の事由となる病気等」に「重度の眠気の症状を呈する睡眠障害」が追加された（法第九十条第一項第一号，令第三十三条の二の三）。実際の使用にあたっては，「一定の病気に係る免許の可否などの運用基準」と『対応マニュアル「一定の病気に係る免許の可否などの運用基準」を踏まえた具体的な対応要領（基準）』が作成された。運用基準では，医師が「現在，睡眠障害で重度の眠気を生ずるおそれがあり，6月以内に重度の眠気が生じるおそれがなくなる見込みがあるとはいえない」旨の診断を行った場合には拒否または取消しとすると記載されている。対応マニュアルによるとESSが16点以上の場合，臨時適正検査，または主治医の診断書が必要になるとされている。ESSは，自記式質問票であり，明らかに免許申請者にとって不利となることがわかっているため，回答にバイアスが入る可能性が高い。また，尺度開発の過程を経た日本語版が作成されていないことも問題である。これらのことから，現段階でのこのような使用は慎重に検討するべきであると考える。このような現状において，今回の調査で得られたESSの平均値は日中の眠気を評価するうえで，限界はあるものの一定の基準になると考えられる。

ESSは海外の研究でも日中の眠気の共通の尺度として利用されている。異なる国で測定されたESS得点を直接比較することはできないが，標準偏差が同程度であればそれぞれの国の得点とその国の患者の差を「標準化した差得点」として算出し，これを異なる国の同様の差得点と比較することは可能であると思われる。これらのことから本研究におけるESSの得点分布は，日々の診療，公衆衛生の面で活用し得る結果であると思われる。

V 結　　語

本研究より，地域の一般住民を対象としたESS得点の平均値とEDS有症割合を推定した。本研究の新たな知見としては，日々の診療に活用し得る性・年齢階級別の得点分布を明らかにしたこと，年齢階級別のEDSは20代，50代，および70代以上に多いW型であったことである。本研究で得られたESSの得点分布は，日本で初めて測定されたものであり，睡眠障害をきたす種々の疾患の診療，臨床疫学研究や公衆衛生施策に活用されることが期待される。また，ESS得点による日中の眠気が年齢で違いがあることについては，生物医学的および社会医学的な諸要因が関係していると考えられ，更なる研究が求められる。

本研究は，平成14年度厚生科学研究補助金特定疾患対策研究事業の一環として行われた。

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（採用　2004.12.17）

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Effects of Obstructive Sleep Apnea Syndrome on Serum Aminotransferase Levels in Obese Patients

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PURPOSE: Obesity has been associated with obstructive sleep apnea and hepatic steatosis. We investigated the effects of obstructive sleep apnea and treatment with nasal continuous positive airway pressure (CPAP) on serum aminotransferase levels in obese patients.

METHODS: We studied 40 obese men with obstructive sleep apnea syndrome. None had hepatitis B antigen or C antibody, autoimmune disease, or an excessive intake of alcohol. Serum levels of aspartate aminotransferase, alanine aminotransferase, triglyceride, glucose, insulin, and leptin were determined in the afternoon and in the morning immediately after sleep, before and after nasal CPAP treatment.

RESULTS: Aminotransferase levels were abnormal in 35% (n = 14) of patients. Before treatment, mean (± SD) aspartate aminotransferase levels were higher in the morning than in the previous afternoon (presleep, 34 ± 20 IU/L; postsleep, 39 ± 28 IU/L; $P = 0.006$). The overnight mean increases in aminotransferase levels were less marked after the first night of nasal CPAP treatment (aspartate aminotransferase: from 6 ± 11 IU/L to 2 ± 6 IU/L, $P = 0.0003$; alanine aminotransferase: from 5 ± 9 IU/L to 2 ± 6 IU/L, $P = 0.006$). Leptin levels (n = 23) decreased significantly after treatment ($P = 0.0002$), whereas insulin resistance (calculated by the homeostasis model assessment method) and triglyceride levels were unchanged. Improvements in aspartate and alanine aminotransferase levels were maintained after 1 and 6 months of nasal CPAP treatment.

CONCLUSION: Nasal CPAP therapy may have beneficial effects on serum aminotransferase abnormalities in obese patients who have obstructive sleep apnea. **Am J Med. 2003;114: 370–376.** ©2003 by Excerpta Medica Inc.

Obesity is an important risk factor for obstructive sleep apnea (1). One quarter of middle-aged men have more than five episodes of apnea or hypopnea per hour of sleep (1). Obstructive sleep apnea affects abdominal visceral fat accumulation (2,3), serum leptin levels (2–5), and insulin resistance (6,7), which increase the risk of developing obesity-related disorders. Both obesity and obstructive sleep apnea are also associated with hypertension, myocardial infarction, and stroke (8–12).

Obesity has been linked to hepatic steatosis (fatty liver), which occurs in about 90% of patients with unexplained chronic elevations in serum aminotransferase levels (13). Hepatic steatosis is common in many industrialized countries (14), with almost a quarter of adults having excessive fat accumulation in the liver (15,16). It is also a significant risk factor for serious liver disease (17), which may contribute to obesity-related morbidity and mortality. At least 20% of patients with hepatic steatosis develop cirrhosis, half of whom die of liver-related causes within a decade of diagnosis, making liver disease the second leading cause of death in these patients (17). Hepatic steatosis is also associated with hyperinsulinemic insulin resistance in humans (18,19) and in various animal models (20–22), raising the possibility that enhancing insulin sensitivity may reduce hepatic fat deposition.

Since obstructive sleep apnea leads to insulin resistance (6,7) and visceral fat accumulation (2,3) and increases serum leptin levels (2–5), it may also affect hepatic function (14). Indeed, hepatocytes from fatty livers have increased sensitivity to anoxia (23), and frequent hypoxic episodes in patients with obstructive sleep apnea syndrome could hinder hepatic function.

We hypothesized that obstructive sleep apnea syndrome with hypoxemia leads to hepatic dysfunction. We investigated the prevalence of aminotransferase abnormalities and the effects of obstructive sleep apnea and nasal continuous positive airway pressure (CPAP) therapy in patients with obstructive sleep apnea.

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METHODS

Subjects

We studied 44 consecutive patients (41 men, 3 women; mean [± SD] age, 47 ± 12 years) with obstructive sleep apnea syndrome who were determined by polysomnography and clinical symptoms to be candidates for nasal CPAP treatment (2). Polysomnography was performed in the hospital before CPAP treatment and on the first night of CPAP therapy 1 week later. All patients were obese by Japanese criteria (body mass index >25 kg/m^2). We could not obtain blood from 2 patients, and samples from 2 other patients had hemolyzed, leaving 40 patients in the study. All patients were hepatitis B antigen and hepatitis C antibody negative, and none had clinical evidence of autoimmune disease. The medical ethics committee approved the study, and all patients provided informed consent.

Study Protocol

Blood samples were drawn at 3:30 PM after a 3-hour fast (afternoon samples) and at 8:15 AM (morning samples) after polysomnography, before and after CPAP treatment (24). All patients had the same light meal without alcohol at 6:00 PM before polysomnography, and they did not eat or drink from 8:00 PM until 8:15 AM the following day. Serum aminotransferase and triglyceride levels were measured using commercial kits. The change in aminotransferase values from afternoon to morning was calculated. A 75-g oral glucose tolerance test was performed before CPAP treatment. Blood samples were collected at 0, 30, 60, 90, 120, and 180 minutes for determination of glucose and insulin levels. Fasting glucose levels greater than 126 mg/dL or glucose levels greater than 200 mg/dL at 120 minutes after 75-g oral glucose administration indicated diabetes. Abnormal glucose tolerance was diagnosed if the fasting glucose level was below 126 mg/dL and the glucose level exceeded 200 mg/dL at any time during the glucose tolerance test, except at 120 minutes. Plasma glucose levels were assayed using the glucose oxidase method, and insulin was assayed using a double antibody radioimmunoassay. We used the homeostasis model assessment method to measure insulin resistance ([glucose {mg/dL} × insulin {μg/ml}]/405) (25). Serum leptin levels at 8:15 AM were determined using a radioimmunoassay with an intra-assay coefficient of variation of 5.3% (n = 10) and an interassay coefficient of variation of 5.9% (n = 10) (26). Serum leptin levels were measured in only 23 of the 40 patients because this measurement was started midway through the study. Abdominal subcutaneous and visceral fat deposition was assessed in 38 patients by computed tomographic scan before CPAP treatment (2). Hypertension was defined as an arterial pressure greater than 140/90 mm Hg or the use of antihypertensive therapy. Serum aminotransferase and triglyceride levels were also measured after 1 and 6 months of CPAP treatment.

Statistical Analysis

The Mann-Whitney *U* test was used to compare patients who had abnormal aspartate aminotransferase levels with those who had normal levels. Differences between two intervals were compared with the Wilcoxon signed rank test. Differences among three intervals were compared using the Friedman test; when there was a significant difference, intergroup differences were evaluated by the Wilcoxon signed rank test. Proportions were compared with the chi-squared test. Spearman rank correlation coefficients were calculated to analyze correlations between two parameters. StatView software for Macintosh, version 5.0 (Berkeley, California) was used. A P value <0.05 was considered significant.

RESULTS

Patients were middle-aged men with minimal use of alcohol (Table 1). All but 1 patient ingested less than 30 g/d of alcohol; that patient ingested 50 g/d. There was no past history of alcohol ingestion greater than 30 g/d. The ratio of the levels of alanine to aspartate aminotransferase was >1 in 35 (88%) of the 40 patients, whereas the ratio of visceral to subcutaneous was >0.4 (the criterion for visceral obesity) in 37 (97%) of the 38 patients in whom it was measured. Eleven patients had noninsulin-dependent diabetes mellitus, and 11 had abnormal glucose tolerance. Twenty-nine patients had hypertension, including 10 who had been taking antihypertensive drugs for several months. Medication use was not changed during the study.

Short-term Effects of Nasal CPAP Treatment

Before CPAP treatment, aspartate aminotransferase levels increased significantly after sleep compared with the previous afternoon (Table 2 ; $P = 0.006$). The amount of increase in aminotransferase levels from afternoon to the next morning declined significantly after the first fasting night of CPAP therapy (Table 2). The overnight change correlated significantly with morning aminotransferase values before CPAP treatment (Figure 1).

Of the 40 patients, 14 (35%) had abnormal (>1.5 times the upper limit of normal) aspartate aminotransferase levels (≥49 IU/L). Aminotransferase levels in these 14 patients increased significantly overnight, and these changes were significantly greater than those in the remaining 26 patients whose aspartate aminotransferase values were normal and who otherwise had similar clinical characteristics (Table 3). However, insulin resistance was greater in the group with elevated aminotransferase levels (Table 3). Indeed, insulin resistance correlated significantly with aminotransferase levels before CPAP

Table 1. Baseline Characteristics of 40 Patients with Obstructive Sleep Apnea Syndrome and Effects of Nasal Continuous Positive Airway Pressure Treatment

Variable	Before CPAP	After 1 Night of CPAP	*P* Value
	Mean ± SD		
Age (year)	47 ± 12		
Body mass index (kg/m^2)	31 ± 4		
Visceral fat accumulation (cm^2)	217 ± 73		
Subcutaneous fat accumulation (cm^2)	232 ± 99		
Visceral fat/subcutaneous fat ratio	1.1 ± 0.6		
Alcohol intake (g/d)	21 ± 13		
Apnea-hypopnea index (number/hour)	57 ± 19	4 ± 5	<0.0001
Lowest arterial O_2 saturation (%)	61 ± 16	87 ± 6	<0.0001
Arterial O_2 saturation <90% (% of time)	33 ± 17	1 ± 3	<0.0001

CPAP = continuous positive airway pressure.

treatment (aspartate aminotransferase: $r = 0.51$, $P = 0.002$; alanine aminotransferase: $r = 0.70$, $P = 0.0001$). The overnight increase in aminotransferase levels among those with elevated aminotransferase levels improved significantly after the first night of CPAP treatment (Figure 2).

Serum leptin levels decreased significantly after the first night of CPAP treatment, while the changes in the serum triglyceride and insulin levels were not significant (Table 2).

Effects after 1 and 6 Months of Nasal CPAP Treatment

After 1 month of CPAP treatment, 34 of the 40 patients returned for evaluation. Their measured compliance with CPAP, using a built-in clock, was 4.3 ± 1.4 hours per day. Aspartate aminotransferase levels (Figure 3) and body mass index (30.1 ± 4.4 kg/m^2 to 29.2 ± 4.1 kg/m^2, $P = 0.0006$) had decreased significantly; however, indexes of insulin resistance did not change significantly (3.4 ± 2.2 to 2.8 ± 1.4, $P = 0.24$). The 21 patients whose body mass index declined by ≤1 kg/m^2 had significant decreases in aspartate aminotransferase levels (35 ± 23 IU/L to 27 ± 12 IU/mL, $P = 0.03$; body mass index: 29.1 ± 3.0 kg/m^2 to 28.9 ± 3.1 kg/m^2, $P = 0.27$) and significant decreases in serum triglyceride levels (221 ± 107 mg/dL to 179 ± 123 mg/dL, $P = 0.01$). Leptin levels also decreased (33 ± 12 ng/mL to 23 ± 12 ng/mL, $P = 0.02$) among the 8 patients in whom they were available. The improvement in ami-

Table 2. Effects of Nasal Continuous Positive Airway Pressure in 40 Patients with Obstructive Sleep Apnea Syndrome*

Variable	Before CPAP	After 1 Night of CPAP*	*P* Value
	Mean ± SD		
Afternoon aspartate aminotransferase (IU/L)	34 ± 20	32 ± 20	0.29
Morning aspartate aminotransferase (IU/L)	39 ± 28	34 ± 24	0.0006
Afternoon alanine aminotransferase (IU/L)	61 ± 53	61 ± 48	0.95
Morning alanine aminotransferase (IU/L)	66 ± 60	62 ± 51	0.55
Afternoon triglyceride (mg/dL)	256 ± 149	260 ± 185	0.40
Morning triglyceride (mg/dL)	216 ± 103	206 ± 128	0.24
Increase in aspartate aminotransferase from afternoon to morning (IU/L)	6 ± 11	2 ± 6	0.0003
Increase in aspartate aminotransferase from afternoon to morning (IU/L)	5 ± 9	2 ± 6	0.006
Afternoon insulin (μg/mL)	49 ± 35	45 ± 35	0.47
Morning insulin (μg/mL)	12 ± 6	12 ± 5	0.85
Insulin resistence†	3.4 ± 2.2	3.2 ± 1.6	0.33
Morning leptin (ng/mL)‡	22 ± 13	17 ± 10	0.0002

* Afternoon values obtained on the afternoon before CPAP.
† See Methods.
‡ Obtained in 23 patients.
CPAP = continuous positive airway pressure.

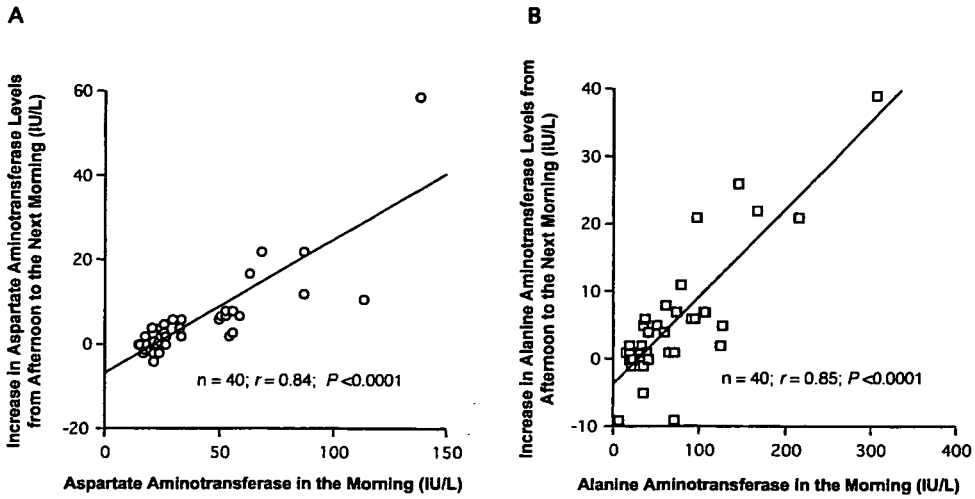

Figure 1. Correlations between serum aspartate aminotransferase (A) and alanine aminotransferase (B) levels in the morning and increase from afternoon to the next morning.

notransferase levels was sustained for 6 months (Figure 3; n = 26).

DISCUSSION

We found that about one third of obese patients with moderate or severe obstructive sleep apnea had abnormal aminotransferase levels, and that aminotransferase levels correlated significantly with insulin resistance. Results from a single night of nasal CPAP treatment, as well as from other reports (3-5,23), suggest that recurrent apnea and hypopnea with hypoxemia may aggravate hepatic dysfunction in these patients, as manifest by release of aspartate aminotransferase, a well-established marker of

Table 3. Comparison of Patients by Aspartate Aminotransferase Level

Variable	Aspartate Aminotransferase ≥49 IU/L (n = 14)	Aspartate Aminotransferase ≤33 IU/L (n = 26)	*P* Value
Age (years)	45 ± 12	49 ± 12	0.30
Body mass index (kg/m^2)	31 ± 3	31 ± 5	0.95
Apnea-hypopnea index (number/hour)	58 ± 16	56 ± 20	0.75
Apnea-hypopnea index after nasal CPAP (number/hour)	4.9 ± 6.0	3.4 ± 4.2	0.34
Lowest arterial O_2 saturation (%)	62 ± 15	61 ± 16	0.80
Arterial O_2 saturation <90% (% of time)	30 ± 16	34 ± 18	0.65
Visceral fat accumulation (cm^2)	235 ± 80	206 ± 68*	0.25
Subcutaneous fat accumulation (cm^2)	211 ± 60	243 ± 115*	0.34
Morning triglyceride (mg/dL)	216 ± 109	216 ± 101	1.0
Morning aspartate aminotransferase (IU/L)	70 ± 27	23 ± 5	<0.0001
Morning alanine aminotransferase (IU/L)	126 ± 66	34 ± 18	<0.0001
Increase in aspartate aminotransferase from afternoon to morning (IU/L)	14 ± 15	1 ± 3	<0.0001
Increase in alanine aminotransferase from afternoon to morning (IU/L)	13 ± 11	1 ± 4	<0.0001
Morning insulin (μg/mL)	15 ± 7	11 ± 5	0.065
Insulin resistance†	5.0 ± 2.6	2.6 ± 1.3	0.003
Morning leptin (ng/mL)*	21 ± 16*	22 ± 14	0.77

* Obtained in 23 patients (8 with abnormal aspartate aminotransferase levels).
CPAP = continuous postitive airway pressure.
† See Methods.

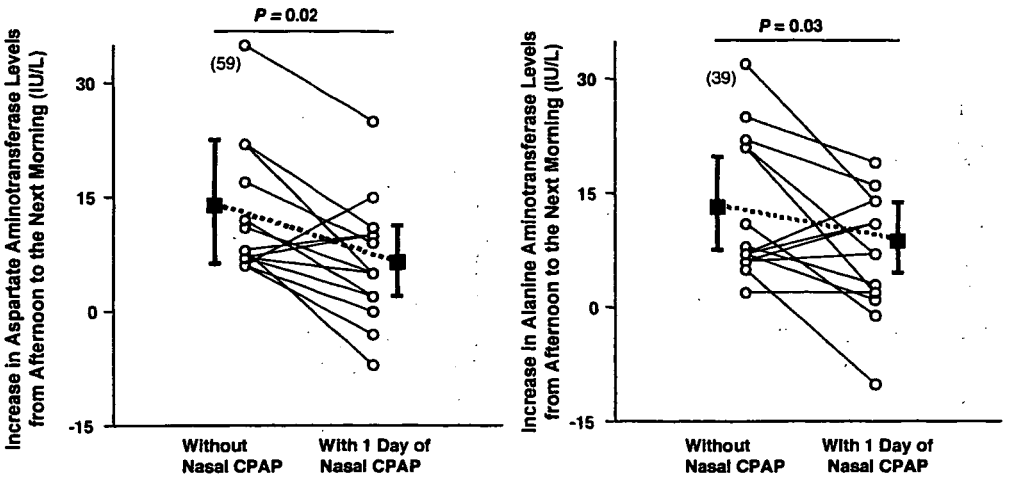

Figure 2. Increase in aspartate and alanine aminotransferase levels from afternoon to the next morning in patients with obstructive sleep apnea syndrome whose aspartate aminotransferase values were ≥49 IU/L (n = 14), without and after the first day of nasal continuous positive airway pressure (CPAP) treatment. Bars indicate mean levels with 95% confidence intervals.

hepatocellular injury after ischemia and reperfusion (27). Hepatocytes from fatty livers may have greater sensitivity to hypoxia (23). However, we did not perform liver biopsies and thus could not show an association between hepatic steatosis or steatohepatitis and sleep apnea with hypoxemia.

Among patients with unexplained elevations in serum aminotransferase levels, 90% have some degree of steatosis (13), which is also common in patients with obesity, especially visceral obesity (28,29), hyperinsulinemia, insulin resistance (18,19), diabetes (18), and ratios of alanine to aspartate aminotransferase levels that are ≥1 (30). We found that insulin resistance correlated significantly with morning aminotransferase levels before nasal CPAP treatment, and that insulin resistance was greater in patients with abnormal aminotransferase levels.

Leptin, a circulating hormone that is expressed in adipose tissue (31-34), induces a complex response affecting control of body weight and energy expenditure (31). Hyperleptinemia increases hepatic triglyceride content and may contribute to hepatic steatosis in obese patients (35). As we found, serum leptin levels are high in patients with obstructive sleep apnea syndrome (3,4) and decrease considerably after nasal CPAP treatment (2,4). The results of a single night of nasal CPAP treatment in our study (Table 2) suggest that leptin resistance may improve before insulin resistance (6,7).

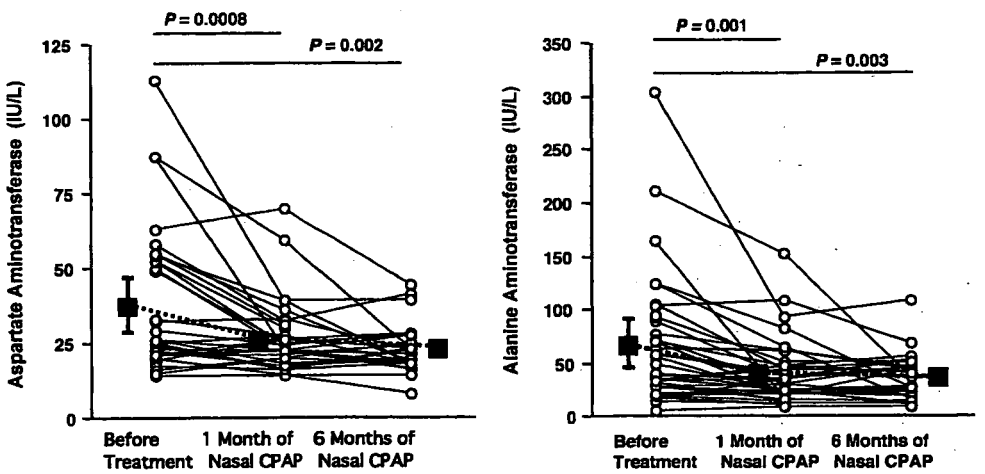

Figure 3. Levels of aspartate and alanine aminotransferase in patients with obstructive sleep apnea syndrome before (n = 34), after 1 month (n = 34) of, and after 6 months (n = 26) of nasal continuous positive airway pressure (CPAP) treatment (circles). Bars indicate mean levels with 95% confidence intervals.

Aspartate aminotransferase levels are subject to small intraday variations (36,37). However, based on 7685 blood samples from adult men, this intraday variance is only about 0.2% (37), much smaller than the approximately 15% overnight increase that we observed in men with obstructive sleep apnea.

Obesity increases the risk of sleep-disordered breathing. For example, an increase of 1 SD in any measure of body habitus is associated with a threefold increase in the risk of an apnea-hypopnea score of five or greater (1), and more than half of obese men may have some degree of sleep apnea. Conversely, 80% of patients with nonalcoholic hepatic steatosis are obese (38). Thus, a substantial proportion of obese patients may have both obstructive sleep apnea and hepatic steatosis, and clinicians should suspect sleep apnea in obese patients with abnormal serum aminotransferase levels.

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ORIGINAL ARTICLE

Nasal Continuous Positive Airway Pressure Improves Quality of Life in Obesity Hypoventilation Syndrome

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ABSTRACT

We studied the quality of life of obesity hypoventilation syndrome (OHS) by comparing it with age- and body mass index-matched patients without hypoventilation and age-matched obstructive sleep apnea (OSA) patients with body mass index (BMI) under 30, and the efficacy of nasal continuous positive airway pressure (CPAP) therapy for 3 to 6 months on the quality of life in these patients. Prospectively recruited patients from six sleep laboratories in Japan were administered assessments of the general health status by the Short-Form 36 Health Survey (SF-36) and subjective sleepiness by the Epworth Sleepiness Scale (ESS). Compared with matched healthy subjects, OHS and OSA patients not yet treated had worse results on the ESS scores and the SF-36 subscales for physical functioning, role limitations due to physical problems, general health perception, energy/vitality, role limitations due to emotional problems, and social functioning. The ESS scores of OHS patients were worse than those of the OSA groups including the age- and BMI-matched OSA patients. In the SF-36 subscales of OHS patients, only the subscale of social functioning showed worse results compared with that of BMI-matched OSA patients. After 3 to 6 months of treatment, ESS scores and these SF-36 subscales in all three patient groups improved to the normal level. These results suggested that the quality of life of OHS before nasal CPAP was significantly impaired and that nasal CPAP for OHS improved

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the quality of life associated with the improvement of daytime sleepiness to the level of the other OSA patients.

KEYWORDS: Sleep apnea, hypercapnia, excessive daytime sleepiness

Obesity hypoventilation syndrome (OHS) is characterized by daytime hypercapnia, daytime hypoxemia, obesity, and sleep-disordered breathing. The severe type of OHS is frequently associated with right heart failure and has a poor prognosis. The most typical cases are called Pickwickian syndrome.[1] Although OHS has various clinical definitions,[2] a Japanese respiratory failure research group recently proposed the following: persistent hypercapnia ($PaCO_2$ > 45 torr on arterial blood gas analysis), remarkable obesity (body mass index (BMI) > 30), the presence of daytime excessive sleepiness, and higher severity in sleep-disordered breathing (apnea/hypopnea index > 40 and/or remarkable oxygen desaturation).[3] It has been reported that apneic episodes are usually terminated by arousals and that the recurrent arousals from sleep cause neurophysiological problems such as daytime excessive sleepiness and poor quality of life in sleep apnea syndrome.[4–9] It is expected that the quality of life in OHS patients, who tend to belong to the most severe group in large populations of sleep apnea syndrome patients, will show worse results compared with common obstructive sleep apnea syndrome (OSA) patients without hypoventilation. However, there are no studies concerning the quality of life in OHS patients. Furthermore, although it has been reported that nasal continuous positive airway pressure (CPAP), which is a major treatment for patients with OSA, improves sleep-disordered breathing,[10] excessive daytime sleepiness,[11,12] cognitive function,[11] mood,[12,13] inspiratory effort sensation,[14] and daily activity[15–17] in OSA, little is known about the effect of nasal CPAP on the quality of life in OHS.

In the present study, we characterized the quality of life of OHS patients by comparing it with age- and BMI-matched patients without hypoventilation and age-matched OSA patients under BMI = 30. Furthermore, we studied the efficacy of nasal CPAP therapy for 3 to 6 months on the quality of life.

METHODS

Subjects

Newly registered patients with OSA from the years 1999 to 2001 were prospectively recruited from six sleep centers of schools of medicine and private sleep centers and divided into three groups: OHS, age- and BMI-matched OSA patients without hypercapnia (for the present study defined as obese OSA), and age-matched OSA patients under BMI = 30 (defined as nonobese OSA). All patients were diagnosed using polysomnography during the time they spent in each laboratory. Each subject gave informed consent to the protocol, which was approved by the Human Research Committee of each institute. Patients with hypoventilation due to chest wall deformity, chronic obstructive pulmonary disease, or hypothyroidism were excluded.

Protocol

Subjects performed pulmonary function tests and were assessed by questionnaires concerning general health and daytime sleepiness before treatment. Vital capacity (VC) and forced expiratory volume in one second (FEV_1) were measured with a rolling-seal spirometer. Blood gas tension analysis including arterial oxygen tension (PaO_2) and arterial carbon dioxide tension ($PaCO_2$) was also done with a blood gas analyzer. The health-related quality of life and

subjective daytime sleepiness were assessed by the Medical Outcome Survey Short Form (SF-36)[18] and the Epworth Sleepiness Scale (ESS),[19] respectively.

The SF-36 is widely used to measure health status. The Japanese version of SF-36 was developed by Fukuhara and colleagues and the validity of this SF-36 was reported.[20] The SF-36 is composed of self-completed questionnaires of items that measure eight multi-item domains of health as follows: physical functioning (PF) with 10 items, role limitations due to physical problems (RP) with four items, bodily pain (BP) with two items, general health perception (GH) with five items, energy/ vitality (VT) with four items, role limitations due to emotional problems (RE) with three items, social functioning (SF) with two items, and mental health (MH) with five items. Each domain is transformed onto a score from 0 (worst possible health) to 100 (best possible health).

The ESS is composed of questionnaires on eight different situations with different levels of stimulation concerning the symptoms of daytime sleepiness, resulting in a final score of 0 to 24.[19]

We also recruited age-matched control subjects who were free from snoring and daytime sleepiness and obtained control scores using SF-36 and ESS. All recruited OSA patients were given nasal CPAP for the purpose of the study. At 3 to 6 months after nasal CPAP, subjects again underwent SF-36 and ESS assessment.

Overnight Sleep Study and Nasal CPAP Titration

An overnight sleep study was carried out for all patients in a darkened quiet room using standard polysomnographic equipment. Briefly, electroencephalography (C4/A1, C3/A2), electro-oculography, submental electromyography and electrocardiography with surface electrodes, airflow at the nose and mouth with thermistors, respiratory movements of the rib cage and abdomen with inductive plethysmography, and percutaneous arterial oxygen saturation with a finger pulse oximeter (SpO_2) were simultaneously measured. All variables were recorded on a computer and the analysis was performed by standard techniques in each institute. Apnea is defined as a cessation of airflow lasting 10 seconds or more, while hypopnea is defined as a more than 50% reduction in airflow for 10 seconds or more, associated with a decline in SpO_2 of more than 3% from the preceding value. The apnea-hypopnea index (AHI) was calculated according to the definition of Guilleminault and associates.[21] Sleep stages were determined according to international standard criteria.[22]

Nasal CPAP titration was performed under standard polysomnography on the day following the diagnostic polysomnography using a commercial CPAP device. The optimal CPAP level was determined as the pressure required to abolish apnea and to maintain SaO_2 > 90% during sleep. Nasal CPAP therapy was continued using the optimal CPAP pressure in each subject.

Statistical Analysis

All data were expressed as means ± standard deviation (SD). For comparison of data among the groups, two-way analysis of variance (ANOVA) was done and, if significant, data between two groups were compared by unpaired *t* test. The parameters before and after nasal CPAP were compared by paired *t* test. A two-tailed p value < 0.05 was considered significant.

RESULTS

Characteristics of Subjects and Patients with OSA

For the present study, 26 patients with OHS, 38 obese OSA patients, and 48 nonobese OSA patients were recruited. Furthermore, 35 normal age-matched sub-

Table 1 Physical and Respiratory Variables of OHS, Obese OSA and Nonobese OSA

	OHS	Obese OSA	Nonobese OSA
n (M/F)	26 (25/1)	44 (39/5)	48 (45/3)
Age (yr)	44.4 ± 9.3	44.6 ± 13.3	48.7 ± 11.0
BMI	36.4 ± 8.8**	36.0 ± 7.2jj	25.9 ± 2.8
VC (L)	3.8 ± 1.1**	3.7 ± 0.6jj	3.9 ± 0.6
%VC (%)	99.9 ± 18.9*	99.8 ± 16.3j	107.3 ± 13.4
FEV_1 (L)	3.0 ± 0.8	3.0 ± 0.8	3.0 ± 0.6
$\%FEV_1$ (%)	93.0 ± 15.4	92.0 ± 17.0	98.0 ± 11.7
PaO_2 (torr)	71.1 ± 8.3##**	78.3 ± 9.1jj	81.5 ± 10.8
$PaCO_2$ (torr)	49.0 ± 2.3##**	41.6 ± 2.8	41.8 ± 4.3
AHI (/hr)	67.0 ± 23.7**	56.1 ± 22.8jj	45.6 ± 25.0
Mean SpO_2 (%)	84.2 ± 7.3**	85.3 ± 7.4jj	91.6 ± 4.4
ESS	14.6 ± 4.9#**	12.5 ± 4.6jj	10.6 ± 3.8

BMI, body mass index; VC, slow vital capacity; %VC, VC for predicted value; FEV_1, forced expiratory in one second; $\%FEV_1$, FEV_1 for predicted value; PaO_2, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension; AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Scale. *, j $p < 0.05$, **, jj $p < 0.01$; significantly different from nonobese OSA. # $p < 0.05$, ## $p < 0.01$; significantly different from obese OSA.

jects (M/F = 33/2, 45 ± 11 years old, BMI = 23.9 ± 3.3) were recruited for assessment of SF-36 and ESS.

The characteristics of the initially recruited patients are shown in Table 1. There were no significant differences in FEV_1 and $\%FEV_1$ among OHS, obese OSA, and nonobese OSA patients. In the comparison between the two obese groups (OHS and obese OSA) and nonobese OSA, BMI and AHI in the two obese groups were greater than the corresponding parameters of the nonobese OSA. VC, %VC, PaO_2 and mean SpO_2 in two obese groups were smaller than the corresponding parameters of the nonobese OSA. In the comparison between OHS and obese OSA, VC, %VC, FEV_1, and $\%FEV_1$ did not differ, but PaO_2 in OHS and $PaCO_2$ in OHS patients were smaller and greater, respectively, than the corresponding parameters in obese OSA patients.

Eight domains of the pretreatment SF-36 levels of three patient groups and normal subjects are shown in Figure 1. The six domains aside from those for bodily pain and mental health were significantly different. In the comparisons between each patient group and the normal group, GH, VT, RE, and SF domains in each patient group were smaller than the corresponding domains in the normal group. RF and RP in OHS and obese OSA patients were smaller than those in the normal group, but RF and RP in nonobese OSA patients were not different from each domain of the normal group. In the comparison among patient groups, PF, GH, and SF domains in those with OHS were smaller than the corresponding domains in nonobese OSA patients, and PF and RP in obese OSA patients were smaller than those in nonobese OSA subjects. In the comparison between OHS and obese OSA patients, only the SF domain was smaller in those with OHS than in obese OSA patients.

The ESS before and after nasal CPAP in three OSA groups is shown in Figure 2. Pretreatment ESS scores were significantly different among the four groups and were largest in OHS patients.

The domains before and after nasal CPAP in each patient group are shown in Table 2 and Figure 3. In OHS, all the domains except for BP were significantly improved to the normal level. In obese OSA patients, all domains were significantly improved to the normal level. In nonobese OSA, the domains except for BP and RE were significantly improved to the normal level.

The ESS after nasal CPAP in the three groups also improved to the normal level as shown in Figure 2. The relationships between improvements of ESS (ΔESS) and each SF-36 score in all patients are shown in Table 3. The correlation coefficients between ΔESS and ΔPF, ΔRP, ΔSF, or ΔMH were not higher but were significant.

DISCUSSION

This study prospectively examined the quality of life before and after nasal CPAP in OHS, obese OSA, and nonobese OSA patients. We observed that (1) the pretreatment ESS scores of the three

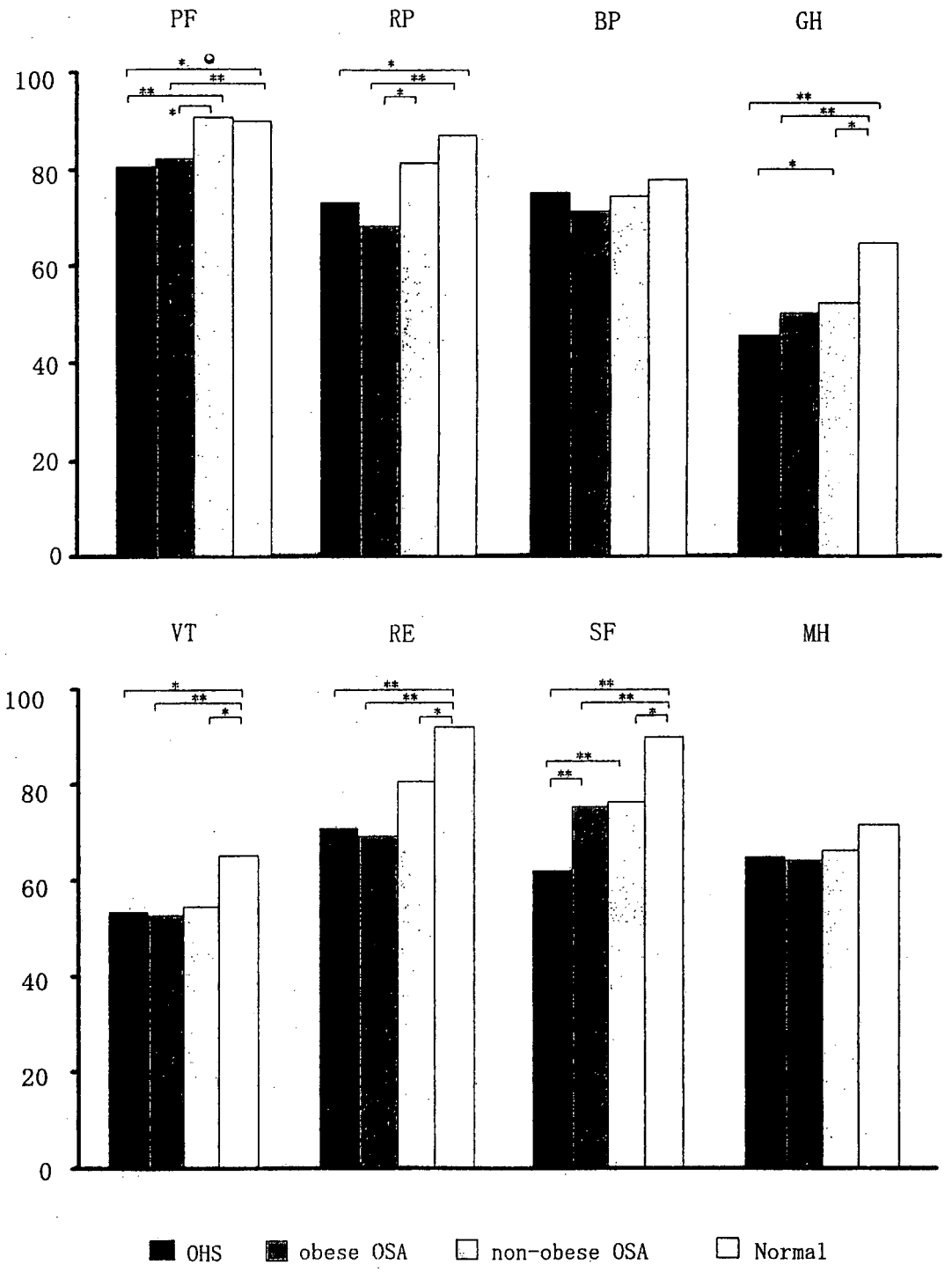

Figure 1 Eight domains of pretreatment SF-36 in patients with obesity hypoventilation syndrome (OHS), obese patients without hypoventilation (obese OSA), patients without moderate or severe obesity (nonobese OSA) and normal subjects. *, $p < 0.05$; **, $p < 0.01$, significant difference between two groups.

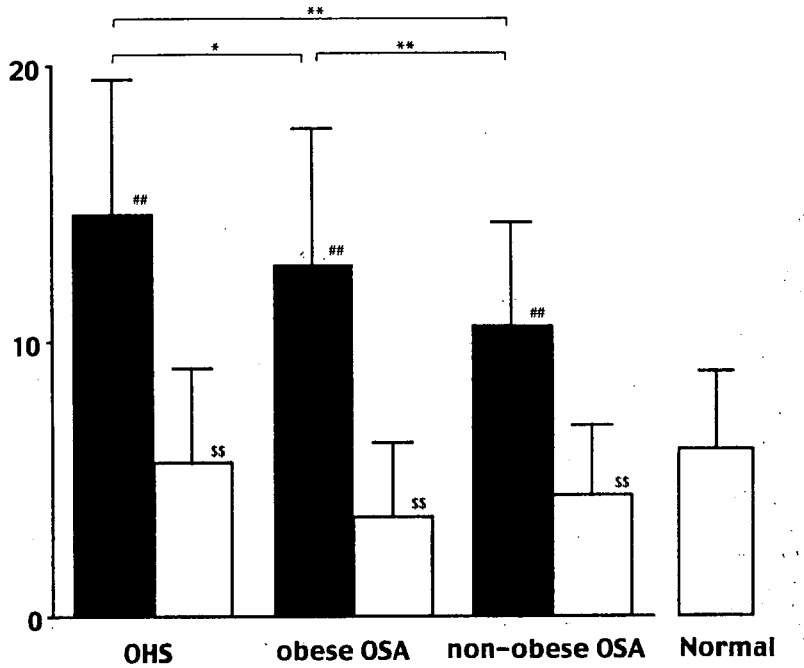

Figure 2 ESS before (black bars) and after (white bars) nasal CPAP in OHS, obese OSA and nonobese OSA. The last white bar on the right shows the ESS in normal group.

OSA groups were greater than those of the normal group, and the pretreatment ESS levels in OHS patients were largest in the three OSA groups; (2) the ESS in the three OSA groups returned to normal levels after treatment; (3) the pretreatment SF-36 scores of the three patient groups were lower than those of the normal group; (4) the SF domain of OHS patients showed a significant decrease compared with that of obese OSA patients without hypercapnia; and (5) the SF-36 scores in OHS patients improved to a normal level after nasal CPAP, similar to the two other OSA groups.

OHS is classified into three grades[2] by $PaCO_2$ and PaO_2: severe OHS shows severe hypercapnia ($PaCO_2$ > 60 mmHg) and hypoxemia (PaO_2 < 60 mmHg), moderate OHS shows moderate hypercapnia ($PaCO_2$ = 51 to 60 mmHg) and hypoxemia (PaO_2 = 60 to 70 mmHg); and mild OHS shows mild hypercapnia ($PaCO_2$ = 46 to 50 mmHg) without hypoxemia. The present OHS patients were classified as having mild or moderate OHS.

The difference between OHS and obese OSA was determined by the presence of daytime hypoventilation. The reason for this difference between the two groups is not clear. Since the ventilatory function shown by VC and FEV_1 was not different between these two groups, the hypoventilation in the OHS group cannot be explained by a mechanical impairment of the respiratory system. However, if OHS patients have impaired chemosensitivity to hypercapnia, the hypoventilation while awake may be explained by this impairment in the ventilatory reponse to hypercapnia. Previously, we observed that OSA patients with chronic hypercapnia had a lower ventilatory response to hypercapnia, which was improved to a normal level after nasal CPAP.[23] In the present study, although we did not examine the chemosensitivity, we speculate that the hypercapnic ventilatory response in OHS patients may be lower than that in obese OSA patients, as reported by previous investigators.[24–26]

Recently, it was reported that obese hypercapnic patients had higher fasting serum leptin levels than eucapnic patients, and serum leptin was a better predictor than body fat for the presence of hypercapnia.[27] Furthermore, leptin prevented res-

Table 2 Values of Domains of SF-36 in OHS, Obese OSA and Nonobese OSA before and after Nasal CPAP Treatment

Domain	Before Nasal CPAP	After Nasal CPAP	
OHS			
PF	80.4 ± 18.3	87.3 ± 11.5	< 0.05
RP	73.1 ± 33.1	88.6 ± 27.4	< 0.05
BP	75.3 ± 26.2	78.3 ± 24.3	NS
GH	45.4 ± 16.8	60.6 ± 16.3	< 0.01
VT	53.3 ± 18.7	72.1 ± 18.0	< 0.01
RE	70.5 ± 33.2	93.0 ± 23.1	< 0.05
SF	61.7 ± 22.1	90.2 ± 17.6	< 0.01
MH	64.8 ± 18.4	80.0 ± 17.6	< 0.01
Obese OSA			
PF	81.9 ± 14.6	88.7 ± 11.4	< 0.01
RP	68.1 ± 40.2	91.0 ± 21.3	< 0.01
BP	71.2 ± 30.2	84.9 ± 18.4	< 0.01
GH	50.0 ± 19.1	62.2 ± 18.1	< 0.01
VT	52.4 ± 23.8	72.0 ± 14.8	< 0.01
RE	69.1 ± 40.4	89.6 ± 26.4	< 0.01
SF	75.1 ± 23.7	91.4 ± 14.4	< 0.01
MH	64.0 ± 20.9	77.6 ± 17.1	< 0.01
Nonobese OSA			
PF	90.7 ± 10.1	92.1 ± 9.3	NS
RP	81.4 ± 30.3	92.2 ± 20.7	< 0.01
BP	74.2 ± 26.6	84.0 ± 18.3	< 0.01
GH	52.2 ± 16.4	64.0 ± 14.0	< 0.01
VT	54.4 ± 25.2	70.8 ± 17.7	< 0.01
RE	80.4 ± 32.8	86.8 ± 28.1	NS
SF	76.1 ± 23.9	88.6 ± 16.3	< 0.01
MH	65.9 ± 21.7	76.4 ± 15.2	< 0.01

CPAP, continuous positive airway pressure; OHS, obesity hypoventilation syndrome; SF-36, Short Form of the Medical Outcomes Survey Questionnaire; PF, physical function; RP, role limitations due to physical problems; BP, bodily pain; GH, general health perception; VT, energy/vitality; SF, social functioning; MH, mental health; NS, not significant.

piratory depression.[28] These papers suggested that the pathogenesis of hypoventilation in OHS was due to a deficiency of the central nervous system leptin level, which could be responsible for the hypoventilation in OHS.[27,28]

We observed an impaired health status assessed by SF-36 in the OSA patients, particularly in the OHS patients recruited in the present study. Why do patients with OSA have depressed health status while awake? First, daytime sleepiness in our patients may have been partly responsible for the impairment of the general health status. This possibility would be supported by the present finding that the excessive daytime sleepiness assessed by ESS was reversible after nasal CPAP and that the relationship between the improvements of ESS and the domains of SF-36 after nasal CPAP was significant, although the correlation coefficient was not large. The improvements in daytime sleepiness after nasal CPAP may produce an increase in daytime activity and greater alertness, leading to improvements in job performance. Even in normal subjects, sleep fragmentation can cause daytime sleepiness and impair their mood.[29]

The alternative possibility is that increased opioid activity in OSA may depress the health status. After nasal CPAP treatment the opioid activity is decreased,[30] which could explain the recovery of the health status.

Previous investigators have observed that SF-36 correlated more closely with ESS in OSA patients.[7,31] In the present study, the relationship between ESS and each domain of SF-36 before nasal CPAP was not significant (data not shown). This was not surprising. The basal health status may be affected by many factors apart from sleepiness such as age, sex, social status, occupation, coexisting diseases, and so on. Interestingly, the improvements of some domains of SF-36 had correlations with improvements of the ESS score, although the correlation coefficients were not very large. The improvement of the general health status by nasal CPAP would be partly influenced by improvements of daytime sleepiness.

We observed that the health status in OHS was lower than that in obese OSA patients without hypercapnia in terms of the SF domain. OHS patients may not be able to have good communication with other persons. The reason for this reduction in social activity in OHS is unclear. However, as the OHS group had a remarkable decrease of ESS, which might mean severe sleepiness, it is reasonable to speculate that OHS had a decrease in daytime activity because of excessive daytime sleepiness.

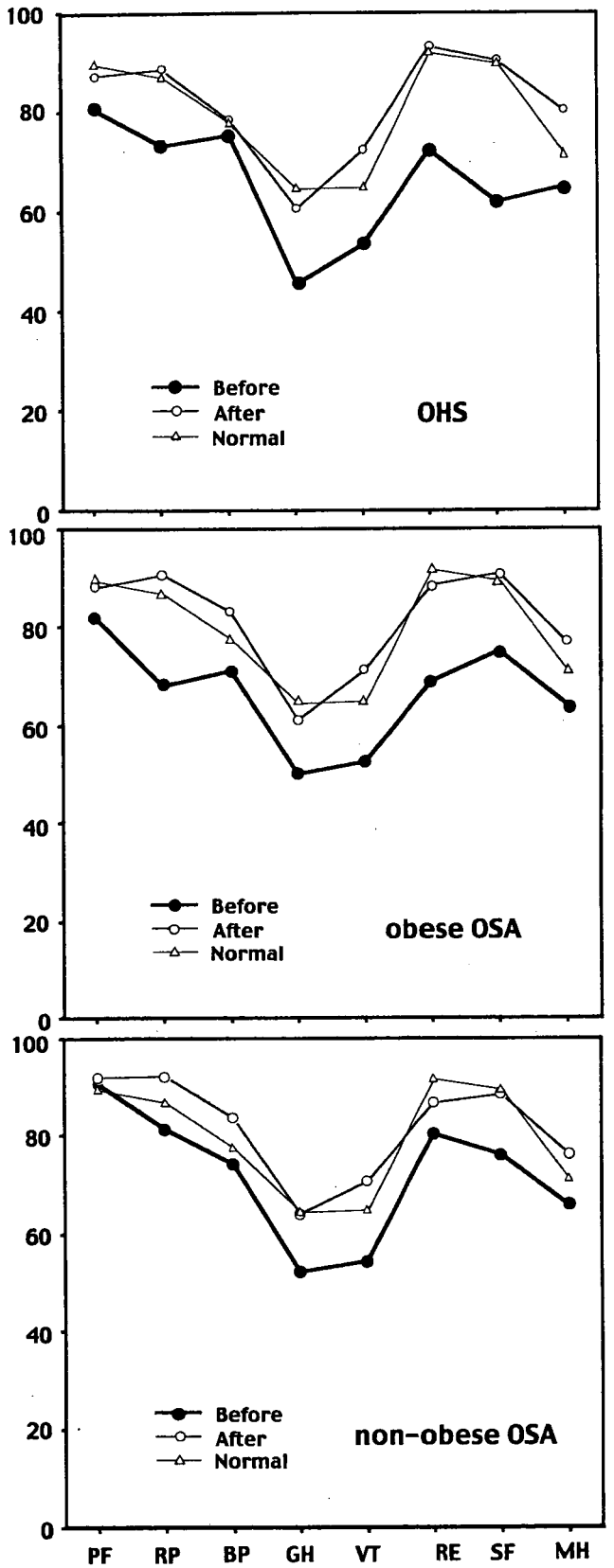

Figure 3 Domains of SF-36 before and after nasal CPAP in OHS, obese OSA and nonobese OSA.