Metabolic Abnormality and Sleep Disturbance are Associated with Clinical Severity of Patients with Schizophrenia

Chung-Chieh Hung a,b, Chin-Chih Liao c, Po-Lun Wu a,b, Shin-Da Lee c,d Hsien-Yuan Lane a,b*

1. Introduction

Schizophrenia, a psychiatric disorder causing deterioration of cognitive and daily function, is associated with obesity and metabolic syndrome, rendering patients vulnerable to morbidity and mortality[1]. Biological factors, lifestyle, and antipsychotics all contribute to obesity of patients[2], [3], which influences their sleep quality[4]. Prevalence of poor sleepers among schizophrenics is around 45%, related to adverse events of medication and accompanying depression and psychological distress[5], [6]. Metabolic abnormality and sleep disturbance seem correlated. Consequently, these patients reportedly have poor life quality; correlation between clinical symptoms and sleep quality remains unclear. We hypothesize patients with severe clinical symptoms as more likely to have metabolic abnormality and sleep disturbance.

2. Methods

Study was approved by China Medical University Hospital Institutional Review Board (IRB). All participants gave written informed consent.

2.1. Participants

We recruited 17 schizophrenic patients from the Rehabilitation Center of the China Medical University Hospital Psychiatric Department. All met criteria of schizophrenia, paranoid type, according to DSM-IV-TR[7]. We rated the subjects by Positive and Negative Syndrome Scale (PANSS) [8], with respective items scored from 1(absent) to 7(extreme severity). We rated their depressive symptoms by Abnormal Involuntary Movement (AIMS) [11], Simpson-Angus (SAS) [12], and Barnes Extrapyramidal symptoms were rated by Abnormal Involuntary Scale[9], and quality of life by Quality of Life Scale (QLS) [10]. We rated their depressive symptoms by Hamilton Depression Rating Scale[13]. Patients' weight and height, body mass index (BMI), neck circumference, waist circumference, waist-hip ratio (WHR) were recorded. Body fat was assessed by Omron body fat scale. Daily antipsychotic doses were recorded as chlorpromazine equivalents [14], and daily benzodiazepine doses as diazepam equivalents [15].

Inclusion criteria included (1) schizophrenic patients stable under current antipsychotics and benzodiazepine for at least three months; (2) engaged in regular rehabilitation program for at least three months; (3) aged between 20 and 50; (4) Han Taiwanese who speak Chinese fluently and understand this study well

Exclusion criteria included histories of (1) cerebrovascular, cardiovascular, and metabolic disorders (stroke, hypertension, diabetes mellitus); (2) neurologic disorders like epilepsy and traumatic brain injury; (3) physical disability (eg, fractures); (4) current DSM-IV-TR diagnosis of substance dependence (such as nicotine); (5) a DSM-IV-TR diagnosis of mental retardation, and (6) acute suicide or aggressive behaviors and (7) regular exercise.

2.2. Cognitive performance testing

Schizophrenic patients show impaired cognitive function [16], [17]. Our study included trail making, semantic association of verbal fluency, maze, verbal and non-verbal working memory, instant word list, instant and, delayed visual reproduction, and digit symbol coding, as conducted by well-trained psychologists.

2.3. Cardiometabolic parameters and physical fitness

Patients' weight and height, body mass index (BMI), neck circumference (NC), waist circumference, hip circumference, and waist-hip ratio (WHR) were recorded. Body fat was assessed by Omron body fat scale. Physical fitness was gauged according to a profile distributed by Bureau of Health Promotion, Department of Health, Taiwan. First, we checked sit-up frequency in one minute. Second, they underwent three-minute 35-centimeter-ladder climbing. We checked post-exercise heart rate.
We drew parameters from sleep polysomnography, including time in bed staging and arousal detection, as well as 2- or 5-minute respiratory data. were scored manually on a small monitor, using 30-second epochs for and C3 (referenced to A2) and F4 and C4 (referenced to A1). PSG data efficiency (TST/TIB).

The presence of metabolic syndrome was recorded as defined by National Cholesterol Education Program (NCEP) guidelines: waist circumference ≥ 102 cm (male) and ≥ 88 cm (female), triglyceride (TG) ≥ 150 mg/dl, HDL-cholesterol < 40 mg/dl (male) and < 50 mg/dl (female), blood pressure ≥ 130/85 mmHg, and fasting glucose ≥ 110 mg/dl [9]. Metabolic syndrome index was summed by the above criteria.

2.4 Sleep measurement
Sleep rating scales were self-recorded by all subjects preceding polysomnography examination: Pittsburgh Sleep Quality Index (PSQI) [20], Insomnia Severity Index (ISI) [21], Epworth Sleepiness Scale (ESS) [22], and Pre-Sleep Arousal Scale (PSAS) [23]. Polysomnography (PSG) followed standardized techniques: digital electroencephalography (EEG), electromyography, and electrooculography signals acquired with Alice 4 system. PSG electrode montage was utilized, composed of EEG sites F3 and C3 (referenced to A2) and F4 and C4 (referenced to A1). PSG data were scored manually on a small monitor, using 30-second epochs for staging and arousal detection, as well as 2- or 5-minute respiratory data. We drew parameters from sleep polysomnography, including time in bed (TIB), total sleep time (TST), sleep latency, waking time, sleep efficiency (TST/TIB).

Sleep architecture was assessed for each 30-second epoch coded as Wake, Stage 1, Stage 2, Stage 3+4 (slow wave sleep, SWS), and Rapid Eye-Movement (REM) sleep according to criteria made by Rechtschaffen and Kales [24]. Arousal were identified according to criteria of the American Sleep Disorders Association (ASDA) 1992 [25].

We identified apnea and hypopnea as flat air flow lower than 20% and 70% of the baseline, respectively, whose amplitude was measured during the nearest preceding period of regular breathing with stable oxygen saturation. We identified Apnea-hypopnea index as total apnea and hypopnea divided by total sleep time.

3. Data analysis
We divided participants into two groups according to severity of clinical manifestation Cut-off value was median number of the PANSS total scores. Student'-T test compared all variables between the two groups.

4. Results
Age and gender between groups were similar, as was duration of education and age at illness onset. Duration of illness of the H-PANSS group was longer. Clinical Global Impression (CGI) [11] tallied higher and Quality of Life Scale (QLS) lower in the H-PANSS group, depressive symptoms rated by Hamilton Depression Scale similar between groups (Table 1). Current medications calculated by chlorpromazine and Diazepam equivalents were also similar. There were no differences between the two groups in severity of EPS rated by Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, and Simpson-Angus Scale (Table 1).

Table 1. Demographic and clinical characteristics

| Demographic characteristics | L-PANSS (n=8) | H-PANSS (n=9) | P value |
|-----------------------------|--------------|--------------|--------|
| Age (years)                 | 35 ± 9.3     | 37 ± 9.6     | 0.801  |
| Male/Female (male percentage) | 2/6 (25%)     | 4/5 (44%)     | 0.434  |
| Duration of education (years) | 13.0 ± 3.3     | 11.6 ± 3.6     | 0.405  |
| Duration of illness (months) | 101.5 ± 71.8    | 186.7 ± 63.8    | 0.021 * |

Clinical psychiatric condition rating scales

| Clinical Global Impression (CGI) | 2.9 ± 0.4 | 3.7 ± 0.5 | 0.002 ** |
| Quality of life scale (QLS) | 63.3 ± 11.4 | 35.4 ± 14.0 | <0.001 ** |
| Hamilton Depression Rating scale | 8.1 ± 5.2 | 12.7 ± 8.4 | 0.207 |

Medication amount

| Chlorpromazine equivalents | 212.5 ± 64.1 | 237.2 ± 91.0 | 0.532 |
| Diazepam equivalents | 12.5 ± 16.9 | 5.0 ± 6.1 | 0.232 |
| Abnormal Involuntary Movement scale | 4.1 ± 6.3 | 5.1 ± 4.5 | 0.712 |
| Barnes Akathisia Rating scale | 0.6 ± 1.2 | 2.1 ± 2.6 | 0.162 |
| Simpson-Angus scale | 5.8 ± 4.7 | 7.3 ± 3.5 | 0.440 |

All data were expressed as mean value ± standard deviation, except gender.

Low-PANSS (L-PANSS) group included schizophrenics with Positive and Negative Syndrome Scale (PANSS) total score below 65 (median of PANSS total scores of all 17 subjects); High-PANSS (H-PANSS) group included those with PANSS total scores 65 or higher.

*:P<0.05 and **:P<0.01, significance between groups.

Cognitive performances between groups were similar. (Table 2)

Table 2. Cognition tests measured in two groups of patients

| Parameters | L-PANSS (n=8) | H-PANSS (n=9) | P value |
|-----------|--------------|--------------|--------|
| Trail making task | 1.6 ± 0.9 | 2.0 ± 1.0 | 0.435 |
| Digit symbol coding | 4.9 ± 2.0 | 4.6 ± 3.1 | 0.807 |
| Verbal association of verbal fluency | 0.6 ± 0.5 | 0.4 ± 0.5 | 0.488 |
| Maze | 3.8 ± 1.6 | 4.2 ± 4.6 | 0.787 |
| Non-verbal working memory | 7.6 ± 3.9 | 8.7 ± 3.9 | 0.590 |
| Instant word list | 4.5 ± 3.1 | 5.6 ± 3.1 | 0.491 |
| Delay word list | 5.6 ± 2.8 | 5.1 ± 3.0 | 0.719 |
| Instant visual reproduction | 4.9 ± 2.2 | 4.8 ± 2.3 | 0.931 |
| Delay visual reproduction | 6.4 ± 2.6 | 5.1 ± 2.2 | 0.291 |

Data were expressed as mean value ± standard deviation.

Low-PANSS (L-PANSS) group included schizophrenics with Positive and Negative Syndrome Scale (PANSS) total score below 65 (median of PANSS total scores of all 17 subjects); High-PANSS (H-PANSS) group comprised those with PANSS total scores 65 or higher. No significance appeared between groups.

Body weight and neck circumference (NC) in the H-PANSS group were higher than those in the L-PANSS group. Body height, BMI, waist circumference, hip circumference, WHR and body fat between groups were similar, as was physical fitness measured by sit-up and climbing (Table 3). Both systolic and diastolic blood pressures in the H-PANSS group were higher. Metabolic index, heart rate, fasting sugar, insulin,
Homa-IR, cortisol, cholesterol, triglyceride, high-density lipoprotein, and low-density lipoprotein between groups were similar (Table 3).

Table 3. Cardiometabolic parameters and physical fitness

| Physical parameters       | L-PANSS (n=8) | H-PANSS (n=9) | P value |
|--------------------------|---------------|---------------|---------|
| Body weight (BW) (kg)    | 65.4 ± 9.6    | 78.3 ± 9.2    | 0.013*  |
| Body height (BH) (cm)    | 144.9 ± 12.5  | 161.1 ± 15.3  | 0.031*  |
| Body mass index (BMI) (kg/m2) | 31.5 ± 5.5  | 30.5 ± 4.1    | 0.653   |
| Neck circumference (NC) (cm) | 35.0 ± 2.6  | 38.6 ± 2.1    | 0.007** |
| Waist circumference (cm) | 91.5 ± 10.5   | 95.8 ± 9.2    | 0.386   |
| Hip circumference (cm)   | 104.4 ± 9.1   | 106.8 ± 6.5   | 0.537   |
| Waist-hip ratio (WHR)    | 0.89 ± 0.07   | 0.87 ± 0.05   | 0.652   |
| Body fat (%)             | 33.8 ± 5.1    | 32.1 ± 6.7    | 0.564   |

Physical fitness

| Physical fitness         | L-PANSS | H-PANSS | P value |
|--------------------------|---------|---------|---------|
| Sit-up (/min)            | 14.5 ± 12.7 | 14.2 ± 9.4 | 0.959   |
| Stair-climbing PEHR 1 (/min) | 52.9 ± 10.4 | 51.3 ± 8.7 | 0.960   |
| PEHR 2 (/min)            | 48.4 ± 9.6  | 47.9 ± 8.5  | 0.913   |
| PEHR 3 (/min)            | 47.0 ± 8.2  | 45.8 ± 8.3  | 0.765   |
| Climbing time (s)        | 114.8 ± 57.4 | 133.3 ± 39.2 | 0.443   |

Cardiometabolic parameters

| Cardiometabolic parameters       | L-PANSS | H-PANSS | P value |
|-----------------------------------|---------|---------|---------|
| Heart rate (minute)               | 83.3 ± 16.8 | 85.9 ± 6.9 | 0.671   |
| Systolic blood pressure (mmHg)    | 107.8 ± 8.2  | 122.7 ± 6.3 | <0.001** |
| Diastolic blood pressure (mmHg)   | 65.8 ± 7.1   | 77.8 ± 10.2  | 0.014*  |
| Fasting sugar (mg/dL)             | 91.1 ± 9.6   | 100.7 ± 17.7 | 0.196   |
| Insulin (uIU/mL)                  | 9.6 ± 10.4   | 30.1 ± 54.06 | 0.322   |
| Homa-IR                           | 2.21 ± 1.01  | 8.48 ± 17.04 | 0.316   |
| Cortisol (ug/dL)                  | 13.4 ± 2.4   | 11.4 ± 4.9   | 0.309   |
| Total cholesterol (mg/dL)         | 202.6 ± 35.0  | 215.1 ± 44.3  | 0.532   |
| Triglyceride (mg/dL)              | 228.5 ± 164.3 | 144.6 ± 77.5 | 0.190   |
| High-density lipoprotein (mg/dL)  | 43.9 ± 16.0   | 41.2 ± 7.2   | 0.661   |
| Low-density lipoprotein (mg/dL)   | 115.0 ± 27.9  | 142.4 ± 37.4  | 0.111   |
| Metabolic syndrome index          | 1.4 ± 1.1    | 1.8 ± 1.6    | 0.549   |

All data were expressed as mean value ± standard deviation.

Low-PANSS (L-PANSS) group included schizophrenics with Positive and Negative Syndrome Scale (PANSS) total score below 65 (median of PANSS total scores of all 17 subjects); High-PANSS (H-PANSS) group included those with PANSS total scores 65 or higher. NREM: non-rapid eye movement, REM: rapid eye movement, SpO2: saturation of peripheral oxygen, ALM: arousal and limb movement. NREM S3+S4 (SWS) in the H-PANSS group was lower. Intergroup NREM S1, S2 and REM sleep were similar (Table 4). Mean SpO2 in the H-PANSS group was lower. Apnea-hypopnea index, Arousal and Limb Movement, and leg movement between groups were similar (Table 4). *:P<0.05 and **:P<0.01, significance between groups.

Table 4. Sleep parameter measurement

| Sleep parameter                | L-PANSS (n=8) | H-PANSS (n=9) | P value |
|--------------------------------|---------------|---------------|---------|
| Sleep continuity               |               |               |         |
| Awakening time                 | 7.0 ± 0.9     | 7.2 ± 0.4     | 0.673   |
| Bed time                       | 22.7 ± 1.8    | 20.9 ± 1.6    | 0.052   |
| Sleep efficiency (%)           | 84.0 ± 12.0   | 63.0 ± 28.3   | 0.071   |
| Sleep latency                  | 30.9 ± 20.2   | 24.3 ± 19.4   | 0.505   |
| Total sleep time               | 7.5 ± 0.7     | 8.4 ± 1.1     | 0.067   |
| Sleep questionnaires           |               |               |         |
| Epworth Sleepiness Scale       | 9.0 ± 5.2     | 8.0 ± 4.0     | 0.663   |
| Insomnia Severity Index        | 9.1 ± 3.7     | 8.3 ± 3.2     | 0.646   |
| Pre-Sleep Arousal Scale        | 32.9 ± 16.6   | 26.4 ± 11.5   | 0.363   |
| Pittsburgh Sleep Quality Index | 13.8 ± 7.1    | 14.3 ± 7.5    | 0.872   |
| Sleep architecture             |               |               |         |
| NREM S1 (%)                    | 12.5 ± 14.6   | 29.3 ± 3.5    | 0.190   |
| NREM S2 (%)                    | 62.8 ± 19.0   | 47.0 ± 21.3   | 0.129   |
| NREM S3+S4 (%)                 | 8.0 ± 9.1     | 11.2 ± 2.9    | 0.047*  |
| REM sleep (%)                  | 16.6 ± 5.5    | 22.7 ± 16.6   | 0.337   |
| Sleep obstruction parameters   |               |               |         |
| Apnea-hypopnea index           | 6.2 ± 8.8     | 8.8 ± 9.4     | 0.560   |
| Mean SpO2 (%)                  | 96.6 ± 1.5    | 95.0 ± 1.5    | 0.046*  |
| ALM (events/hour)              | 88 ± 8.1      | 194 ± 19.0    | 0.164   |
| Leg movement                   | 53.1 ± 100.2  | 11.6 ± 34.7   | 0.295   |

All data were expressed as mean value ± standard deviation.

The mean scores of respective sleep questionnaires, including ESS, ISI, PAS, and PSQI, were similar between L-PANSS and H-PANSS groups (Table 4). Parameters of sleep continuity measured by PSG, including awakening time, bed time, sleep efficiency, sleep latency, and total sleep time between groups were all similar. Marginal difference between the two groups were noted in the ratio of stage 3 and 4 sleep (slow wave sleep) and oxygen saturation rates.
4. Discussion

To our knowledge, this is the first study to suggest that severe clinical symptoms are associated with metabolic and sleep disturbance in patients with schizophrenia. In more detail, this study demonstrates that schizophrenia patients with severe symptomatology may have more metabolic abnormalities including heavier body weight, wider neck circumference, and elevated systolic/diastolic blood pressure. We found no intergroup statistical significance in terms of blood sugar, insulin, cortisol, and lipid profiles. This is the first study to suggest that schizophrenic patients with more severe symptoms might have decreased oxygen saturation. It also demonstrated that patients with more severe symptoms had reduced SWS when their sleep efficiency and total sleep time were similar to the low PANSS group. Results concurred with prior studies: positive symptoms of schizophrenia increased REM sleep eye movement density, short REM latency, reduced sleep efficiency and prolonged sleep latency [26], [27], [28], [29]. Conversely, negative symptoms relate to short REM latency and SWS deficit [30], [31]. Cognitive symptoms to SWS deficit [28], [29]. Sarkar et al. [32] found significant difference in SWS parameters (including increased Stage 3 and decreased Stage 4 latency between patients and controls.

The strength of this study is control over two groups of patients similar in basic demographic data, cognitive function performance, and physical fitness. Limitations of the study included small sample size and cross-section design. In sum, this study suggests clinical symptoms as linked with heavier body weight, wider neck circumference, elevated blood pressure, and shorter SWS in schizophrenic patients. Further studies must confirm preliminary findings and elucidate the underlying mechanism.

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