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Effect of Tai Chi Chuan on serotonin and cortisol for monitoring stress and quality of life in post-treatment breast cancer patients

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[Abstract] Objective Immediate physical exercise has been recommended for patients in the recovery phase to improve survival and quality of life (QOL) and reduce recurrence of disease. The new NCCN Guidelines for Survivorship also highlighted the role of exercise in post-cancer health, encouraging patients to perform light physical activity following treatment. The aim of our study is to effect of Tai Chi Chuan (TCC) on serotonin and cortisol for monitoring stress and QOL in post-treatment breast cancer patients. **Methods** Totally 85 post-treatment breast cancer patients were enrolled in this study to observe the effects of practicing TCC on recovery, as well as stress and happiness which are indicators of QOL of in patients. Peripheral blood was drawn from study subjects to analyze the levels of serotonin, cortisol and high sensitive C-reactive protein (HS-CRP) at baseline, and at 3, 6 and 12 months of TCC practice. Blood was drawn from healthy subjects only at baseline. A QOL questionnaire was administered to study subjects at three time points throughout the study, and once for healthy controls. The data were processed by analysis of variance of repeated measurement. **Results** At 3, 6 and 12 months time points following regular TCC exercise, WBC, RBC, hemoglobin in blood samples showed a statistically significant difference ($F = 161.55, 172.14, 289.73$; all $P = 0.00$); the level of serotonin (biomarker for well-being), cortisol (indicator of stress) and HS-CRP (biomarker for inflammation) showed a statistical improvement ($F = 307.46, 182.85, 102.23$; all $P = 0.00$). After 3, 6 and 12 months of regular TCC exercise, according to the results of QOL questionnaire, the indicators including quality of sleep, perceived hunger, fatigue, contentment, stress and social interaction presented a significant difference ($F = 312.98, 222.64, 543.90, 46.05, 28.10, 78.92$, all $P < 0.05$), while there was no statistical difference in life dissatisfaction ($F = 56.61, P = 0.166$). **Conclusions** TCC physical activity for post-treatment breast cancer patients improved QOL and overall well-being, leading to improved mental, physical and psychological functioning. Regulated levels of serotonin and cortisol mediated by TCC exercises are proved to be vital for continued good health.

[Key words] Tai Ji; Breast neoplasms; Quality of life; Serotonin

Breast cancer has the highest incidence of all female cancers in Hong Kong, surpassing other cancers with 3014 newly diagnosed cases per

year^[1-3]. While breast cancer is predominantly diagnosed in 40–45 years old females, the incidence has been rising in younger cohorts of 20–25 years old females^[1].

Mortality for breast cancer has been on the rise in Asia prominently owing to adoption of westernized lifestyles, stress, busy schedules, and insufficient exercise^[4-7]. Survival is observably higher in developed countries with implemented breast screening programs for prevention with ultrasound and mammography^[6].

Regular physical activity correlates with reduced risk of cancer in healthy individuals^[8-12]. Regular

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exercise is correlated with regulated levels of body hormones, which have been linked to 20%–40% lowered breast cancer risk^[9-10]. Regular exercise has also been linked to a better quality of life (QOL) for breast cancer patients^[11-13], in addition to reducing the risk of death, thus increasing survival^[9]. For diagnosed breast cancer females, weight gain during and after treatment has been correlated with lowered survival^[9-10,14]. Therefore, post-treatment exercise would be vital for recurrence risk, longer survival and good health.

The new National Comprehensive Cancer Network (NCCN) Guidelines for Survivorship highlighted the importance of exercise for cancer survivors^[15]. Generally, exercises should be light to begin, in order to encourage patients to perform physical activity. Physicians are recommended to work with the patient to determine exercise ability and to give advices accordingly^[15-18].

Light exercises such as Tai Chi Chuan (TCC) could be appropriately incorporated into a rehabilitation program for survivors. Tai Chi is a form of martial arts involving meditation and slow, graceful, extended movements to build strength and muscle in the core areas of the body. The benefits of TCC as a form of meditative mind exercise have been studied in breast cancer survivors in various pilot studies. Application of TCC has also been extended to the patients with cardiac diseases, hypertension, Parkinson's disease, psychological diseases, osteoporosis and others, with proved positive effects^[16-19]. Research demonstrated that TCC has helped cancer patients recover, sleep better and cope with pain, anxiety and depression, which are often associated with traditional cancer treatment^[20-23].

To investigate the relationship of breast cancer recurrence, survival and QOL with regular TCC physical activity, this study analyzed blood biomarkers [white blood cells (WBC), red blood cells(RBC), hemoglobin, serotonin, cortisol and C-reactive protein (CRP)], and a psychological QOL questionnaire.

1 Materials and Methods

1.1 Subject eligibility and recruitment

Eligible subjects were post-treatment breast

cancer patients aged 20–50 years with confirmed invasive ductal carcinoma, who underwent modified mastectomy and 4 or 6 cycles of FEC (500 mg/m² 5-fluorouracil, 75 mg/m² epirubicin and 500 mg/m² cyclophosphamide) chemotherapy for six months.

Healthy subjects were disease-free females aged over 18 years. Exclusion criteria for all subjects included diagnosis of other systemic diseases, regular alcohol intake; and regular smokers or subjects with a previous smoking history.

A total of 80 post-treatment female breast cancer patients and 43 healthy female controls meeting the prescreening criteria were recruited from UNIMED Medical Institute and Organisation for Oncology and Translational Research, Hong Kong, and School of Chinese Medicine, Li Ka Shing Faculty of Medicine, University of Hong Kong. The study was conducted from January 2012 to June 2013 under the study protocol UW 12-046 approved by the Hong Kong University/Health Authority Hong Kong West Cluster Institutional Review Board (HKU/HA HKW IRB). Consent was given by all subjects prior to study start-up. Socio-demographic information for age, education of all subjects, and clinical data regarding disease stage and treatment were extracted from patients' records.

1.2 Subject demographics

The healthy females were aged between 24–39 years. One female received primary education only, 10 attended secondary school and 32 attended tertiary school, respectively. The breast cancer patients were 28–50 years old. Three females attended primary school, 20 received secondary education and 57 received tertiary education respectively.

Among all 80 breast cancer subjects, 86% ($n=69$) of the tumors were confirmed to be ER positive, 79% ($n=63$) were PR positive, and 36% ($n=28$) were HER-2 positive. Furthermore, 62% ($n=50$), 32% ($n=25$), and 6% ($n=5$) corresponded to grade 1, 2 and 3 tumors respectively.

1.3 Blood collection

Peripheral blood samples were collected by direct venipuncture from the arm vein of each subject, 20 ml in lithium heparin tubes and 10 ml in blood clot tubes (BD Vacutainer, USA),

respectively, for analyzing the levels of cortisol (7–10 am: 171–536 nmol/L; 4–8 pm: 64–327 nmol/L) and high sensitive CRP (HS-CRP, <1.0) by an automated multi-analyte analyzer COBAS INTEGRA 400 (Roche, Germany). The normal ranges of blood parameters were as follows: WBC ($4.00 - 11.00$) $\times 10^9$ /L, RBC ($3.80 - 5.80$) $\times 10^{12}$ /L, and hemoglobin 115–165 g/L^[24].

1.4 Preparation of blood samples

The samples were centrifuged for 10 min at 1500 r/min, and the serum and plasma were then collected for enzyme-linked immunosorbent assay (ELISA). The remaining cellular components were transferred to a 50 ml centrifuge tube with an addition of RBC lysis buffer up to 45 ml. The mixture in the tube was inverted several times, and then centrifuged for 10 min at 1500 r/min

1.5 ELISA

The 100 μ l of the standard group solutions and serum of each subject were pipetted into a 96-well plate in the Serotonin ELISA Kit (DRG International Inc, USA). ELISA was performed according to the manufacturer's protocols from the Serotonin ELISA Kit, and the plates were read at 450 nm wavelength using Universal Microplate Reader (Sunrise, Tecan, Australia). The normal detection range of serotonin was 101–283 ng/ml.

1.6 QOL questionnaire

A questionnaire was designed to detect QOL of post-treatment patients. Physical functioning was measured by the quality of sleep, perceived hunger, and fatigue, while psychological functioning included degree of contentment, stress, social interaction, and overall satisfaction of life. The posed questions were intended to correlate with the effects of a regular TCC exercise program as rehabilitation for patients following surgery and chemotherapy. Preliminary raw data were scaled from 1 to 10 (1 for the lowest state and 10 for the best state accordingly).

1.7 Supervision of regular Tai Chi Chuan exercises

All post-treatment subjects were taught a total of 115 postures of the Yang style TCC exercises and required to follow each posture demonstrated by the Tai Chi practitioners. The subjects were required to practice TCC for 45 min per day, six times a week for 12 months. Healthy subjects were not required to

practice TCC. To ensure that the patients were performing the exercises correctly, Tai Chi practitioners were present to lead the TCC routines, give advices and provide help as needed.

1.8 Statistical analysis

All calculations were performed using SPSS version 17.0. Analysis of variance was applied to measure physical and psychological functioning parameters of the healthy and patient groups at baseline, and additionally for the patient group at 3, 6 and 12 months. $P < 0.05$ was considered statistically significant.

2 Results

2.1 Evaluation of blood indicators

The levels of WBC, RBC, hemoglobin, serotonin, cortisol and HS-CRP for healthy group were collectively within normal ranges at (7.80 ± 0.95) $\times 10^9$ /L, (4.85 ± 0.55) $\times 10^{12}$ /L, (139.00 ± 25.00) g/L, (149.42 ± 6.49) ng/ml, (256.50 ± 15.30) nmol/L, and (0.46 ± 0.25) pg/ml, measured only once at baseline. In patient group, the same blood parameters, including WBC (3.00 ± 0.88) $\times 10^9$ /L, RBC (2.99 ± 0.65) $\times 10^{12}$ /L, hemoglobin (90.00 ± 16.60) g/L, serotonin (45.32 ± 5.77) ng/ml, cortisol (615.50 ± 28.44) nmol/L, and HS-CRP (3.10 ± 0.85) pg/mL collectively fell outside the normal ranges.

At 3, 6 and 12 months time points following regular TCC exercise, statistically significant improvements were exhibited in WBC, RBC and hemoglobin. The statistical values were shown in Table 1.

At 3 months after TCC exercises, the level of serotonin (biomarker for well-being) increased to (88.57 ± 7.57) ng/ml, cortisol (indicator of stress) decreased to (566.42 ± 56.70) nmol/L, and HS-CRP (biomarker for inflammation) decreased to (2.06 ± 0.42) pg/ml in the patient group. The levels of serotonin and cortisol in the patients group were (99.48 ± 5.21) ng/ml and (424.20 ± 25.86) nmol/L at 6 months, (108.28 ± 9.85) ng/ml and (305.20 ± 50.68) nmol/L at 12 months respectively, which were significantly increased compared with baseline. The inflammatory biomarker, HS-CRP, decreased significantly to (1.85 ± 0.15) pg/ml after 6 months

and (0.86 ± 0.52) pg/ml after 12 months of TCC exercise (Table 1).

2.2 QOL questionnaire: physical and psychological functioning

The results of the questionnaires were collected, grouped, analyzed, and presented in Table 2. At baseline, for physical functioning, the score of quality of sleep was 8.10 ± 0.40 vs 2.10 ± 0.00 , perceived hunger 7.90 ± 0.77 vs 3.20 ± 0.95 , and fatigue 1.90 ± 0.60 vs 7.90 ± 1.00 ; for psychological functioning, the score of contentment was 7.50 ± 0.54 vs 4.50 ± 0.39 , stress 5.60 ± 0.94 vs 7.30 ± 1.15 , social interaction 8.60 ± 0.50 vs 5.50 ± 0.82 , and life dissatisfaction 2.10 ± 0.82 vs 4.00 ± 0.18 (healthy individuals vs breast cancer survivors). All indicated significant differences between the healthy

and patient group.

After 3, 6 and 12 months of regular TCC exercise, according to the results of QOL questionnaire, the indicator for physical functioning, including quality of sleep, perceived hunger and fatigue all showed a significant difference; the indicators for psychological functioning, including contentment, stress and social interaction presented a significant difference, while there was no statistical difference in life dissatisfaction (all statistical values were shown in Table 2).

3 Discussion

The importance of exercise was highlighted in the new National Comprehensive Cancer Network (NCCN) Guidelines for Survivorship^[15]. The role of

Table 1 Blood biomarker parameters of healthy controls at baseline, and patient group at baseline, 3, 6 and 12 months of Tai chi chuan exercises ($\bar{x} \pm s$)

Groups	<i>n</i>	White blood cells ($10^9/L$)	Red blood cells ($10^{12}/L$)	Hemoglobin (g/L)	Serotonin (ng/ml)	Cortisol (nmol/L)	C-reactive protein (pg/ml)
Healthy group							
Baseline	43	7.80 ± 0.95	4.85 ± 0.55	139.00 ± 25.00	149.42 ± 6.49	256.50 ± 15.30	0.46 ± 0.25
Patient group							
Baseline	80	3.00 ± 0.88	2.99 ± 0.65	90.00 ± 16.60	45.32 ± 5.77	615.50 ± 28.44	3.10 ± 0.85
3 months ^a	80	4.12 ± 0.43	4.05 ± 0.99	122.20 ± 18.90	88.57 ± 7.57	566.42 ± 56.70	2.06 ± 0.42
6 months ^a	80	6.02 ± 0.78	4.22 ± 0.92	130.00 ± 13.50	99.48 ± 5.21	424.20 ± 25.86	1.85 ± 0.15
12 months ^a	80	7.01 ± 1.12	4.54 ± 1.05	138.50 ± 15.00	108.28 ± 9.85	305.20 ± 50.68	0.86 ± 0.52
<i>F</i> value		161.55	172.14	289.73	307.46	182.85	102.23
<i>P</i> value		0.00	0.00	0.00	0.00	0.00	0.00

a: $P < 0.05$, compared with baseline in patient group

Table 2 Scores on physical and psychological functioning according to quality of life questionnaire for healthy controls at baseline, and for patient group at baseline, 3, 6 and 12 months of Tai chi chuan exercises ($\bar{x} \pm s$)

Groups	<i>n</i>	Physical functioning			Psychological functioning			
		Quality of sleep	Perceived hunger	Fatigue	Contentment	Stress	Social interaction	Life dissatisfaction
Healthy group								
Baseline	43	8.10 ± 0.40	7.90 ± 0.77	1.90 ± 0.60	7.50 ± 0.54	5.60 ± 0.94	8.60 ± 0.50	2.10 ± 0.82
Patient group								
Baseline	80	2.10 ± 0.00	3.20 ± 0.95	7.90 ± 1.00	4.50 ± 0.39	7.30 ± 1.15	5.50 ± 0.82	4.00 ± 0.18
3 months	80	2.85 ± 0.20	4.10 ± 0.05^a	7.15 ± 0.80	5.20 ± 0.82^a	7.00 ± 1.39	7.00 ± 0.15^a	3.20 ± 0.09^a
6 months	80	3.60 ± 0.40	5.00 ± 0.74^a	6.40 ± 1.20^a	6.14 ± 0.54^a	6.40 ± 1.63^a	7.50 ± 0.55^a	2.40 ± 0.18^a
12 months	80	6.80 ± 0.30^a	6.90 ± 0.73^a	3.20 ± 0.70^a	6.90 ± 0.52^a	6.00 ± 1.27^a	7.60 ± 0.63^a	2.10 ± 0.13^a
<i>F</i> value		312.98	222.64	543.90	46.05	28.01	78.92	56.61
<i>P</i> value		0.006	0.007	0.000	0.013	0.006	0.014	0.166

a: $P < 0.05$, compared with baseline in patient group

exercise in post-cancer health should be discussed between physicians and patients, and physical activity should be encouraged. Light exercises should be performed in 20-min sessions for one to three times a week to begin with, and survivors can slowly work toward an overall weekly schedule of 75–150 min exercise and two to three sessions of training exercises for strengthening^[15].

TCC is traditionally practiced nationwide in China, but has been well received and practiced in Western countries in the last ten years for the potentials of TCC to ail various illnesses^[23,25]. Practice of this traditional martial art is typically linked to improved mental state, incorporating mind-body practice^[23,25]. This study illustrated the positive influence of regular TCC physical activity on the mental, physical and psychological states of post-treatment breast cancer patients. Mental well-being was measured by serotonin and cortisol, while physical and psychological functionings were indicated by such blood parameters as WBC, RBC and hemoglobin, and measured by a self-rated QOL questionnaire. Participation in regular TCC exercises helped to regulate levels of stress in study subjects, increase happiness and well-being, and overall status of health and QOL.

To understand the mechanism by which TCC directly improved blood biomarker results and led to decreased levels of stress, the philosophy behind TCC should be discussed. TCC is a low-impact, moderate-intensity exercise that promotes relaxed breathing, flexibility, and mental concentration^[25,27]. By practicing TCC, the slow movement and continuity gradually increases the body's metabolism^[25] and blood circulation^[26-27]. Improved metabolism and blood circulation enhance the nutrients uptake and oxygen to be distributed throughout the body.

Physical activity is vital for strengthening the body's defense mechanism and is crucial for post-treatment patients. However, although exercise will help to rebuild the body's defense system, strenuous activity may overwork fatigued patients, thus leading to adverse reaction. TCC exercises allowed the breast cancer survivors of this study to perform physical activity without overusing limited energy. TCC exercise was positively correlated with the increase of

WBC, RBC and hemoglobin. It has been reported that TCC exercises can subtly enhance the immune system^[27-32]. Therefore, TCC may provide benefits to cancer patients who represent a population with multiple needs related to psychological stress and biological deterioration.

Practicing TCC exercises as part of a rehabilitation program led to elevation of serotonin levels in our study. Regular exercise increases the rate that serotonin is created in the brain, leading to an increase in the release and synthesis of the neurotransmitter^[33]. The level of tryptophan in the brain, an amino acid necessary for the formation of serotonin, is increased with regular physical activity^[34]. At minimum, 3 hours (180 min) exercise per week would be necessary to optimally enhance serotonin synthesis in the brain^[33-36]. As part of the TCC rehabilitation program, participants of the study were asked to practice TCC for 45 min a day, six times per week for the entire 12-month duration of the study. The post-treatment patients performed 270 min TCC routines per week, higher than the optimally suggested time.

Serotonin is a neurotransmitter involved in transmitting nerve impulses^[37-39] in the brain. Created from tryptophan, serotonin is typically found in platelets, central nervous system (CNS) and in the gastrointestinal (GI) tract. The primary functions of serotonin synthesized in the CNS are to regulate mood, appetite and sleep. Additionally, serotonin can maintain calm state, relieve depression, and alleviate anxiety. Serotonin is therefore typically described as a chemical that maintains levels of "well-being" in individuals. Low or imbalanced levels of serotonin in individuals affect mood, causing symptoms of anxiety, fear, insignificance, and insomnia, in such a way that leads to depression^[40-41]. In addition to low serotonin levels, precursors for depression include low brain cell production of serotonin, few receptor sites to receive the neurotransmitter, or depleted supply of tryptophan from which serotonin is derived^[39-41]. Another theory regarding regeneration of brain cells correlates serotonin production with the development of depression. Suppression of new brain cells, stipulated by serotonin, is theorized to lead to

depression in individuals with high levels of stress.

The observable decrease in the level of stress is mainly attributed to TCC which requires the participant to be peaceful, focused, and relaxed. TCC exercise comprising long rhythmic movements and controlled breathing techniques requires high concentration of the mind and a relaxed state of the body^[40-41].

Lowered stress levels were accompanied by higher levels of social interaction and life satisfaction^[40-42]. The observed decreases in the cortisol levels of study subjects could be partially attributed to the support of fellow breast cancer peers of the study, who shared similar fears and anxiety of their illness. Study subjects who participate in the study together had opportunities to meet fellow breast cancer survivors and provide support and share feelings, calm nervous state and improve self-esteem^[40-42]. There are ample similarities in demographics, disease stage and condition between fellow patients. Subjects are more easily relatable to one another knowing that the status of their illness, treatment methods and options are similar. The support gained from patients with a similar illness provided additional help that family and friends may not be able to offer. Study subjects who practiced TCC noted that they felt happier and more relaxed with peer support^[40-41].

For study subjects, physical functioning was shown to improve with ongoing TCC physical activity. Improved scores for quality of sleep, perceived hunger and fatigue were positively correlated with extended commitment to TCC exercise. Regular physical activity induces tiredness, allowing people to fall asleep more easily at night^[43]. Patients' appetite was also noticeably better after practicing TCC^[44].

Regulated levels of serotonin and cortisol mediated by TCC exercises proved to be vital for good health. TCC exercises were pivotal for normalizing depleted levels of serotonin in subjects, which in turn were proven to be correlated with happiness and various elements of good health. Additionally, regulated levels of serotonin are also vital for supporting good body health, such as a healthy cardiovascular system, muscles and

endocrine system.

Maintenance of a low-stress, healthy lifestyle with regular TCC exercises are encouraged for better health, well-being in breast cancer patients. The positive effect of TCC for breast cancer survivors on health, well-being and disease recurrence is warranted in a future longitudinal study to study such variables.

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