

Review

Shingles Immunity and Health Functioning in the Elderly: *Tai Chi Chih* as a Behavioral Treatment

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Both the incidence and severity of herpes zoster (HZ) or shingles increase markedly with increasing age in association with a decline in varicella zoster virus (VZV)-specific immunity. Considerable evidence shows that behavioral stressors, prevalent in older adults, correlate with impairments of cellular immunity. Moreover, the presence of depressive symptoms in older adults is associated with declines in VZV-responder cell frequency (VZV-RFC), an immunological marker of shingles risk. In this review, we discuss recent findings that administration of a relaxation response-based intervention, *tai chi chih* (TCC), results in improvements in health functioning and immunity to VZV in older adults as compared with a control group. TCC is a slow moving meditation consisting of 20 separate standardized movements which can be readily used in elderly and medically compromised individuals. TCC offers standardized training and practice schedules, lending an important advantage over prior relaxation response-based therapies. Focus on older adults at increased risk for HZ and assay of VZV-specific immunity have implications for understanding the impact of behavioral factors and a behavioral intervention on a clinically relevant end-point and on the response of the immune system to infectious pathogens.

Keywords: behavioral treatment – elderly – shingles – *tai chi chih* – immunity health status.

Introduction

Behavioral factors are hypothesized to influence the immune system, with implications for infectious disease risk (1–3). Other studies have found that older adult populations show a substantial decline in immune function and are at increased risk for a number of infectious diseases (4,5). Taken together, the untoward effects of age and behavioral symptoms (e.g. depressed mood or insomnia) raise the question of whether behavioral interventions might augment immune responses in older adults who may be risk for a decline of viral-specific immunity. In this review, we focus on an infectious disease model related to reactivation of a latent herpes virus, varicella zoster virus (VZV); examine the risk factors associated with the increased incidence of herpes zoster (HZ) in older adults; discuss the psychosocial

influences that may modulate VZV-specific immunity in older adults; and report on the use of a mind–body, behavioral intervention to ameliorate these risk factors.

Herpes Zoster

HZ or shingles is caused by reactivation of an endogenous VZV infection that has persisted in a latent form within sensory ganglia following an earlier attack of varicella (chickenpox) (6). Both the incidence and severity of HZ increase markedly with increasing age, and the majority of episodes occur in persons over the age of 60 years (7,8). At age 50, the annual incidence of HZ is 2.5–4.0 cases per 1000; this rate nearly doubles by the age of 60 years, HZ afflicts more than 500 000 persons per year in the USA (8).

HZ and VZV-specific Immunity

The factors associated with increased risk of HZ in the older adult and the mechanisms responsible for maintaining VZV in

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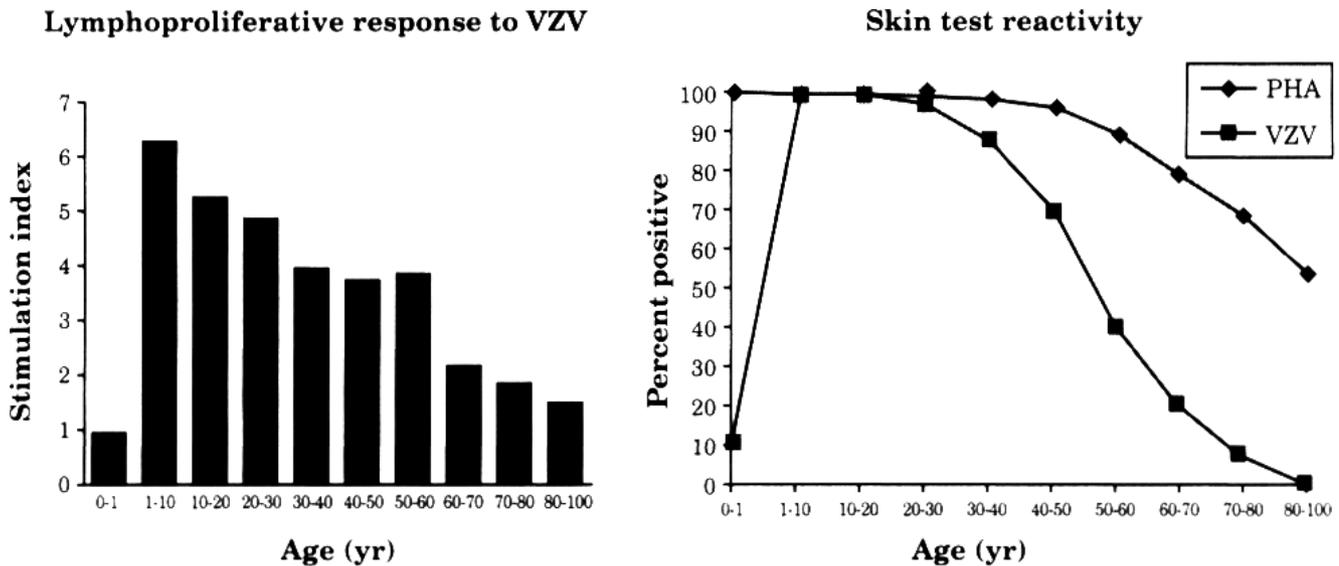


Figure 1. Varicella zoster virus specific cellular immunity and age. The relationship between human age, level of lymphocyte proliferative response to varicella zoster virus antigen and phytohemagglutinin (PHA), and delayed-type hypersensitivity response to varicella zoster virus antigen skin challenge. There is a marked attenuation of varicella zoster-specific cellular immunity in persons over the age of 60 years. Reprinted from Burke *et al.* (13).

the latent state are not fully understood. Nevertheless, there is much circumstantial evidence that cell-mediated immunity plays a critical role in limiting the occurrence of HZ and its complications (6,9,10) (Fig. 1). Age-related decline in VZV-responder cell frequency (RCF; frequency of lymphocytes that proliferate in response to VZV antigen) is temporally related to an increase in the incidence and severity of HZ and its complications in older rats (7,8,11–14). Further, iatrogenic immunosuppression with diminished VZV-specific T-lymphocyte proliferation is associated with greater susceptibility to VZV reactivation and HZ (15–17). In contrast to the age related decline of cellular immunity, levels of antibodies to VZV do not appear to be significantly diminished in the elderly, nor is there any increased frequency of HZ in individuals who lack VZV antibodies (i.e. patients with congenital or acquired γ -globulin deficiencies) (6,18). Moreover, in elderly subjects, there is no decline in the number of memory CD45RO⁺ T cells, a finding that argues against the selective loss of this subset as the cause of decline in VZV-RCF with age (19). The proliferative response to VZV is confined to CD4⁺ CD45RO⁺ T cells in the assay of VZV-RCF; the number of antigen-presenting cells is not limiting (11).

Individual Variability in VZV-specific Immunity and the risk of HZ

It has been hypothesized that HZ does not occur at random in older adults, but rather selectively strikes individuals whose cell-mediated immunity to VZV is reduced (14) (Fig. 2). Older adult populations are very heterogeneous with respect to baseline VZV-specific immunity as well as other aspects of cellular immunity (20). Moreover, we have found that the immunological response to varicella zoster vaccine is variable and not

universal. The factors that account for this variability, selective response to immunization and altered risk for HZ in older adults are not well understood, but within-population differences in physical and psychological functioning have been implicated.

Depressive Symptoms, Health Behaviors and VZV-specific Immunity in the Older Adult

In view of recent evidence that the immune system is integrated with other homeostatic processes ultimately regulated by the brain (1,2) (Fig. 3), the influence of biobehavioral factors on the incidence of HZ and on VZV-specific immune responses deserves attention. Thus, we have examined the effects of major depression on VZV-specific immunity by comparing VZV-RCF levels in middle-aged depressed patients versus controls who were matched on the basis of age and gender (21). All subjects were in good physical health and none were receiving psychotropic medications or other treatments that are known to alter immune responses. VZV-RCF was significantly lower in the subjects with major depression than in matched normal controls, indicating that depression and possibly other behavioral factors such as disordered sleep (22) are associated with a marked decline in VZV-specific cellular immunity, as measured by the frequency of peripheral blood mononuclear cells capable of proliferating in response to VZV antigen.

In the older adult, other factors such as the presence of chronic disease, increased risk of exposure to stressful life events and personal losses, diminished social supports and declines of self-concepts of efficacy and mastery might also impinge on immune defences and increase the risk of HZ and possibly other infectious diseases (3,23). However, there are few clinical data that have addressed the confluence of behavioral, immunological and health outcome variables in the same

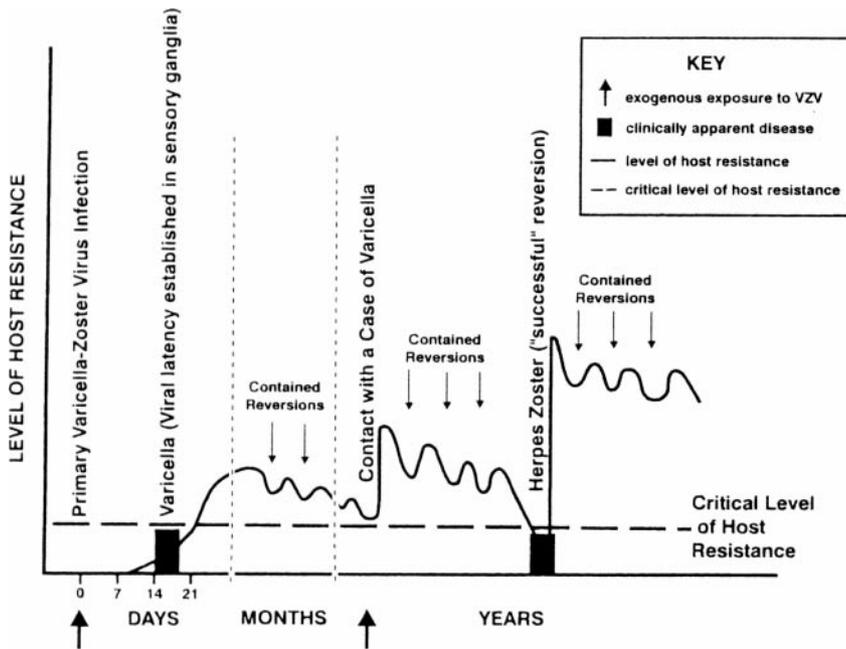


Figure 2. Pathogenesis of herpes zoster. Reprinted with permission from Oxman (111).

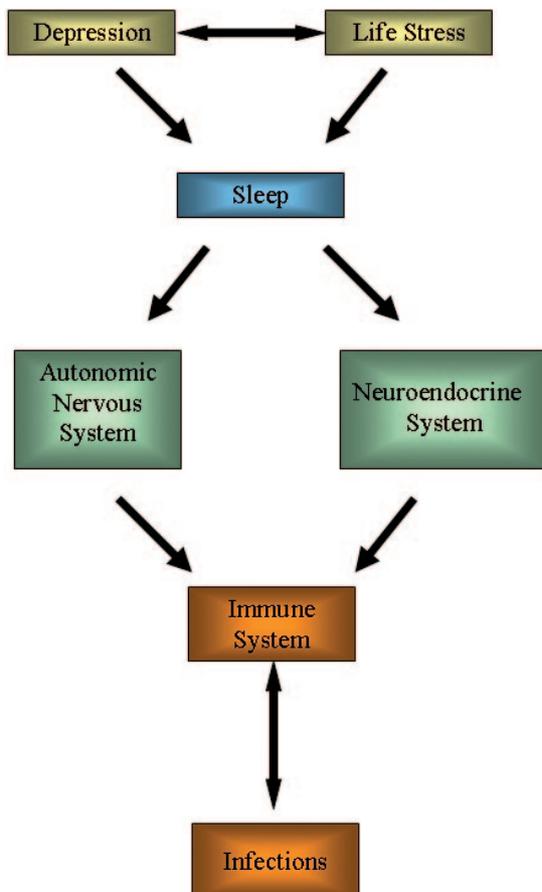


Figure 3. Relationship between depression, life stress, sleep and the autonomic, neuroendocrine and immune systems. The evidence for the relationship between life stress and depression and varicella zoster-specific immunity and herpes zoster risk is the subject of this review. Possible mechanisms for these effects including alterations in behavioral responses such as disordered sleep or abnormal activation of the sympathetic nervous system are also considered.

individuals at the same time, despite the promise of animal studies showing a link between behavioral stressors and viral infectious disease susceptibility (24,25). In humans, psychosocial stress (e.g. caregiving for an ill relative or marital distress) is reported to correlate with reduced immunological control of latent herpes viruses [Epstein-Barr virus (EBV), herpes simplex virus (HSV) and cytomegalovirus (CMV)], as evidenced by elevated antibody titers and reduced memory T-cell responses (26–28). In addition, beyond the effects of chronic stress on latent herpes viral models, perceived life stress correlates with increased rates of respiratory infection after experimental inoculation with common cold viruses (29,30) and with decreased immunological responses following vaccination against hepatitis B (31). However, no studies have examined the relationship between behavioral factors and HZ other than the retrospective and prospective analyses of Schmadler *et al.* (32–34). In the first study, 101 individuals with recent HZ reported a significantly higher number of stressful, and particularly ‘negative’ life events, in the 6 months before rash onset compared with 101 age-matched controls (34). The second study involving 2568 persons found that negatively perceived events were modestly associated with an increased risk of zoster over 8 years of follow-up (33). Another recent study reported that space flight was associated with increases of viral reactivation and shedding into saliva (35). In older adults, who are on average at increased risk for infectious disease due to age-related declines of immune function, the link between psychosocial factors, immunity and infectious disease outcomes is relatively unexplored apart from the observations of Kiecolt-Glaser *et al.* and Vedhara *et al.*, who found that Alzheimer caregiver stress depresses cellular immune responses to influenza vaccination (36,37). If the decline of immunity to VZV and the increased risk of HZ in older adults were shown

to be related psychosocial factors alone or in combination with the effects of age and chronic disease, this could provide invaluable insight into the biobehavioral mechanisms of immune changes in older adults and these insights could refine behavioral strategies for amelioration of these immune effects.

Biological and Behavioral Changes in the Older Adult: Implications for Declining Immune Responses

Older adults are at increased risk for infectious and inflammatory disorders (38), which is thought to be due at least in part to autonomic and behavioral abnormalities associated with aging (39) (Fig. 3). In addition, stress may compound these abnormalities in older adults (40,41). Aged organisms show an exaggerated autonomic and neuroendocrine responsivity to stress in which responses are delayed in shutting off, with attendant suppressive effects on natural and cellular immunity (42). Likewise, depressed and/or psychologically stressed persons show elevations of sympathoadrenal activity at rest and in response to acute challenge; such cardiovascular and sympathetic abnormalities correlate with many of the immunological changes found in these populations (43,44). Other studies on behavioral mechanisms suggest that sleep disturbance uniquely contributes to the multi-system physiological effects of aging, stress and affective disorders (22,45). Sleep disturbance, prominent in older adults, results in sympathoadrenal activation (46) and is associated with declines in immune function (47–49) (Fig. 3).

Successful Adaptation: Role of Psychological and Behavioral Interventions

Psychobiological models posit an inter-relationship between aging, stressor, cognitive appraisal of stress, affective integration and translation of the cognitive and affective processes into changes in immunity and HZ risk. However, feedback systems are also operative to VZV. Not only can one's appraisal of stressors elicit affective and physiological arousal but, conversely, physiology can influence one's thinking (23). Consequently, several strategies for intervention can be deduced from consideration of a reciprocal interaction between mind–brain–body. One approach involves modifying cognitive appraisal and ameliorating emotional distress (e.g. cognitive–behavioral therapy), whereas another focuses on reducing psychophysiological arousal through the use of relaxation response-based training. In a model that is reciprocal, the causal priority of the intervention is less of a concern than the view that effective stress management is related to its impact on the interaction of cognitions, affective responses, physiological activity and behavior (50).

As reviewed by Miller and Cohen (51), few studies have reported on the effects of behavioral interventions on cellular immunity. As an example, four studies have evaluated the immune effects of hypnosis and relaxation (5,52–54). In two of these studies, medical students were assigned randomly to a

hypnotic/relaxation group prior to examination stress (52,53). Both studies found that the frequency of relaxation correlated with an amelioration of stress-induced changes in lymphocyte proliferation, natural killer (NK) cell activity and T-cell subset enumeration, although neither study found significant effects for the intervention due in part to variability in the practice of relaxation. In older adults, progressive muscle relaxation training was also found to produce significant increases in NK cell activity and decreases in HSV antibody titers (5). Other behavioral intervention studies have focused on development of supportive social relationships, education and cognitive re-appraisal of events. In patients with malignant melanoma, supportive group psychotherapy was associated with increases in NK cell activity that correlated with lower rates of recurrence in a 6 year follow-up (55). In homosexual men and women undergoing human immunodeficiency virus (HIV) antibody testing, omnibus cognitive–behavioral interventions were reported to show increases of CD4 T lymphocytes and NK cells and decreases in EBV and human herpesvirus type 6 antibody titers (56). Finally, one study showed that simple emotional disclosure enhanced the immune response to hepatitis B vaccination (57).

Limitations of Prior Behavioral Intervention Strategies in Psychoneuroimmunology

Taken together, these data suggest that behavioral interventions impact immune system functioning. However, there are several limitations. Much more is known about the role of behavioral factors in the suppression of immunity than about what behavioral strategies may be important in boosting immune function, especially in those at-risk populations who are aged, undergoing stress or suffering from chronic disease. Secondly, in many of the studies, standardization of techniques and/or participant adherence (i.e. frequency of relaxation practice) was variable or incompletely assessed. Thirdly, immunological outcomes (e.g. non-specific lymphocyte proliferation) typically relied on measures that were non-specific and for which clinically relevant disease end-points had not been determined (58).

Tai Chi: Effects on Health Outcomes and HZ Immunity

Increasing interest has focused on the use of *tai chi* for promoting health in persons with chronic disease (59–61), and a recent review suggested the promise of *tai chi* as a means of improving a number of health outcomes (59). However, the majority of studies did not use randomized control trial methodologies, and the efficacy of *tai chi* on physiology and health outcomes remains poorly characterized (59). Nevertheless, some trials suggest that *tai chi* can improve health functioning, have effects on both physical and emotional health (62), reduce the risk of falls (63–65) and possibly enhance cardiovascular functioning in sedentary and older adults (62,66–69). Randomized, controlled trials are needed to test the effects of this novel behavioral intervention on specific immunity and infectious disease risk in vulnerable older adult populations.

Tai chi offers special promise as a mind–body intervention that might enhance immune and health outcomes in older adults, because it incorporates elements of meditation and physical activity, both of which have been found to have salutary effects on immune responses (40). Our laboratory has proposed recently that *tai chi chih* (TCC), a westernized version of *tai chi*, might be particularly suitable for evaluation in randomized controlled trials (70), as TCC is a standardized series of 20 simple, repetitive non-strenuous movements. TCC, a form of ‘meditation through movement’, involves a series of fluid, continuous forms of movement which are integrated by mind concentration, balance and shifting of body weight, muscle relaxation and breathing control. Because of its moderate intensity, steady rhythm and low physical and mental tension, TCC has been suggested as an appropriate intervention for elderly patients (64) who are not otherwise able to adhere to physical exercise. TCC incorporates physical activity, the maintenance of which predicts better physical performance, lower frequency of health conditions and lower risk of functional declines and mortality in older adults (71–73), possibly by on reducing autonomic and inflammatory responses to challenge (74–77). In this review, we discuss our recent findings that this ‘meditation through movement’ has immunological effects. In a controlled trial, we assessed the effects of TCC on clinically relevant immunity to VZV in older adults who were randomized to either TCC or a waiting list control group (70).

The study sample included 36 adults older than 60 years of age, all of whom were in good health; 18 persons were randomly allocated to the TCC group and 18 persons were allocated to the waiting list control group. Randomization procedures were successful in delineating two groups of subjects who were similar in age, gender, ethnicity, marital status, current employment status and educational level. Inclusion criteria were as follows: 60 years of age or older at time of entry, geographically accessible, history of varicella (chickenpox) and long-term (>30 years) residence in the continental USA. The latter two inclusion criteria are indicative of the prior occurrence of varicella and the potential for a specific immunological memory response to VZV as measured by VZV-RCF (78,79). Exclusion criteria were as follows: immunosuppression resulting from neoplastic disease, corticosteroids or other therapy; significant underlying illness that would be expected to prevent completion of the study; any other condition (e.g. extensive psoriasis, chronic pain syndrome, cognitive impairment or severe hearing loss) that in the opinion of the investigator might interfere with the required evaluations; not ambulatory; prior HZ; receipt of immunizations (e.g. hepatitis B vaccine or influenza vaccine) within 1 month of study entry; current depression, suicidal risk, use of mood-altering medications or a combination of these depressive factors; any acute intercurrent illness that might interfere with interpretation of the study (such as an acute viral illness within the last 2 weeks); and unable to commit to the intervention schedule. Women were post-menopausal.

Subjects in the TCC group learned to perform 20 standardized movements during a 15 week intervention period under the

guidance of an expert TCC teacher who had 20 years of experience in teaching this mind–body intervention. TCC is performed as slow, relaxed, continuous movements incorporating elements of balance, postural alignment and concentration. It also requires a considerable amount of work by the leg muscles and thus is thought to have an aerobic component of moderate intensity (67). Thus, each TCC session was restricted to 45 min with a 10 min warm-up, a 30 min TCC practice and a 5 min cool-down period. Sessions were given three times per week (45 sessions over 15 weeks). The level of participation in the TCC was high, with median compliance at 39 of 45 possible sessions with a range of 29–42 sessions attended. Participants assigned to the waiting list control group were instructed to maintain their routine activities and not to begin any new meditation, mind–body (e.g. yoga) or exercise programs; adherence was confirmed by self-report. The control participants were promised a TCC program and given a voucher for instruction at the end of the study.

The results of this randomized controlled trial showed that shingles immunity, as measured by VZV-RCF, increased from baseline to 1 week post-intervention in the TCC intervention group whereas the wait list control group did not change significantly (Fig. 4). This effect of TCC was tested statistically using a conservative intent-to-treat approach. To provide a further indication of the effects of the intervention on VZV-RCF, percentage change from baseline to post-intervention was examined in individual subjects. Within the TCC intervention group, VZV-RCF increased in nine subjects, was unchanged in seven (including four who were analyzed as intent-to-treat cases) and decreased in one subject; whereas in the control group, three subjects increased, eight were unchanged (one intent-to-treat case) and five decreased (likelihood ratio = 6.1, $P < 0.05$). Importantly, the TCC group showed a robust increase of

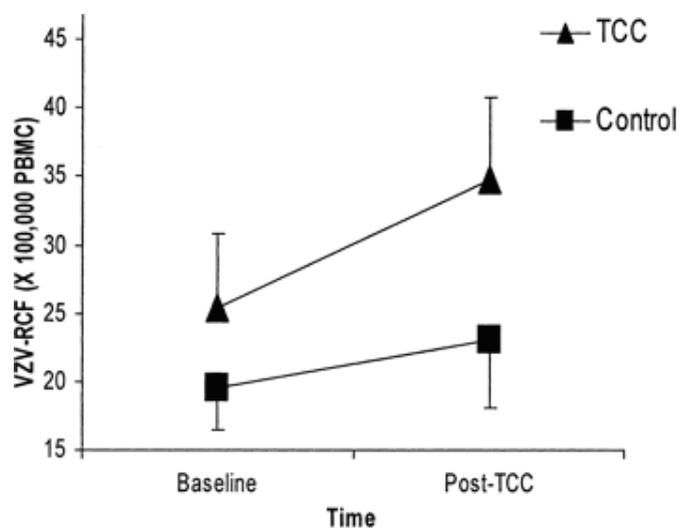


Figure 4. VZV-specific CMI (VZV-RCF) at baseline and at 1 week post-intervention in the intent-to-treat sample. VZV-RCF increased from baseline to 1 week post-intervention in the TCC group [$F(1,31) = 4.4$, $P < 0.05$] but not in the control group. Data are mean \pm SEM values. Reprinted with permission from Irwin *et al.* (70).

VZV-RCF, and on average had a nearly 50% increase of VZV-RCF from baseline to 1 week post-intervention using this intra-subject approach. In response to vaccination with live attenuated Oka/Merck varicella vaccine, Levin *et al.* have demonstrated an ~75% increase above baseline in >200 seropositive elderly adults (mean age 67 years) (80,81), an increase that is similar to that induced by an episode of HZ (82). Response to vaccination is sustained for months to years (82), but further research is needed to evaluate the durability of the effects of TCC on VZV-RCF levels. Increases of VZV-RCF are driven primarily by the response of CD4⁺ CD45RO⁺ T cells or memory T cells (83), and we speculate that TCC might have comparable effects on these cell types across the full spectrum of antigenic challenge, with potential implications for multiple infectious diseases for which no vaccine is yet available (e.g. HIV infection; respiratory infection). Moreover, the increase of VZV-RCF in this sample is even more striking because the older adults were in good health, not depressed and had higher baseline levels of VZV-RCF than had been reported previously in this at-risk population (84). Future studies could extend these findings and examine the effects of TCC on other memory T-cell responses (e.g. to influenza virus) and/or test whether this mind-body treatment alters response to a primary immunological response. Smith *et al.* have found that psychological stress impairs development of a delayed-type hypersensitivity response to a novel protein antigen, keyhole limpet hemocyanin, in humans (85), whereas older adults who are more physically active show higher antibody and delayed-type hypersensitivity responses to this antigen as compared with sedentary older adults (86). These data showing an increase of VZV immunity following TCC contrast with those of Locke *et al.* who found that hypnosis had no effect on varicella antigen-induced delayed-type hypersensitivity responses in humans (87).

It is thought that an increase in VZV-RCF may be associated with better control of latent VZV virus, an assumption that has led to the development of a varicella vaccine that induces increases of VZV-RCF in older rats (82). In an ongoing Veterans Affairs Cooperative Trial ($n = 38\,546$), this investigational varicella zoster vaccine is currently being tested to determine its efficacy in the prevention of onset and severity of HZ and postherpetic neuralgia. The present TCC study does not have an adequate sample size to address whether TCC can alter the incidence of shingles, given its annual incidence at <8 cases per 1000 persons. Alternatively, it is possible that the increase of VZV-RCF associated with TCC might be secondary to viral reactivation. Mehta *et al.* recently reported that non-surgical stress induces subclinical reactivation of VZV as evidence by the detection of VZV DNA by polymerase chain reaction in saliva samples, although no change in the levels of anti-VZV IgG was found before and after the stress. Others indicate that viral reactivation and shedding of VZV occur HZ clinical outbreak (88) and/or zoster sine herpette (pain without rash) (89,90), in contrast to mucosal shedding of other herpes viruses that continues for decades after primary infection (91). Importantly, none of our subjects evidenced HZ or reported symptoms of pain or distress during the course of the trial.

Nevertheless, even if the intervention acts to induce subclinical reactivation, increases of VZV-RCF, induced by contained reversions may help to maintain immunity to VZV in older adults and prevent future occurrences of HZ in older adults, as suggested by Hope-Simpson (see Fig. 2) (14).

This study also found that TCC was associated with improvements in physical functioning and physical role limitations, especially in those older adults who had impairments in physical status at entry. In the sample who completed the intervention, the TCC group had significantly higher scores on the Medical Outcomes Scale, SF-36 role-physical scores (Fig. 5) and physical functioning scores at 1 week post-intervention as compared with controls. Moreover, in those older adults whose baseline scores were at or below the population norm for men and women aged 60 years and older (92), these observations were particularly striking. After completion of the intervention, TCC participants showed increases of health functioning scores to levels that were at or above the population norms. Moreover, those participants who had low health functioning at baseline showed more marked improvements over time with significantly greater increases of SF-36 role-physical and physical functioning as compared with changes in the TCC group who had minimal impairments of physical status at baseline. The magnitude of change from baseline to post-intervention was large for these measures of health functioning and was comparable with that reported for certain medical procedures. For example, in the instance of SF-36 role-physical scores, the average change in the low TCC group was comparable with or exceeded that reported for hip replacement surgery (93) or for heart valve replacement in older adults (94), although it is not known whether the effects of TCC persist in the long term.

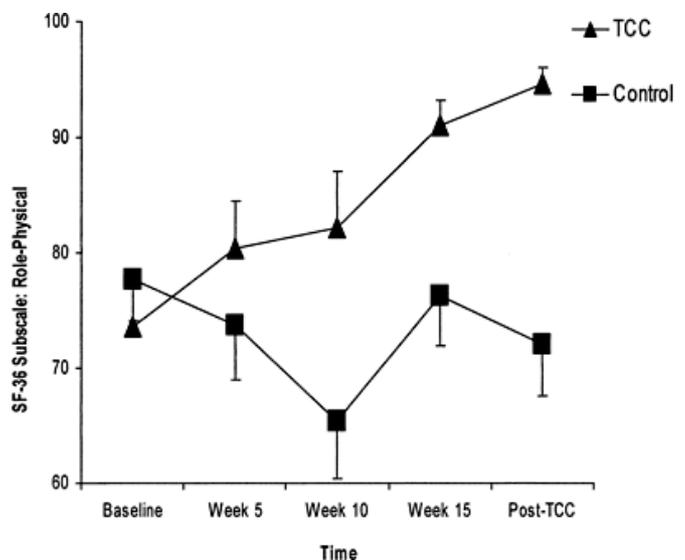


Figure 5. SF-36 scale score role-physical at baseline, during the intervention at weeks 5, 10 and 15, and 1 week post-intervention in the completer sample, TCC ($n = 14$) and control group ($n = 17$). SF-36 role-physical scores were higher in the TCC group compared with controls [$F(1,28) = 5.1$] at post-intervention. Data are mean \pm SEM scores. Reprinted with permission from Irwin *et al.* (70).

Several pathways may mediate the effects of TCC on immunity and health functioning. Although none has yet been established, we have hypothesized that two components, relaxation and exercise, may mediate the observed changes in immunity and health outcome (Fig. 6). In a meta-analysis on the effects of relaxation training, Hyman *et al.* (95) found that various relaxation response-based interventions led to a reduction of clinical somatic symptoms with additional effects on symptoms of anxiety and depression (96), blood pressure (97) and recovery from immune-mediated diseases such as psoriasis (98). Decreases of autonomic arousal that follow relaxation-based interventions, and possibly TCC, may modulate immunity. Substantial evidence suggests that sympathetic activation has inhibitory effects on cellular immune responses in the elderly (99–102), whereas decreases of sympathetic outflow, adrenergic receptor antagonism, or both abrogate stress-induced immune suppression (99,101,103,104). In contrast, TCC might increase parasympathetic, vagally mediated tone which has been found to inhibit proinflammatory cytokine mechanisms (105,106). Importantly, the effects of TCC were not mediated by social functioning, mental health functioning or changes in physical health status, as the intervention did not alter SF-36 measures of social functioning or role-emotional, and SF-36 scores of physical functioning were not correlated with changes in VZV-RCF.

The benefits of exercise and exercise training on immunity in the elderly have been reported previously (107,108) and, as

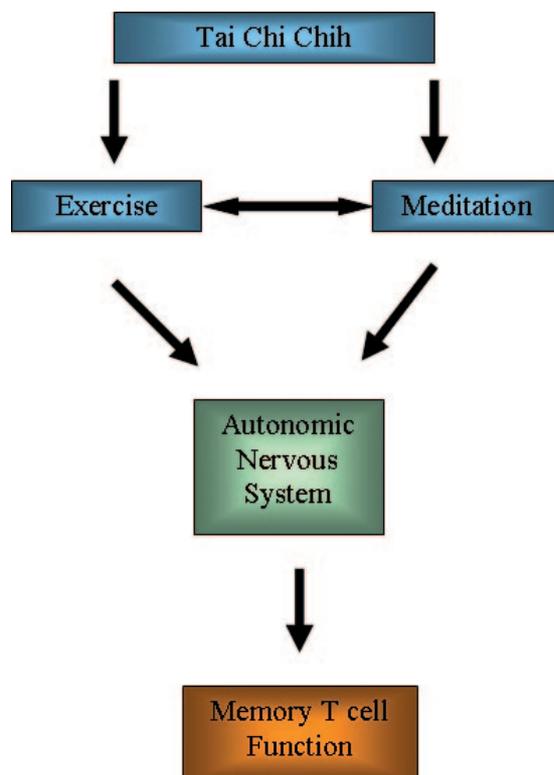


Figure 6. Hypothesized mediators of the effects of *tai chi chih* on varicella zoster virus memory T-cell responses. The evidence for the pathway components of exercise and relaxation or meditation with changes of sympathovagal balance are considered.

noted above, physically active older adults have more robust primary humoral and delayed-type hypersensitivity responses to a novel antigenic challenge (86). In addition, moderate exercise training for 8 weeks has been found to promote increases of herpes viral-specific immunity in mice (109) and this effect is mediated by adrenergic receptor mechanisms (110). Indeed, TCC is a multifaceted intervention that includes not only relaxation, but also components of aerobic exercise (61,66). During the acute practice of TCC, for example, increases of heart rate, oxygen consumption and lactate accumulation are reported, indicating that TCC serves as an aerobic exercise of moderate intensity (66). Further data show that TCC training over 12 months enhances cardiorespiratory function as measured by increases of VO_2 MAX and decreases of blood pressure (68).

TCC Boosts Immunity to VZV and Health Status in Older Adults: Need for Further Trials

Our research shows that an alternative medicine, mind–body intervention, namely TCC, results in improvements in measures of immunity to VZV in an older adult population at risk for HZ. TCC is a standardized and manualized series of exercises that can be readily administered in a group setting to older adults with cost-effectiveness, supporting the exportability of this intervention for community-dwelling older adults. In addition, this study indicates that TCC has value for improving functional limitations in physical domains. Other forms of *tai chi* are purported to have physiological and psychological benefits and to promote balance control and cardiovascular fitness in older adults. Further high quality, randomized controlled trials are needed to further delineate the effects of these mind–body practices on health risk factors and on chronic medical outcomes, especially in vulnerable older adult populations.

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Conflict of Interest

Michael Oxman is currently the National Study Chairman of VA Cooperative Study #403: The Shingles Prevention Study which is supported in part by a grant from Merck and Co., Inc, the producer of the investigational shingles vaccine to the VA congerative studies program.

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