wjpmr, 2019,5(10), 19-26

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Review Article

ISSN 2455-3301

WJPMR

BIOMARKERS USED FOR ASSESSING THE EFFECTS OF TAI CHI CHUAN IN BREAST CANCER SURVIVORS

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Article Received on 05/08/2019 **Article Revised on 26/08/2019** **Article Accepted on 16/09/2019**

ABSTRACT

Tai Chi Chuan (TCC) is a traditional Chinese exercise, its movement is slow in order to achieve a state of relaxation and balance of both body and mind. TCC shows positive effects in relieving symptoms in patients with chronic diseases and malignant diseases after treatment. Research has proven that TCC helps improve the quality of life in breast cancer patients who had undergone surgery and chemotherapy. Studies have also demonstrated that TCC may exert its effects psychologically and physiologically. In order to document current researches of TCC in a scientific way, we tried to evaluate the changes of biological markers in breast cancer survivors who has been practicing TTC and its potential benefits in reducing treatment-related adverse effects, improving immunity and personal wellbeing. Cancer survivors suffer from a variety of psychological responses including depression, sadness, anxiety, fear and adverse effects from surgery and chemotherapy. Some studies confirmed that cancer survivors' physical and psychological functions can be improved by regular exercises. Many studies have shown that regular physical exercises are particularly important in reducing the incidence and recurrence of breast cancer, prolonging the survival of patients and even improving the side effects during and after the treatment. It has also been linked to a better quality of life (QoL) for breast cancer survivors. After surgery, the shoulder function of breast cancer survivors would be impaired and their arms would show signs and symptoms including diminished tactile sensation in the arm or armpit, weakness, stiffness and lymphedema of the surgical sided arm. Conventional exercises such as running and/or swimming involves rigorous arm movements which require full mobility of the arms and legs. Such exercises are not recommended immediately following surgery. TCC exercises may help regain upper limb functional mobility for breast cancer survivors by slow and continuous movement of upper limb. Practicing TCC in a smooth and relaxed way will lessen tension and promote relaxation which may alleviate stress, depression and anxiety. TCC has been demonstrated in improving psychological well-being of breast cancer survivors by reducing anxiety or depression through stabilizing the level of cortisol and serotonin. Studies showed that TCC improves immunity in breast cancer survivors by means of hematological markers and cytokines. In this review, there were only four randomized controlled trials have made use of biological markers to monitor the effects of TCC in breast cancer survivors although most researchers tend to assess by means of aerobic capacity, muscular strength, and flexibility, as well as QOL. None of the studies investigated the relationship between TCC and treatment-related adverse effects or immunity through changes in biological markers. Therefore, researchers could develop the use of more cytokines, stressors (melatonin), activated natural killer cells, free radicals, biochemical markers or c-miRNAs to determine the effects of TCC.

KEYWORDS: Tai Chi Chuan, breast cancer survivor, biological markers.

INTRODUCTION

Tai Chi Chuan (TCC) is a traditional Chinese exercise form that uses slow, smooth body movements to achieve a state of relaxation and balance of both body and mind. The concept of Tai Chi exists long before the creation of TCC. The term "Tai Chi" first appeared in "Yìjīng", an ancient Chinese philosophy book with a history of over 3000 years since the Zhou Dynasty. The book introduced that Tai Chi has "Yin and Yang", and thus evolves two poles. Tai Chi and the two opposites exists in everything.[1-3] The essential principles of Tai Chi are based on the ancient Chinese philosophy of Taoism, which stresses the natural balance in all things and the need for living in spiritual and physical accord with the patterns of nature. According to this philosophy, everything is composed of two opposite, but entirely complementary, elements of yin and yang, working in a relationship which is in perpetual balance.[4,5] Based on

the Taoism, changes originated in the Ultimate (Tai Chi) and the Ultimate generated the two spheres – Yin and Yang. All things and creatures were created from there. The sage kept this theory and managed the flow of Qi in the universe. Such as the circulation of the sun, moon and other natural phenomena, all follow the motion of the universe.[1,2,4,5] Meanwhile, there is also a mini cosmos inside or surrounding our body, which goes with the rhythm of the universe. For instance, the four seasons change with the time, the five internal organs of the body and the five normal human relationship in the Chinese ethical tradition all respond to the concept of the five elements; 24 hours a day; 12 months a year; 360 solar terms a year; all these evidence demonstrate that people live with the motion and rhythm of the universe.[1,4,5] Traditionally, practicing TCC not only balance or smoothen our emotion, but also strengthen our body. Now, TCC's supportive effects have been reported in patients with cardiac diseases, hypertension, Parkinson's disease, psychological diseases, osteoporosis and others chronic diseases with proven, positive effects for the tested parameters.[6-8] TCC as a regularly practiced form of physical activity for breast cancer survivors has been studied in recent years for its biological effects. Research has proven that TCC helped improve quality of life of breast cancer patients who had mastectomy and chemotherapy and/or radiation.[9,10] A lot of studies have demonstrated that TCC may exert its effects psychologically and physiologically. However, few studies have used biological markers to monitor the changes in breast cancer survivors objectively.

In this study, we tried to evaluate the changes of biological markers in breast cancer survivors who has been practicing TCC and the potential benefits of TCC in reducing treatment-related adverse effects, improving immunity and personal wellbeing.

Breast cancer is the most common cancer in women in the world. It was estimated that almost 1.7 million cases of female breast cancer were diagnosed worldwide during 2012 (GLOBOCAN 2012) and over 508 000 women died because of the breast cancer (Globe Health Estimates, WHO 2013). In Hong Kong, there are over 3,000 newly registered cases annually, comprising almost one-forth (24.1%) of the top 10 female oncological diseases.[11-13] The mean age at diagnosis of breast cancer in China is 45–55 years. Similar situation have been reported in the East such as Taiwan and Hong Kong. The incidence has been on the rise in younger cohorts in Asian countries.[11,13] for the adoption of westernized lifestyles, stress, busy schedules, and insufficient exercise.[14-17] Nowadays, cancer survival is largely improved due to the implementation of breast screening programs with advanced technologies,[17] lifestyle modification avoiding certain risk factors and improvement of chemotherapy regimens. While cancer treatment has been shown to be effective in prolonging survival, it can be intense and may lead to increased fatigue, decreased physical activity and deterioration in the quality of life.[18] The experience of surviving cancer can be stressful for the fears of recurrence or a second primary tumor. Such cancer related concern can be particularly lead to increased psychological distress that encompasses a variety of psychological responses including depression, sadness, anxiety, fear or worry.[19] Moreover, the central nervous system and peripheral nervous system are very susceptible to chemotherapy treatment. The incidence of acute chemotherapy-related cognitive dysfunction ranges from 15 to 70%.[20,21] and cognitive impairment is long-term effect in cancer survivors which will last 2-10 years after completion of chemotherapy.[22]

Some excellent systematic review confirmed improvements in physical indicators, psychological well-being, and overall health-related quality of life for exercise group compared with control groups, regardless of disease type and whether exercise was taken during or after cancer treatment.[23-25] Cancer survivors' physical function can be improved by regular exercise has been supported by many studies.[18,26,27] It has been reported that strength exercise can enhance physical function from 7% to 38% for patients who completed cancer related treatment,[26] and the positive effectiveness of exercise training on muscle strength is promising in different cancer survivors.[26,27] Frequent physical activity for post-treatment cancer survivors will help them regain depleted strength and energy lost (reflected in lowered white, red blood levels and hemoglobin) as a result of toxic chemotherapy treatment and surgery.[28-31]

1. Potential Applications of TCC in breast cancer

Numerous epidemiological studies have shown that regular physical exercise is particularly important in reducing the incidence and recurrence of breast cancer, prolonging the survival of patients,[18,28,29,32,33] and even improving the side effects during and after the treatment. The risk of breast cancer development was found to be lowered by 20%-40% in the most physically active females, irrespective of the exercise performed.[28] Regular exercise is correlated with regulated body hormones, including the levels of ovarian hormones, which have been linked with lowered breast cancer risk.[16,29] Regular exercise has also been linked to a better quality of life (QoL) for breast cancer patients.[30,31,34] by improving cardiopulmonary function, muscular strength, and endurance in breast cancer survivors.

TCC exercise is a form of physical exercise of lightweight at begin. It will avoid overworking fatigued post-treatment patients, and thus allowing their bodies to regain strength and energy (reflected in improvement of immunity). Surgery, radiotherapy, and /or chemotherapy are the conventional treatments for cancer patients. For some survivors, only surgery and chemotherapy are adequate, but a combination of two or three treatment regimens is necessary for advanced cases. Breast cancer patients requiring radical mastectomy or modified

mastectomy will frequently require lymph node resection for removal of metastases of lymph nodes,[35] which will impair the shoulder function by reducing the muscular strength and shoulder mobility.[18,33,36,37] Following surgery, patients will also experience signs and symptoms including diminish of skin sensation in the arm or armpit, weakness, stiffness and lymphedema of the arm. Moreover, poor immunity or oral mucositis,[38] often occur, and post-traumatic stress disorder (PTSD) and raised anxiety have been reported in the breast cancer survivors. TCC exercises may help regain upper limb functional mobility for breast cancer patients by slow and continuous movement of upper limb. TCC also includes backward walking that may improve muscle strength and enhance the stepping ability that is needed in daily life. Conventional exercise such as running and/or swimming involves rigorous arm movements which require full mobility of the arms and legs. Such exercises are not recommended immediately following surgery. Overtime, the immunity of breast survivors might slowly be reversed, and the side effects brought about by treatment will diminish.[30,31,34,39] Participation in Tai Chi exercise group with cancer peers will allow women to share their feelings of anxiety or sadness, helping them to cope with stress and depression. As one of main characteristic, performing TCC in a smooth, relaxed way will lessen tension and promote relaxation which may have potential effect on alleviate stress depression and anxiety symptoms for breast cancer survivors. Psychological factors, including improvements in happiness, stress, satisfaction of life, insomnia and appetite,[40] have been documented in patients who practiced TCC.

The new NCCN Guidelines for Survivorship highlighted the importance of exercise for cancer survivors.[41] The role of exercise in post-cancer health should be discussed between physicians and patients, thus encouraging patients to perform physical activity. Physicians are recommended to work with the patient to determine exercise ability and advise patients accordingly. Generally, exercises should be light to begin.[41] Light exercises comprising of TCC could be appropriately incorporated into a rehabilitation program for survivors.[42] TCC can be practiced easily without equipment, and is thus practical without external restrictions. It can easily learn in groups or in individuals, and may through regular practice facilitate a lifestyle which promotes wellness at both healthy and rehabilitation subjects in all age. People can benefit from the practice of TCC, which not only balances and smoothens the emotions, but can also strengthen human bodies to achieve homeostasis.[42]

2. TCC improves psychological well-being of breast cancer survivors

TCC is believed to favor the psychological well-being of cancer survivors through its characteristics of relaxation, deep and regulated breath, and slow movements. Currently, the most widely accepted research intervention to enhance self-esteem and health related quality of life (HRQOL) in cancer survivors is psychosocial support therapy (PST). HRQOL is composed of psychological functioning, social adjustment, functional ability, and disease- and treatment-related symptoms. Mustian's research group compared the efficacy of TCC and psychosocial support (PST) for improving HRQOL.[42] and self-esteem.[43] among breast cancer survivors. In his study, the result showed the TCC group exhibited improvements in HRQOL and self-esteem from baseline to 6 and 12 weeks, while the PST group exhibited declines. Improvement of HRQOL by TCC exercise is supported by other research groups.[10] They found that participants in the TCC group improved throughout the course of the 12-week intervention in numerous components of HRQOL, including total HRQOL, physical functioning, physical role limitations, social functioning, and general mental health.[10] However, Fong's group fail to prove the improvement effect of TCC on psychological status (e.g., self-esteem relating to sexual attractiveness) in breast cancer survivors, as reflected by the FACT-B breast CA-specific concerns score, compared to CA-control group participants.[44] (Table1).

Studies have also shown that a woman's breast cancer risk is directly related to her daily emotional responses,[45-47] and psychological factors, such as anxiety/depression, may be a cause of breast cancer development.[45,46] Stress hormones (cortisol) may uphold inflammation through induction serum levels of IL-6, TNF-α and C-Reactive protein.[45,48] Those factors were dramatically raised in patients who are positively associated with anxiety or depression, and there is a dose-response relationship between anxiety/depression and these inflammatory markers.[45,49] Several studies reported that stress is correlated with increases in cortisol, and that such increases affect the brain and memory functioning. Patients receiving chemotherapy treatment, increased cortisol levels will lead to worse memory and cognitive performance.[50]

Serotonin is a neurotransmitter involved in transmitting nerve impulses,[50] in the brain. Created from tryptophan, serotonin is typically found in platelets, central nervous system 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.[50] Our previous study found that the level of serotonin and cortisol in breast cancer survivors who practiced TCC for 12 months would return to normal.[50]

Table 1: RCT studies to evaluate TCC's effects on psychological aspects of breast cancer survivors.

Groups & subject number	Methods	Outcome measures (psychological status)	Results	Reference
Taichi/Qigong CA group (n=11) CA-control group (n=12) Healthy-control group (n=16)	QoL assessed by the Functional Assessment of Cancer Therapy-Breast (3 times a week, for at least 6 months)	breast cancer-specific concerns (i.e. depression, anxiety, distress and sleep disturbance)	TCC has no support effect on breast cancer survivors' psychological status.	Shirley S. M. Fong *et al.* (2013)[35]
Tai Chi Chuan group(TCC) (n=9) Standard Support Therapy (SST) (n=10)	QoL assessed by MOS SF36 (3 times a week, for 12 week)	General mental health	Tai Chi Chuan improved breast cancer survivors in general mental health.	Lisa K. Sprod *et al.* (2012)[10]
TCC group (n=11) Psychosocial support therapy (PST) group (n=10)	Functional Assessment of Chronic Illness Therapy-Fatigue survey (3 times a week, for 12 week)	concerns associated with breast cancer (i.e. depression, anxiety, distress and sleep disturbance)	TCC has positive effect on QoL among breast cancer survivors	Karen M. Mustian *et al.* (2008)[33]
TCC group (n=11) PST group (n=10)	Rosenberg Self-esteem Scale (RSE) 3 times a week, for 12 week	Self-esteem	TCC improved self-esteem	Karen M. Mustian *et al.* (2004)[34]
	Functional Assessment of Chronic Illness Therapy-Fatigue survey 3 times a week, for 12 week	Qol (including physical, functional, social, cognitive-emotional)	TCC group showed improvements in QoL from baseline to 6 and 12 weeks	Karen M. Mustian *et al.* (2004)[34]

Table 2: RCT studies application of biological markers to measure TCC intervention.

Groups & subject number	Methods	Outcome measures	Results	Reference
1) Taichi 2) Standard support therapy Breast cancer survivors (n=16)	Bone Metabolism	1. N-telopeptides of type I collagen (NTx) 2. bone-specific alkaline phosphatase (BASP) 3. Bone Remodeling Index (BRI) 4.IL-6, IL-2,IGFBP-1,IGFBP-3	TCC might help maintain BMD (TCC group showed higher but not statistically significant level of NTx; TCC group exhibited lower BASP, but there is no statistically significance) BRI were increased in TCC group, $p<0.05$. Declining levels of IGFBP1 and increasing levels of IL-6 in TCC group were correlated with increasing bone formation.	Peppone LJ (2010) [70]
1) Taichi 2) Cognitive behavioral therapy for insomnia (CBT-I)Breast cancer survivors with insomnia disorder (n=90)	Inflammation	1. Level of C-reactive protein (CRP) 2. toll-like receptor-4–activated monocyte production of IL-6 and TNF combined	3 months of TCC may reduce cellular inflammatory responses. Levels of C-reactive protein did not change in the TCC and CBT-I groups. Levels of IL-6 and TNF combined showed an overall decline in TCC versus CBT-I ($P < 0.02$),	Irwin MR (2014) [76]
1)Taichi 2) non-physical activity control (PST) Breast cancer survivors (n=19)	Glucose Metabolism	1.Level of Insulin 2.IL-2 3.IL-6	After 12-week exercise, insulin level were stable in TCC group but increased in control group ($p=0.099$). Increased IL-6 and decreased IL-2 levels were correlated with decreased fat mass and increased fat-free mass in TTC group($p<0.05$). insulin levels and changes in cytokine levels that may be important for maintenance of lean body mass	Janelsins MC (2011)[64]
1)Tai Chi 2) standard support therapy control (SST) Breast cancer survivors (n=19)	Glucose Metabolism	IL-6, IL-8, IGF-1, IGFBP-1, IGFBP-3, glucose, insulin, and cortisol	There was a statistical trend toward an increase in insulin among the SST group ($P=0.08$), but not among the TCC participants ($P=0.56$).There was a statistical trend for an increase in glucose in the TCC group ($P=0.08$) but not in the SST group. There is no significantly changes in IL-6, IL-8,IGF-1,IGFBP-1/3 or cortisol from pre- to postintervention ($p>0.05$).	Sprod LK (2012) [10]

3. Tai Chi improves blood immune function in breast cancer survivors

During the practice of TCC, deep diaphragmatic breathing is integrated into body motions to achieve a harmonious balance between body and mind and to facilitate the flow of internal energy.[5] The aerobic capacity of body could be improved by TCC exercise. The quantity of peripheral blood mononuclear cell (PBMC) and myeloid dendritic cells were reported to increase in the circulation in healthy individuals after TCC exercise.[51] PBMCs consist of lymphocytes, monocytes, and macrophages, etc., and they are critical components in the immune system to fight infections. Study has shown a significant reduction of peripheral blood natural cytotoxicity in patients with various cancers, compared with healthy controls.[52] TCC exercise has been shown to increase in natural killer (NK) cell, cytotoxic activity, monocyte function, and the proportion of circulating granulocytesin cancer survivors.[53] Fairey's study,[54] showed that 15-week cycle ergometer exercise improved NK cytotoxic activity on a single cell basis in breast cancer survivors. Our research team has proven that white blood cell, red blood cell and hemoglobin recovered to the normal range at 3, 6 and 12 month time in blood samples of breast cancer survivors who practiced TCC for 45 minutes every day, six times a week for 12 months.[50,55] Although evidence is accumulating for TCC's improvement effect on blood cell immunity in cancer survivors, relatively little was known about possible mechanism for such changes. Yeh's group conducted 12 weeks of TCC exercise in healthy subjects. Although their total white and red blood cells has not been increased significantly after 12 weeks of TCC,[56] changes in lymphocyte subpopulations, CD4CD25 positive regulatory T cells had significantly increased by the end of the programme. Their mediators (TGF-beta and IL-10) had significantly increased after the exercises. Therefore, this study suggested TCC exercises may subtly boost the blood immune system through modulation of regulatory T cell functions.[56]

4. Immunological consequence of TCC through cytokines regulation

The improved immunity of body is not only presented in cellular level of the blood but is also demonstrated in serum cytokines which may be the key mediators affecting recovery, recurrence, and survival of breast cancer patients. Multiple pro-inflammatory signaling pathways involving cytokines have been implicated in cancer development, progression, and recurrence. These cytokines can alter proliferation, lead to malignant transformation, and promote metastasis.[57] Numerous studies in healthy individuals have revealed that exercise can reduce chronic inflammation by inducing anti-inflammatory effects.[58] On a molecular level, during exercise, IL-6 is rapidly produced in blood cells exhibiting anti-inflammatory effects to inhibit pro-inflammatory cytokine expression.[59] The studies have investigated possible biomarkers to monitor the improvement of immune function by an intervention of regular TCC exercise.[57,58]

Pro-inflammatory cytokines including IL-6 and IL-8 are produced at high levels in the breast tumor microenvironment.[60,61] and are also expressed at high rates in breast cancer cell during chemotherapy resulting in multidrug resistance.[62] IL-6 secreted from adipose tissue has been implicated in promoting invasion of breast cancer cells,[62] and in a chronic inflammatory setting, IL-6 may be secreted by T-cells leading to growth factor expression that may promote survival of tumor cells.[63] Janelsins and her colleagues found that TCC can also reduce adiposity by IL-6-mediated lipolysis and by diminishing levels of circulating and adipose-derived cytokines (e.g. TNF-α, IL-1β) in breast cancer survivors. The change of pro-inflammatory cytokines (IL-6 and IL-1) are also implicated in the development of fatigue and sleep disturbance in cancer survivors.[64] Elevated IL-6 levels is a marker of the positive effects of TCC on fat-free mass. TCC-induced IL-6 is a responder that reflects fat reduction and it may have direct anti-inflammatory effects on risk of recurrence.[65,66] Exercise-mediated anti-inflammatory mechanisms (IL-6) are thought to be the most plausible explanation for the protective effects of exercise on weight gain and recurrence.[64]

IL-2 is produced by T cells as a necessary proliferative factor; these cells accumulate in adipose tissue,[65] and likely play a role in promoting tumor progression within this tissue.[66] Physical activities like TCC exercise, therefore, by increasing fat free mass and reducing fat mass may lead to reduced adiposity, leading to reduce accumulation of T cells within adipose tissue and decrease the levels of IL-2,[64] which may ultimately lower the possibility of tumor progression.

Our previous study,[55] reported that 12-weekTCC enhanced the production of IFN-γ significantly for breast cancer survivors as compared to baseline. As proven by Yeh's study conducted that TCC can enhance production of CD4+CD25+ regulatory T cells,[56] which could mitigate IFN-γ production from inflammatory T cells in adipose tissue. In an animal study of diet-induced obesity, IFN-γ promoted inflammation in adipose tissue and promoted insulin resistance,[67] which provides a rationale for the positive correlation of IFN-γ and insulin observed in non-exercising group.

5. Additional biomarker and benefits in breast cancer

Treatments for breast cancer accelerate bone loss, leading to osteoporosis and an increase in fracture risk. Cancer treatment–induced bone loss affects both premenopausal and postmenopausal breast cancer patients [68]. Breast cancer patients who receive chemotherapy have a significantly lower bone mineral density (BMD) than breast cancer patients who do not receive chemotherapy.[69,70] Chemotherapy also exerts an

indirect effect on the skeleton through its effects on the ovaries. Premenopausal women who experience ovarian failure as a result of chemotherapy lose up to 7.6% of BMD annually, compared with < 1% for a healthy premenopausal woman,[69,70] The bone loss is much more profound in young women with treatment-induced ovarian suppression followed by aromatase inhibitor therapy (average 7-8% per annum).[69,70] Peppone reported that TCC could reduce the bone loss after chemotherapy by measuring the levels of serum alkaline phosphatase, osteocalcin (bone formation marker) and NTx (bone resorption marker).[68]

Accumulating evidence showed that mastectomy, chemotherapy and standard radiotherapy for breast cancer patients will impair their shoulder function by decrement in shoulder muscular strength and shoulder mobility.[44,71,72] Most breast cancer survivors will experience dysfunction of skeletal muscle as a result of cancer treatment. The arm and leg skeletal muscle accounts for approximately 40% of the total body mass, enabling the body to maintain posture, to control shoulder movements and to store energy.[73] Some studies suggest that physical exercise can transiently or adaptively change the level of c-miRNAs, thus post transcriptionally regulate proteins associated with energy metabolism, myogenesis, and angiogenesis to improve the muscle healthy.[74,75] The c-miRNAs maybe useful as biomarkers to reflect the relationship between TCC exercise and breast cancer survivor's physical fatigue.

6. CONCLUSION

In this review, there were only four randomized controlled trials have made use of biological markers to monitor the effects of TCC in breast cancer survivors (Table 2) although most researchers tend to assess by means of aerobic capacity, muscular strength, and flexibility, as well as QoL. None of the studies investigated the relationship between TCC and treatment-related adverse effects or immunity through changes in biological markers. Therefore, researchers could develop the use of more cytokines, stressors (melatonin), activated natural killer cells, free radicals, biochemical markers or c-miRNAs to determine the effects of TCC.

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