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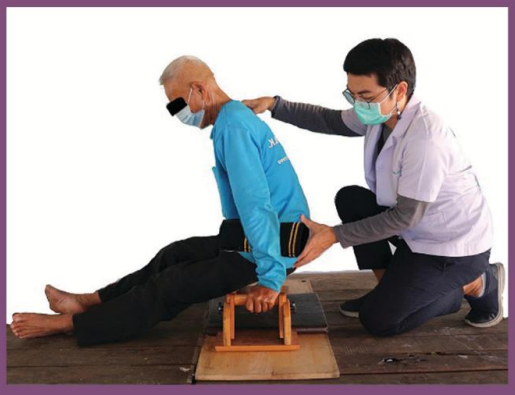

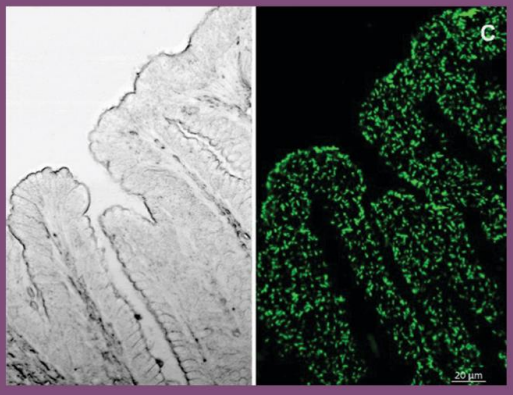

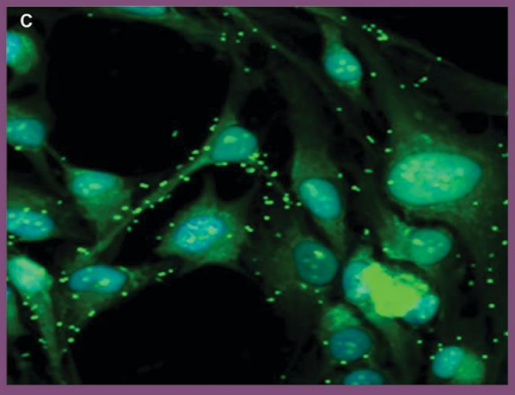

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ORIGINAL ARTICLE

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Effects of aromatherapy massage with bergamot essential oil on vital sign, flexibility, stress level and stress hormone in healthy adults: a pilot study

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KEYWORDS
Aromatherapy massage;
Bergamot essential oil;
Vital sign;
Flexibility;
Stress.

ABSTRACT
Aromatherapy with essential oils has been shown to relieve stress and alleviate symptoms of musculoskeletal diseases. However, physiological changes generated by aromatherapy massage with bergamot oil are still limited. The objective of this study was to determine the effect of aromatherapy massage with bergamot essential oil in healthy subjects. Thirty-one healthy subjects received a 14-minute aromatherapy massage with bergamot oil at the back region three times a week for four weeks. Blood pressure, heart rate, respiratory rate, skin temperature, stress level, back flexibility, cortisol levels, and aldosterone levels were measured at baseline and the end of a 4-week aromatherapy massage with bergamot oil. The result showed that all parameters mentioned above except skin temperature, back flexibility, and diastolic blood pressure were significantly decreased after the intervention. Skin temperature and back flexibility were significantly increased after the intervention with aromatherapy massage with bergamot oil. Diastolic blood pressure was decreased after the intervention but did not reach statistical significance. In conclusion, a 4-week course of aromatherapy massage with bergamot oil at the back region could improve physiological parameters including autonomic, stress, back flexibility, and hormonal parameters.

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Introduction

Stress is a major mental health issue that affects people of all ages and genders[1]. Stressful life events and personal life changes, such as bereavement or job loss, have been identified as risk factors for mental disorders[2]. Stress refers to human reactions or responses to stressors, which can occur immediately or later after the incidence of stressors. It is partly due to the rapidly changing socio-economic conditions and social crises that lead to various sorts of problems such as unemployment, poverty, criminal activity, and economic crisis[3]. When the body is under stress, it reacts both physically and psychologically. The endocrine system emits more cortisol hormone, stimulating the autonomic system and leading to physical, mental, and behavioural abnormalities[4]. Moreover, the stress-induced elevation of aldosterone secretion was most significant. According to a previous study, aldosterone is an important hormone that regulates water and salt balance as well as blood circulation, resulting in better blood pressure regulation[5]. Physical abnormalities generated by stress include increased heart rate, blood pressure, respiratory rate, muscle tension, and muscle pain[6]. Chronic stress causes fatigue, muscle atrophy, and weakening by constantly mobilizing energy at the expense of energy storage. Worries, anxiety, muddled thinking, forgetfulness, poor concentration, annoyance, and other mental abnormalities are examples of mental abnormality[7].

Nowadays alternative medicine is taking more roles to treat and relax patients with stress. Aromatherapy is a complementary therapy that utilizes essential oils as the primary therapeutic agent to treat a variety of illnesses. It is one of these options that has attracted the public interest. The inhalation or absorption of essential oils through the skin stimulates physiological responses of the nervous and endocrine systems[8]. It has the effect of restoring mental and physical balance, and so relieving stress[9]. Patients with mental problems who got aromatherapy had lower cortisol levels and were more relaxed as a result. Previous studies have shown that essential oils including lavender, sandalwood, ylang-ylang, and sweet orange oil have effects on the body and autonomic system, including lowering blood pressure, heart rate, respiratory rate, pain, and inflammation[10]. Furthermore, it has been revealed that these essential oils reduce cortisol, a stress hormone. Bergamot essential oil aromatherapy can be a helpful supplement to other treatments for improving mental health and well-being. It promotes happiness and proper brain function. Moreover, it has been demonstrated that bergamot essential oil reduces cortisol levels. In addition, aromatherapy with bergamot essential oil has been shown to reduce heart rate, blood pressure, anxiety, stress responses, and improve mood[11].

It is well known that massage therapy promotes relaxation and reduces stress[12]. Swedish massage is a well-known treatment that has been practiced in a bunch of countries. This massage technique relaxes the muscles while simultaneously increasing blood flow back to the heart. Furthermore, it has been demonstrated to improve blood pressure, heart rate, respiration rate, reduced anxiety, and reduced stress levels[13]. Being considered the advantages of bergamot oil aromatherapy and Swedish massage, combining aromatherapy and massage with bergamot oil may bring extra health benefits. A previous study reported that the massage with blended lavender and bergamot essential oils reduced autonomic arousal by decreasing heart rate, blood pressure and promote relaxation[14]. There is currently insufficient research on aromatherapy with bergamot essential oil and massage as a combined therapy. Thus, the goal of this research is to see how this combination affects physiological markers.

Materials and methods

Participants

The one group pretest-posttest study was conducted on 31 healthy subjects. The inclusion criteria were aged between 18 and 25 years, not sensitive to aroma, and not having irritation or allergy to essential oils. If subjects had coronary heart disease, asthma, cancer, a fractured or inflamed bone, diabetes, autonomic dysfunction,

hypertension, fever, or obesity, they were excluded from the study because these conditions may influence the measured parameters. In addition, if subjects did not complete the aromatherapy massage course, they were also excluded from this study. To avoid the impacts on physiological parameters, the participants were requested not to consume caffeinated drinks such as tea or coffee for a period of 12 hours and not to exercise vigorously for 24 hours before participating in the study. The study protocol was approved by the Ethics Committee in Human Research (ID. 5202040013). Before signing the consent form for participation, subjects were informed about the experimental protocol and possible risks. All subjects signed informed consent before study enrolment.

Preparation of the essential oil

Bergamot oil was mixed with a sweet almond oil for body massage (approximately 10-15 drops of bergamot oil per 30 ml base oil, or one ml of essential oil per 30 ml of base oil. The dose of bergamot oil was modified from a previous study[15]. The mixture was then poured in a foam cup at each bed for massage.

Preparation of the participants

Before participating in the study, the volunteers were asked to come in for a blood test to evaluate their cortisol and aldosterone levels. This was done between 1:00 and 3:00 p.m. Cortisol levels range from 2.3 to 11.9 ug/dl, while aldosterone levels range from 1.4 to 16 ng/dl. Hormones have a half-life of about 1-3 hours. The subjects were then asked to change their clothes into a back-opening gown and complete a stress questionnaire. They took a 15-minute rest before the outcome's measurement and massage. The subjects' blood pressure, heart rate, respiration rate, temperature, and back flexibility were all measured by the researchers before and immediately after the last aromatherapy massage. Throughout the trial, all volunteers were requested to maintain their usual activities of daily life and degree of exercise. All experiments were conducted in a bright and separate room free from noise and stimulation. The ambient temperature was 27 °C.

Blood pressure and heart rate measurement

Blood pressure and heart rate were measured two times at one-minute intervals by using OMRON (HEM 7203, USA). The average data were used for statistical analysis. The stress level was measured by using a Thai self-reported stress questionnaire. The questionnaire consists of 20 questions with four alternative answers about current events (never, sometimes, often, and always). A total score of 60 represents a typical stress level, whereas a score of less than 17 indicates normal stress level. The questionnaire was developed by the Department of Mental Health.

Measurement of flexibility

Flexibility was evaluated by the sit-and-reach test using a trunk flexometer. Subjects performed long sitting with straight knees, feet together to the wall of flexometer. The subjects moved their arms forward, both hands above the flexometer, and their trunk in a forward bending position until they reached their limit motion, which they maintained for two seconds. The investigator measured from the zero scale to the tip of the middle finger. Each subject performed two times and the highest score in centimeter (cm) was chosen.

Measurement of cortisol levels, and aldosterone levels

The blood sample was collected from the median cubital vein by a medical technologist immediately after the last aromatherapy massage. The determinations of cortisol and aldosterone levels were performed by a lab technician at Chiangmai R.I.A Lab, Mueang Chiang Mai District, Chiang Mai Province, Thailand.

Procedure of massaging

The volunteers received aromatherapy massage with bergamot oil at the back region three times per week for four weeks[16]. The massage was started by asking the volunteer to lie prone and turn their heads to any side they felt comfortable with. Two little pillows were placed under their ankles and a small pillow was placed under their abdomen. A blanket sheet was placed over their legs, kept open only at the

massaged areas. The massage was performed from the 7th cervical spinous process and the most protruding part of the shoulder bone adjacent to the shoulder (acromion process), and the line on their side from the mid axillary line and the iliac crest, (L4-5). Seven massage steps made up the whole therapeutic time of 14 minutes (Figure 1). Each step took two minutes to complete. Before rubbing the volunteer, the massage therapist rubbed bergamot oil all over the volunteer's back.

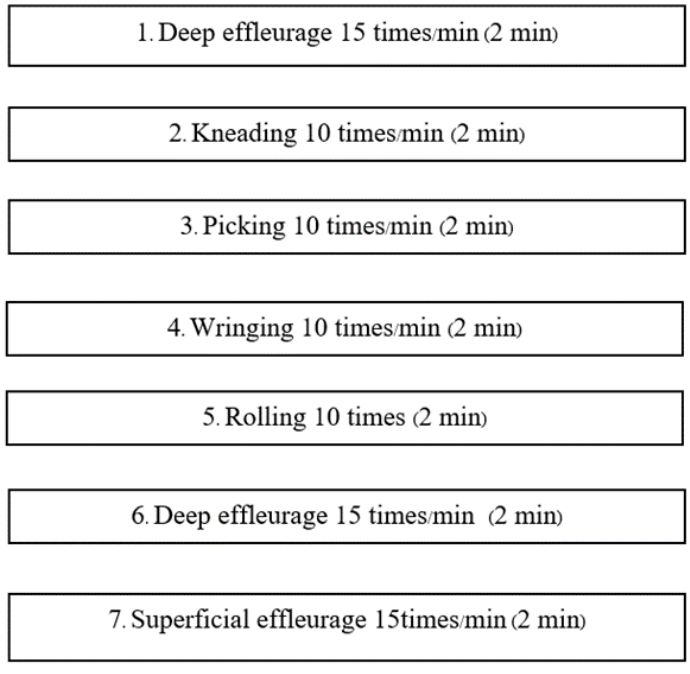

Figure 1 Seven steps of massaging with a total massage time of 14 minutes

Statistical analysis

The data were analyzed using SPSS version 17. All data were shown in means and standard deviations (SD). Normality was tested using the Shapiro-Wilk test. In each participant, all continuous variables were normally distributed and compared using the paired t-test. Significance was defined as a *p*-value of less than 0.05.

Results

There were 40 subjects who were enrolled at the beginning of the study. Nine subjects were excluded due to an incompletion of the study protocol. Therefore, a total of 31 subjects completed the study. There were no adverse events during the assessments and massage. The average age of the participants was 23.08 years. There were 11 males (35.5%) and 20 females (64.5%) among the participants. Table 1 lists the characteristics of the subjects. A 4-week aromatherapy massage with bergamot oil increased body temperature and back flexibility (p-value < 0.001 and p-value = 0.014, respectively), but decreased heart rate, respiratory rate, systolic blood pressure, and stress score (all p-value < 0.001) (Table 2). The diastolic blood pressure was observed to be reduced from 75.9 to 74 mmHg (p-value = 0.208) (Table 2). Furthermore, after completing the aromatherapy course, cortisol and aldosterone levels reduced significantly (p-value = 0.009 and p-value < 0.001, respectively) (Table 3).

Table 1 Subject characteristics

Characteristic	Value (n=31)
Age (years)	23.08 ± 0.8
Gender, male (%)	11 (35.5%)
Gender, female (%)	20 (64.5%)
Body weight (kg)	56.64 ± 5.27
Height (cm)	159.70 ± 4.12

Note: All data were shown in means and standard deviations (SD).

Table 2 Measured parameters before and after the 4-week intervention

Variables	Before (n = 31)	After (n = 31)	95%CI	*p*-value
SBP (mmHg)	114.4 ± 8.8	107.1 ± 9.5	(4.79) - (10.21)	< 0.001
DBP (mmHg)	75.9 ± 8.6	74.0 ± 7.2	(-1.30) - (4.86)	0.208
HR (beats/minute)	72.7 ± 7.6	67.8 ± 8.5	(3.08) - (6.70)	< 0.001
RR (times/minute)	17.9 ± 3.1	16.4 ± 2.7	(0.90) - (2.26)	< 0.001
Temperature (°C)	35.9 ± 0.4	36.5 ± 0.3	(-0.58) - (-0.40)	< 0.001
Back flexibility (cm)	6.6 ± 8.0	8.3 ± 7.3	(-3.10) - (-0.98)	0.014
Stress score	20.0 ± 7.9	16.5 ± 8.2	(-3.32) - (-2.29)	< 0.001

Note: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; (°C), Degree Celsius; kg, kilogram; cm, centimeter; mmHg, millimeter mercury; 95% confidence interval.

Table 3 Cortisol and aldosterone levels of subjects before and after the intervention

Data	Before (n = 31)	After (n = 31)	95%CI	*p*-value
Cortisol (ug/dl)	10.3 ± 4.4	7.7 ± 3.0	(2.36) - (7.58)	0.009
Aldosterone (ng/dl)	4.8 ± 2.8	0.3 ± 0.1	(1.04) - (0.23)	< 0.001

Note: ug, microgram; ng, nanogram; dl, deciliter; 95% confidence interval.

Discussion

The results of this study showed that a 4-week aromatherapy massage with bergamot oil improved autonomic, stress, back flexibility, and hormonal parameters. This suggests that the combination of aromatherapy and massage may have a beneficial effect. After the intervention, autonomic measures such as heart rate, respiratory rate, and systolic blood pressure all improved significantly. In addition, there is a downward tendency in diastolic blood pressure. Massage has been shown to accelerate the pace of venous return to the heart[17]. Furthermore, prone lying promotes relaxation, which lowers heart rate and systolic blood pressure[18]. It is well recognized that cortisol activates the sympathetic nervous system (SBP). We found that aromatherapy massage with bergamot oil significantly lowered cortisol levels in the current study. As a result, the sympathetic nervous system function was reduced, resulting in lower SBP, heart rate, and respiratory rate; all of which are indicators of sympathetic function[19]. Aromatherapy massage with bergamot oil lowered the secretion of aldosterone, a hormone that

regulates water and mineral balance, as well as cortisol levels, resulting in improved blood pressure regulation. Low levels of aldosterone have been linked to lower blood pressure[20]. We observed a trend of reduced diastolic blood pressure in this study, although the change was not significant. As a result, we suggest that aromatherapy massage with bergamot oil had some effect on diastolic blood pressure, due to lower levels of aldosterone.

The results of a 4-week aromatherapy massage with bergamot oil showed a considerable increase in skin temperature, which is consistent with earlier research. Heavy pressing and squeezing of the muscles have been shown to improve blood circulation, body metabolism, and skin friction, as heat is liberated from the muscles and transmitted to the vessels, the temperature rises[21]. Following an aromatherapy massage with bergamot oil, back flexibility increased significantly, indicating improved muscle relaxation. Massage improved relaxation by reducing adrenocorticotropic hormone (ACTH)[22]. In addition, the generation of ATCH by the adrenal glands was suppressed, resulting in lower levels of adrenalin. Blood pressure and heart rate are also reduced when adrenalin levels are low[23]. Aromatherapy with bergamot essential oil was found to increase relaxation and emotional status in a previous study[11]. It can be a useful supplement to other treatments for improving mental health and well-being. Our results confirmed this hypothesis by the evidence that both cortisol (adrenalin-like) and aldosterone hormone from the adrenal gland were significantly reduced after the intervention. The massage itself also increased blood circulation at the massaging spot and thus relaxed muscles and promoted more flexibility.

We found that following a 4-week aromatherapy massage using bergamot oil, stress levels decrease. These findings support prior research that showed slow stroke back massage decreased psychological stress as measured by a subjective visual analog score[24]. The lowering of cortisol hormone after massage therapy was linked to stress levels in various situations[25]. Another study found that a 12-week aromatherapy massage combined with music reduced stress and anxiety over the summer and winter months[26]. Furthermore, previous studies found that a 10-minute back massage helped reduce vital signs and anxiety levels. Fifteen-minute back massage to enhance anxiety levels, cortisol levels, blood pressure, heart rate, and sleep quality[27]. Aromatherapy using bergamot essential oil vaporized for 15 minutes reduced saliva cortisol levels significantly[28]. Therefore, we suggest that the stress score was decreased possibly related to the reduction of cortisol levels.

Massage benefits include reducing muscle tension, increasing joint range of motion, and reducing stiffness, as well as improving and maintaining normal flexibility. The length of the back muscles partly influences body flexibility. Back muscle spasms or shortening can obstruct back motion, resulting in reduced flexibility[29]. As a result, we chose to massage the back region using the seven-step procedure. The duration of the back massage employed in this study was modified based on previous research that revealed that 10 minutes of massage significantly improved physiological measures[30]. We found an increase in flexibility after an aromatherapy massage using bergamot oil in this study. Therefore, the increased flexibility that occurs after receiving an aromatherapy massage with bergamot oil could be attributed to both the aromatherapy and the massage. Nevertheless, we also aware that the resting alone (without either massage or aromatherapy) in the same position and environment could provide these effects. The lack of a control group for comparison was one of the study limitations. However, in the one-group pre-test and post-test experimental design, the results of this intervention regimen were good, given the intervention being a combination of massage and bergamot aromatherapy. Thus, the authors are unable to indicate whether the benefit of the intervention generated by both massage and bergamot oil, or by each of them. Therefore, further studies with different experimental designs are still required.

Conclusion

In conclusion, a 4-week course of aromatherapy massage with bergamot oil could improve physiological parameters including vital sign, stress, back flexibility, and hormonal parameters.

Take home messages

A 4-week course of aromatherapy massage with bergamot oil at the back may reduce blood pressure, heart rate, respiratory rate, stress, cortisol, and aldosterone levels while increasing skin temperature and back flexibility. This intervention could help people improve their mental health and well-being.

Conflicts of interest

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

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Vojta therapy versus balance training program on dynamic sitting balance in chronic motor complete spinal cord injury: a single-blind crossed-over trial study

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KEYWORDS
Vojta therapy;
Balance training program;
Dynamic sitting balance;
Gross motor function assessment;
Spinal cord injury.

ABSTRACT
The purpose of this blind-assessor randomized crossover trial was to evaluate the effect of Vojta therapy (VT) and a balance training program (BTP) on dynamic sitting balance in individuals with thoracic chronic motor complete spinal cord injury (SCI). Eleven individuals with SCI (T2-T12, American Spinal Injury Association (ASIA) class A-B) were randomly assigned to undergo either VT or BTP for 45 minutes. One week later, the interventions were alternated. The primary outcome measures were dynamic sitting balance assessed via the modified Functional Reach Test (mFRT) and the ability to don and doff a T-shirt (the T-shirt test). Gross motor function assessment (GMFA) was the secondary outcome. All assessments were performed immediately before and after the intervention. The Mann-Whitney U test was used to compare the change score between interventions, and the Wilcoxon signed rank test was used to analyze the data within an intervention. There was not significant difference at before between interventions. VT was superior to BTP in yielding a statistically significant difference in dynamic sitting balance and gross motor function (p-value < 0.05). However, both interventions proved effective in improving dynamic sitting balance and gross motor function (p-value < 0.05) in those suffering from motor complete chronic SCI. A 45-minute VT and BTP program was able to improve dynamic sitting balance and gross motor function relating to the functional ability and activities daily living of individuals with thoracic SCI with a long post-injury time.

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Introduction

Thoracic spinal cord injury (SCI) results in impaired sensorimotor function of the trunk and legs below the injury level. Due to a decreased control of the trunk, many individuals with thoracic SCI have poor sitting balance and remain wheelchair-dependent even after rehabilitation[1]. Good sitting balance is a fundamental component for functional activities of daily living in both the home and the community, such as grooming, dressing, wheelchair propulsion, transfer to and from the wheelchair, and reaching objects[2]. Furthermore, a previous study found that 31 percent of their participants reported more than 500 fall events in wheelchair-dependent SCI patients[3]. Therefore, improving the sitting balance is essential for achieving independence activities daily living in individuals with thoracic spinal cord injury[4].

There are different intervention methods for improving dynamic sitting balance in individuals with SCI [2,5-7]. Task-specific training is commonly used[5-7], and it involves intensive and repetitious practice following the principle of motor relearning[8,9]. A systemic review in 2018 found a moderate level of evidence that task-specific training interventions can improve sitting balance in the chronic stages of the disease[4]. In addition, these treatments require six to twelve weeks to yield any improvement in dynamic sitting balance[4]. The balance training program (BTP) is one type of task-specific training. Furthermore, a new intervention, Vojta therapy (VT), has been shown to improve balance[10].

VT was first used by Prof. Dr. Vaclav Vojta in 1959 for the treatment of children with cerebral palsy. Later, it was successfully applied to treat movement disorders in adults[11]. The basic principle of VT is reflex locomotion[12,13]. The reflex locomotion pattern is the "building blocks" used for movement and postural control, which are emerged by position correction and stimulation of the appropriate zone[12-14]. The position consists of supine and side lying (reflex rolling) and prone lying (reflex creeping)[12,13]. There are ten different zones on a human body[13]. Isometric muscles, which take part in the locomotion of the whole body, are activated via exteroceptors and the enteroceptors[10,12]. Afferent stimulation goes to the central nervous system and a connection between the spinal cord and the brain is established by propriospinal neurons[12,13]. In addition, a previous study also found that VT activated the transversus abdominis muscle which is one of the core muscles for providing proximal stability to improve balance[10,15-17].

To our knowledge, no study has used VT as an intervention in SCI patients. Hence, the aim of this study was to investigate the effects of VT and BTP on improving dynamic sitting balance in people suffering from chronic thoracic motor complete SCI.

Materials and methods

Trial design

An assessor-blind, randomized, 2x2 crossover trial study (switching from one intervention to another during study)[18] was undertaken at the Department of Physical Therapy, Faculty of Medicine, Prince of Songkla University from December 2019 to February 2020. A computer-generated random intervention was obtained before beginning the trial by a person not involved in the recruitment of the participants. The participants, who passed the screening process and completed the initial assessment, were informed which intervention they received first. Using a repeated-measures crossover design, participants were randomized to receive 45 minutes of either VT or BTP, followed by a 1-week wash-out[18], after which the participants received the other intervention paradigm (Figure 1). This study used the crossover deign as a way to minimize the occurrence of participant heterogeneousness (e.g., age, gender, body mass index, etiology of disease, neurological level of injury which could have affected the results of the study).

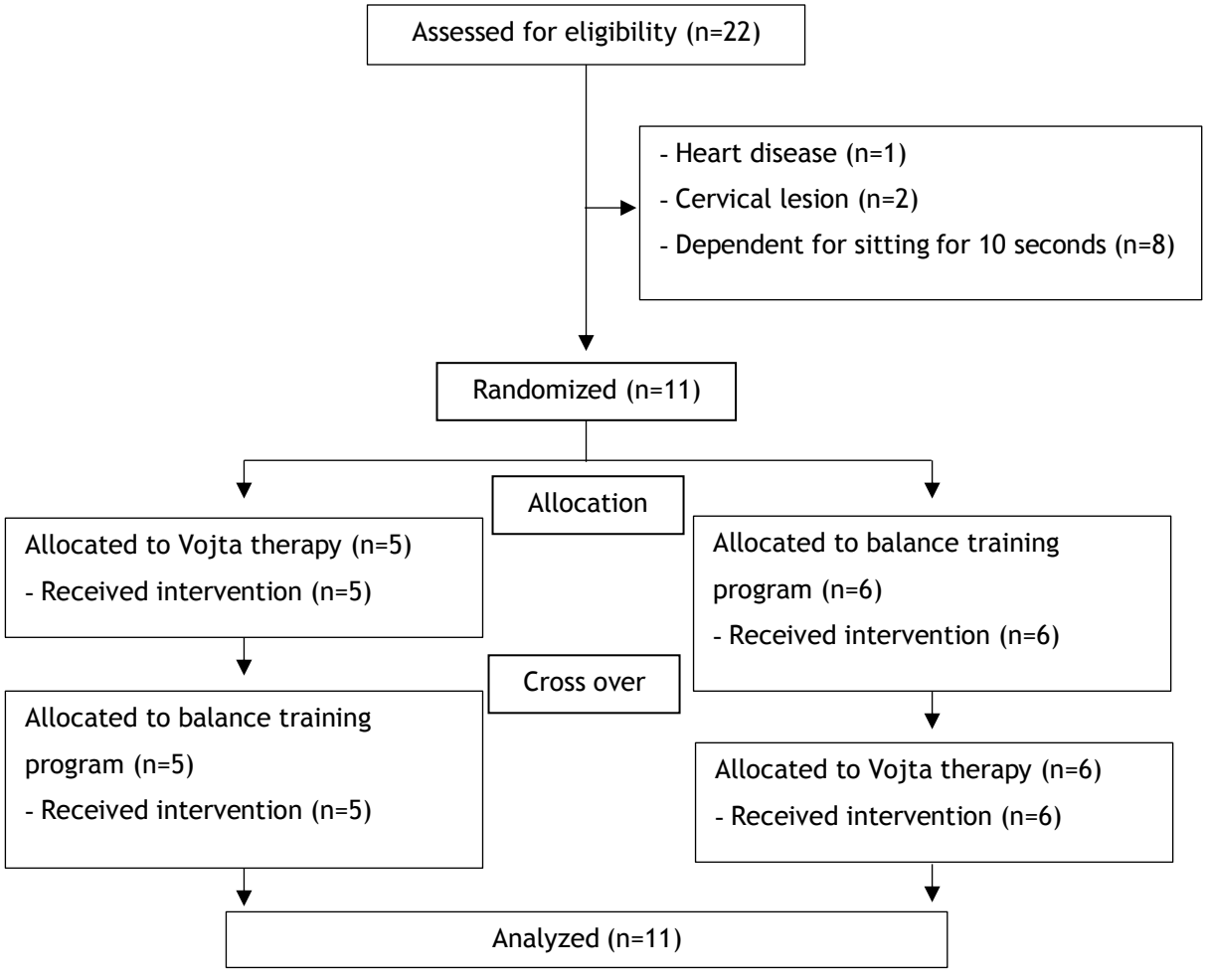


Figure 1 CONSORT (Consolidated Standards of Reporting Trial) flow diagram of randomized crossover design.

Participants

Participants were included if they had a motor complete SCI (classified as ASIA Impairment Scale (AIS) A to B) at a neurological level of injury between T2 and T12 for a duration of more than 12 months[19]. The additional inclusion criteria were the following: age between 18 and 60 years and the ability to sit unsupported for more than 10 seconds with a shoulder flexion of more than 90 degrees. Potential participants were excluded according to the following: had experienced VT within one month, had other neurological (e.g., stroke, traumatic brain injury, or Parkinson's disease, and had musculoskeletal (e.g., osteogenesis imperfecta) or cardiovascular problems (heart disease) that are precautions and contraindications for VT. The study protocol was approved by the Human Research Ethics Committee (HREC), Faculty of Medicine, Prince of Songkla University (No. 62-292-30-2). All the participants understood and acknowledged the details of the study and the risk involved and provided a written informed consent before the study's commencement.

Sample size calculation

The sample size was calculated based on a pilot study among five participants using the formula described below

$$n = \left[\frac{(Z_{\alpha/2} + Z_{\beta})\sigma}{\Delta} \right]^2$$

The sample size was estimated on the basis of the dynamic sitting balance measured on a modified functional reach test (mFRT) after intervention and assuming an 80.0% power, 5.0% significance, and 20.0% dropout rate. In order to detect a statistical significance between interventions on mFRT, a minimum total sample size of 11 was required for the study.

Interventions

Participants received two programs for 45 minutes. The programs consisted of 15 minutes of prolonged passive stretching before the intervention and 30 minutes of VT or BTP depending on the treatment order. The prolonged passive stretching consisted of five poses: trunk rotator muscles, hip flexor muscles, hip adductor muscles, ankle plantar flexor muscles, and hip extensor muscles. The participants were stretched holding each pose for 15 seconds and repeating it five times.

VT was administered by a Vojta therapist, who is licensed and has an experience of more than two years. The participants received 30 minutes of VT in the supine position (reflex rolling) for the chest zone, the side lying position (reflex rolling) for the scapular and anterior superior iliac spine (ASIS) zone, and the prone position (reflex creeping) for the calcaneus zone[20]. Each position was stimulated for 10 minutes on both left and right sides (Figure 2).

A. Chest zone in reflex rolling

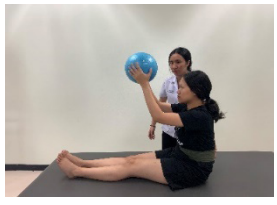
B. Scapular and ASIS zone in reflex rolling

C. Calcaneus zone in reflex creeping

Figure 2 Vojta therapy

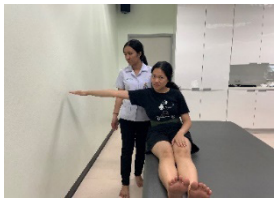
The BTP is modified from previous study[6]. It comprised 24 different exercises in three sitting positions, which consisted of long sitting on the bed, side sitting, and side sitting on the balance board. Each position involved eight poses composed of static sitting balance training for one minute, ball elevation 10 times, front reaching 10 times, right and left side reaching 10 times, cross right and left side reaching 10 times, and front reaching to contact the feet 10 times (Figure 3).

A. Static sitting balance on the bed



B. Ball elevation sitting on the bed

C. Front reaching sitting on the bed



D. Right side reaching sitting on the bed

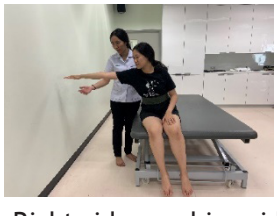
E. Crossed right side reaching sitting on the bed

F. Front reaching to contact the feet sitting on the bed

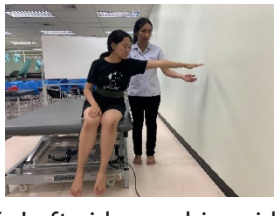
G. Static side sitting balance

H. Ball elevation side sitting

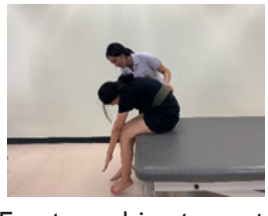
I. Front reaching side sitting



J. Right side reaching side sitting



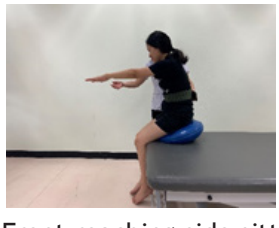
K. Left side reaching side sitting



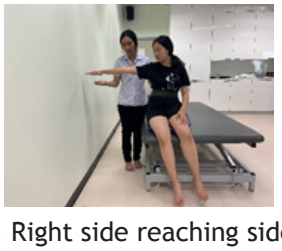
L. Front reaching to contact the feet side sitting

M. Static balance side sitting on the balance board

N. Ball elevation side sitting on the balance board



O. Front reaching side sitting on the balance board



P. Right side reaching side sitting on the balance board

Q. Left side reaching side sitting on the balance board

R. Front reaching to contact the feet side sitting on the balance board

Figure 3 Examples of exercises in the balance training program

Outcome

All assessments were made both before and after the intervention by one assessor blinded to the participants' treatment allocation. Participants were asked not to discuss their intervention allocation with the assessor.

Primary outcome

Dynamic balance was the primary outcome of this study, which was measured using two assessments-mFRT and T-shirt test. mFRT measures spatial variables, while the T-shirt test measures temporal variables. mFRT has been modified to evaluate dynamic balance in a sitting position in individuals with SCI[21]. This test has excellent reliability and is not complicated for assessment[21]. Participants sat at the edge of the bed with hips and knees flexed at 90° and feet resting on the floor[21]. The distance between the popliteal fossa and the edge of the bed was about two inches[21]. The tape measure was placed along the subject shoulder at the level of the acromion[21]. The tip of the middle finger served as the landmark for measuring the distance in centimeters. For forward mFRT, the participants flexed the dominant shoulder at 90° reaching forward as far as possible without turning the trunk or using the hand for support[19]. During right mFRT, the participants abducted the right shoulder 90° reaching forward as far as possible without turning the trunk or using the hand for support[22]. When performing the left mFRT, the participants abducted the left shoulder 90° reaching forward as far as possible without turning trunk or using the hand for support[22]. Each participant had two practice trials followed by three trials tested with a 15-second rest between trials. The average of the results from three trials was used for data analysis.

In addition, the T-shirt test was used to assess dynamic balance in the sitting position as a functional task, which measured the time required to put on and take off the shirt[23]. This test has excellent reliability, takes less than three minutes, and requires a minimal amount of equipment[23]. Participants sat at the edge of the bed with the feet resting on the floor. A T-shirt one size larger than the participants' normal size was placed face down on a table in front of the participants that was at the height of their iliac crests[23]. The participants were asked to put on and take off the T-shirt as quickly as possible. The test was repeated twice, and the average times calculated from each component (on, off, and total time) was used in data analysis.

Secondary outcome

This study used gross motor function assessment because it is one of the components of functional ability. It evaluates the amount of time to move from supine position to another position; from the supine position to right side lying, from the supine position to left side lying, and from the supine position to sitting. The test was repeated for three times, and the average times were used in data analysis.

Statistical analysis

SPSS 23.0 was used for the statistical analysis of this study. Due to the small number of participants, this study used non-parametric statistics to analyze the data. The Mann-whittney U test was employed to compare the change in scores between VT and BTP. A Wilcoxon signed rank test was also performed to investigate whether there was any within-group difference. The level of statistical significance was set at $\alpha = 0.05$.

Results

Table 1 presents demographics and baseline characteristics of 11 participants (eight male and three females). The median of age, weight, height, and BMI were 49.00 years (interquartile range (IQR) 35.00 to 53.00), 65.00 kg (IQR 62.80 to 70.00), 165.00 cm (IQR 165 to 168), and 23.59 kg/m^2 (IQR 20.76 to 25.71), respectively. All participants had etiology from trauma. Four participants had the 12th thoracic level, three participants had the 11th thoracic level, and another one had the 2nd, 4th, 5th, and 6th thoracic level. The median of months post injury was 214.00 months (IQR 164 to 240). Six participants had AIS class A, while five participants had AIS class B.

Table 1 Demographics and baseline characteristics (n=11)

Participants	Age (year)	Gender	Weight (kg)	Height (cm)	BMI (kg/m²)	Etiology	Level of lesion	Months post injury	ASIA Impairment Scale	Presence of the spasticity	Treatment 1	Treatment 2
1	35	Male	65	167	23.31	Trauma	Thoracic 5	157	A	No	Balance	Vojta
2	59	Male	65	165	23.88	Trauma	Thoracic 11	240	A	No	Vojta	Balance
3	33	Male	70	162	26.67	Trauma	Thoracic 4	187	A	Yes	Vojta	Balance
4	47	Male	65	166	23.59	Trauma	Thoracic 11	214	A	No	Vojta	Balance
5	51	Female	65	165	23.88	Trauma	Thoracic 6	154	A	No	Balance	Vojta
6	48	Male	64	178	20.20	Trauma	Thoracic 2	354	A	Yes	Balance	Vojta
7	52	Female	48	160	18.75	Trauma	Thoracic 12	164	B	Yes	Vojta	Balance
8	34	Male	62.8	168	22.25	Trauma	Thoracic 12	218	B	No	Vojta	Balance
9	49	Female	83	165	30.49	Trauma	Thoracic 11	221	B	No	Balance	Vojta
10	53	Male	60	170	20.76	Trauma	Thoracic 12	172	B	No	Balance	Vojta
11	58	Male	70	165	25.71	Trauma	Thoracic 12	380	B	No	Balance	Vojta
Median	49.00		65.00	165.00	23.59			214.00				
Q1, Q3	35.00, 53.00		62.80, 70.00	165.00, 168.00	20.76, 25.71			164.00, 240.00				

Table 2 Comparisons of variables between pre- and post-intervention in the Vojta therapy (VT) and balance training program (BTP)

Variables	Vojta therapy			Balance training program			Change		
	Before	After	*p*-value	Before	After	*p*-value	Vojta therapy	Balance training program	*p*-value
Modified FRT (cm)									
Forward	26.00 (23.47, 36.07)	31.67 (24.80, 37.57)	0.016*	28.57 (23.70 ,35.90)	29.90 (23.07, 32.73)	0.790	1.77 (0.10, 4.13)	0.13 (-4.37, 2.37)	0.049*
Right	8.37 (6.77, 10.93)	11.07 (9.10, 12.07)	0.003**	8.80 (6.40, 11.23)	9.67 (7.83, 11.73)	0.010*	1.67 (0.87, 2.23)	0.80 (0.17, 2.87)	0.123
Left	7.73 (6.87, 10.63)	9.63 (8.00, 11.10)	0.062	7.93 (6.37, 10.07)	8.13 (7.10, 10.37)	0.563	0.77 (0.30, 2.13)	0.17 (-0.63, 0.90)	0.052
T - shirt test (s)									
On	8.07 (6.32, 9.16)	6.95 (5.75, 8.33)	0.003**	8.11 (6.70, 9.95)	7.89 (5.86, 8.60)	0.004**	-0.69 (-1.80, -0.11)	-0.47 (-1.48, -0.33)	0.693
Off	4.97 (4.26, 6.05)	4.25 (4.13, 5.22)	0.016*	5.00 (4.03, 6.33)	4.71 (3.91, 6.27)	0.328	-0.53 (-0.80, -0.01)	-0.24 (-1.00, 0.25)	0.309
Total	12.46 (11.28, 14.11)	11.58 (10.29, 13.55)	0.003**	13.77 (10.56, 16.13)	12.59 (10.35, 14.80)	0.003**	-1.34 (-2.33, -0.76)	-0.60 (-2.47, -0.26)	0.375
Gross motor function (s)									
Supine to right side lying	1.92 (1.68, 2.40)	1.74 (1.60, 2.14)	0.722	1.77 (1.62, 2.24)	1.60 (1.47, 1.96)	0.041*	-0.02 (-0.27, 0.09)	-0.18 (-0.28, 0.01)	0.200
Supine to left side lying	1.77 (1.68, 1.96)	1.64 (1.51, 1.93)	0.013*	1.63 (1.42, 2.15)	1.74 (1.46, 1.96)	0.328	-0.24 (-0.42, -0.03)	-0.11 (-0.19, 0.08)	0.041*
Supine to sitting	2.99 (2.51, 3.57)	2.90 (2.65, 3.56)	0.248	2.99 (2.69, 3.27)	2.76 (2.37, 3.36)	0.109	-0.05 (-0.31, 0.07)	-0.24 (-0.43, 0.09)	0.869

Note: Median (Q1, Q3), [a]test by the Wilcoxon signed rank test, [b]test by the Mann-whittney U test, * *p*-value<0.05, *** *p*-value<0.01

Discussion

This study aimed to evaluate the efficacy of VT as compared with BTP in chronic motor complete SCI. The primary findings of this study demonstrated that VT elicited greater gains in dynamic sitting balance and gross motor function than BTP in motor complete SCI. This study is inconsistent with the findings of the study by Ha and Sung[20], which compared VT and traditional physical therapy after 6 weeks in 10 children with spastic cerebral palsy (CP). That study found no significant improvement in gross motor function using gross motor function measure (GMFM)-88. Nevertheless, they found significant difference in diaphragm movement between the study groups. However, this study is consistent with the finding of Epple et al. in 2020[24], which found that Vojta therapy was statistically superior to traditional physical therapy in postural control of individuals with severe acute stroke. The researcher hypotheses corresponding to the changes observed in this study were caused by VT activating the diaphragm, transversus abdominis muscle, and deep muscles of the spine[10,11,20]. The transversus abdominis is activated first among the trunk muscles before the extremities move to control trunk stability and the movement of the spine[25]. Furthermore, the transversus abdominis and diaphragm muscles work together to increase pressure in the abdomen, which provokes the physiological extension of the axial axis by rotating and extending each of its segments; this mechanism may help improve balance and gross motor function in VT more than BTP[10,11,20,25].

VT significantly immediately improved dynamic sitting balance and gross motor function in motor complete SCI. This result is consistent with Tayati et al[26], who found VT can immediately improve in dynamic balance in individuals with chronic stroke. In addition, this result is consistent with a previous study which found a significant improvement in sitting ability after VT in the children with CP[20]. Furthermore, the study of Lim and Kim (2013) also found a significant improvement in spatiotemporal gait parameters in the children with CP after VT when measured using the Vicon motion analysis[27]. This improvement can be attributed the ability of VT to stimulate reflex locomotion, which enables the proper sequential activation of motor centers controlling the muscles of both upper and lower extremities via propriospinal neurons[12]. Propriospinal neurons communicate information over short and long distances within the spinal cord to play a crucial role in motor control and sensory processing[28,29]. They act to coordinate between upper extremities, lower extremities, and the trunk based on the Sherrington's concept[12,28]. Furthermore, it has been reported that the activation of propriospinal circuits can promote the recovery of locomotion in individuals with SCI[28]. Furthermore, VT promotes the establishment of the pontomedullary reticular system and the function of the putamen[30]. This portion of the brain coordinates with the brain stem to govern posture control and locomotion before initiate movement[31]. Furthermore, VT also activates the transversus abdominis and diaphragm muscles and increases spinal elongation, which help improve both sitting balance and mobility[10,20,27,32].

The BTP improved significantly the dynamic balance and gross motor function in complete SCI. This result is supported by an earlier study, which found a significant immediately improvement in the dynamic balance of 20 individuals with SCI measured using the timed up and go test (TUG) after obstacle crossing training and conventional overground walking training[18].In addition, the study of Saensook et al. found an immediate significant improvement in dynamic balance after sit-to-stand training evaluated via the TUG in 27 individuals with SCI[33]. Moreover, a previous study in 2019 found a significant improvement in the ability to transition from supine position to right side lying after activity-based therapy assessed using the Modified Rivermead Mobility Index in 91 individuals with SCI[34]. This is consistent with the findings of a previous study, which suggested that task-specific balance training may augment plastic neuromuscular changes[35]. It has been reported that it can influence locomotor performance in individuals with SCI[35]. Furthermore, the core or trunk muscles used in the balance

training program can contribute to increased functional abilities[36].

In light of the fact that no side effects were observed in this study, it can be concluded that both VT and BTP are safe for individuals with SCI. However, a limitation of this study is the fact that the assessment was conducted immediately after the intervention, so any short-term or long-term effects of VT or BTP on dynamic sitting balance could not be determined. Future studies should employ a suitable follow-up as well as measure other parameters such as electromyography, muscle tone, muscle power, etc.

Conclusion

In conclusion, both VT and BTP were effective in the treatment of dynamic sitting balance and gross motor function in chronic motor complete SCI. However, the researchers observed a greater overall improvement in the scales of dynamic balance and gross motor function when the individuals were treated via VT.

Clinical implication

- VT achieves a significantly greater improvement in dynamic sitting balance and gross motor function in motor complete SCI
- Both VT and the BTP results in an immediate improvement of dynamic sitting balance and gross motor function in motor complete SCI.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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ORIGINAL ARTICLE

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Host-pathogen interaction between Helicobacter pylori and biliary cells mediated by sialic acid receptor

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KEYWORDS
Helicobacter pylori; Sialyl-Lewis X; Cholangiocytes; Adhesion.

ABSTRACT
Commensalism involving H. pylori and O. viverrini may have evolved and may facilitate conveyance of the bacillus into human bile duct. The adherence between bacterial ligands and host receptor is an initial step in colonization of H. pylori in bile duct epithelium leading to disease pathogenesis. We investigated tissue adhesion of FITC-labelled H. pylori on normal, pre-cancerous and cancerous bile duct epithelium from 42 cholangiocarcinoma (CCA) cases. The results revealed that all cases exhibited different degrees of the bacterial adhesion. Quantitatively, normal and pre-cancerous bile duct epithelium showed significantly higher number of H. pylori adhesion per area than those of CCA tissue (p-value < 0.001). The mechanism by which H. pylori binds to the bile duct epithelium was then explored. A H. pylori adhesin, specifically sialic acid-binding adhesin (SabA) which recognizes sialyl-Lewis X glycan receptor was studied in human normal cholangiocytes (H69 cell line). The results revealed that the number of FITC-labelled H. pylori adhesion was significantly decreased after blocking with wheat germ agglutinin (WGA) which binds to sialic acid (p-value < 0.05) but not with Ulex eropaeus agglutinin I (UEA I) which is specific for alpha-L-fucose. Pretreatment of H69 cells with antibody to sialyl-Lewis X resulted in significantly decreased adhesion of H. pylori-in a dose dependent manner, particularly at a dilution of 1:200 (p-value < 0.005) and 1:1000 (p-value < 0.05). The results clearly show that H. pylori can colonize on the bile duct epithelium and sialyl-Lewis X may be a receptor for the adhesion.

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Introduction

Cholangiocarcinoma (CCA) is a major public health problem in Thailand and neighboring Mekong countries where the liver fluke, Opisthorchis viverrini (O. viverrini), is endemic[1, 2]. In recent years, there have been increasing evidence that the carcinogenic bacterium Helicobacter pylori (H. pylori) co-infected with the liver fluke may a play major role in cholangiocarcinogenesis[3-7]. Commensalism involving H. pylori and O. viverrini may co-evolved, given that the liver fluke has been shown to harbor the bacteria, and may facilitate conveyance of the bacteria into the bile ducts[3, 8]. Thus, the H. pylori might be transported by the migrating parasites, further adhere to the cholangiocytes, and activate cascades of signaling downstream leading to carcinogenesis in a similar way to those described for the gastric epithelium[9, 10].

Colonization of H. pylori on host epithelium requires bacterial adhesins and host cell receptors. Several adhesive factors belong to the largest of outer membrane proteins (OMPs) family of the bacterium, the Hop family. This contains blood group A antigen binding adhesin (BabA), sialic acid-binding adhesin (SabA), AlpA/B, HopZ and outer inflammatory protein (Oip)A[11], heat shock protein 60 (Hsp60), H. pylori outer membrane protein (HopZ), neutrophil-activating protein (NAP), adherence-associated proteins (AlpA and AlpB), and lacdiNAc-binding adhesin (LabA)[12, 13]. Of these, BabA mediates binding of the bacteria to Lewis B antigens[14] and related terminal fucose residues found on blood group O (H antigen), A and B antigens[15]. SabA binds to sialyl-Lewis X[16] which has been reported in biliary epithelium and CCA[17]. Wheat germ agglutinin (WGA) binds to N-acetyl-D-glucosamine and sialic acid residues of glycoproteins and glycolipids and has been described in human normal bile duct epithelium and CCA tissue[18]. UEA1 is specific for a-L-fucose which is variably found in normal bile duct epithelium[18-20]. Upon adherence of H. pylori to the human epithelium allows its colonization and activates host responses leading to inflammation and promoting carcinogenesis. However, the interaction between human cholangiocyte receptors and H. pylori adhesins have yet been described. We, therefore, aimed to investigate the adhesion between H. pylori and bile duct epithelium and its interaction with host receptors, specifically sialyl-Lewis X in human cholangiocytes.

Materials and methods

Helicobacter pylori strains

A *cagA*-positive *H. pylori* Thai isolate BT112 was cultured on brain heart infusion medium agar with 5% human blood or sheep blood, at 37°C in a microaerophilic condition for 3-5 days. The bacterial colonies were picked up, mixed, and washed in PBS prior next step of experiments. For bacterial adhesion assays, the *H. pylori* was labeled with fluorescein isothiocyanate, FITC as previously described[21]. Briefly, FITC (Thermo Scientific) diluted in dimethyl sulfoxide (10 mg/ml) was incubated with the bacterial suspension for one hour in the dark at room temperature. The bacteria were recovered by centrifugation at 3000 x g for five min, resuspended by gentle pipetting in one ml of PBS/0.05% Tween 20, and pelleted by centrifugation as above. The wash cycle was repeated three times before used.

Liver tissue specimens and tissue adhesion assay

Paraffin sections containing non-tumorous normal, precancerous and cancer tissue were obtained from 42 CCA cases who underwent surgery at Srinagarind Hospital, Khon Kaen University (HE42075). The sections were deparaffinized in xylene, hydrated in a series of alcohol and PBS for tissue adhesion assay. Adhesion of *H. pylori* to bile duct epithelium was performed in the tissue sections by using FITC-labeled bacteria as previously described[17]. Briefly, the deparaffinized tissue sections were incubated for 30 min in blocking buffer (0.2% bovine serum albumin/0.05% Tween 20, prepared in PBS). The FITC-labeled bacterial suspension was diluted in blocking buffer and 200 µl was placed on the slide and incubated for 1 hour at room temperature. Slides were subsequently washed six times with PBS prior to inspection. The stained sections were viewed and

photographed under a confocal microscope (ZIESS, LSM800). Analysis of *H. pylori* adhesion in non-tumorous normal, precancerous (dysplastic) and cancerous tissue was done in 8-10 fields of each tissue type by ImageJ software and expressed as the number of bacterial cell adhesion per square millimeter (mm^2).

Cell culture

Immortalized nontumorigenic human cholangiocyte cell line (H69) was used in this study. The H69 cholangiocytes were cultured in DMEM plus DMEM/F12 supplemented with 10% fetal bovine serum, adenine, insulin, epinephrine, T3-T, hydrocortisone and epidermal growth factor. The cells were grown until reaching 70% confluence before being subjected to bacterial adhesion assays.

Bacterial adhesion assay to H69 cholangiocytes

Binding between *H. pylori* and H69 cholangiocytes as well as blocking assays using antibody to a host receptor, sialyl-Lewis X (*Thermo Fisher* Scientific) and specific lectins wheatgerm hemagglutinin (WGA) and *Ulex europaeus* agglutinin I (UEA I) (Vector Laboratories) were performed. Briefly, H69 cells were fixed in cold 4% paraformaldehyde, washed with PBS, and incubated with increasing dilutions of sialyl-Lewis X; 1:200, 1:1000, 1:5000, 1:25,000 for 2 hours. Similarly, WGA and UEA I at a dilution of 1:200 were used. After washing with PBS, FITC labeled *H. pylori* were then added to H69 cells and incubated at 37°C for 1 hour. The cells were washed, and nuclei were stained with Hoechst *33342* dye (Sigma-Aldrich) prior to inspection and photograph under a confocal microscope (ZIESS, LSM800). Control H69 cells were parallelly performed without antibody or lection treatments. The number of bacteria binding to the H69 cells was analyzed in a total of 1,500 cells by using ImageJ software with four biological replicates.

Statistical analysis

Correlation between number of bacterial adhesions in H69 cells was analysed by one-way ANOVA. For tissue adhesion assay, non-parametric analysis using Man Whitney test was employed, given that the data were not normally distributed. Analysis and graphic generation were accomplished either using GraphPad Prism version 7 software (GraphPad, San Diego, CA) or *IBM® SPSS® Statistics V.* 26. A *p*-value < 0.05 was considered to be statistically significant.

Results

Tissue adhesion assay for H. pylori

H. pylori was detected in normal bile duct epithelium (large and medium size bile ducts), precancerous (dysplastic) epithelium, and CCA tissue in all 42 cases studied (Figure 1). The labeled bacteria were rarely seen in the small bile ducts. The number of bacterial adhesions varied greatly among the cases and different tissue types. Significant higher *H. pylori* adhesion per mm^2 was observed in non-tumorous normal (15.95 ± 10.94) and dysplastic bile duct epithelium (14.16 ± 9.861) than CCA tissue (8.636 ± 7.868) (*p*-value < 0.001) (Figure 2).

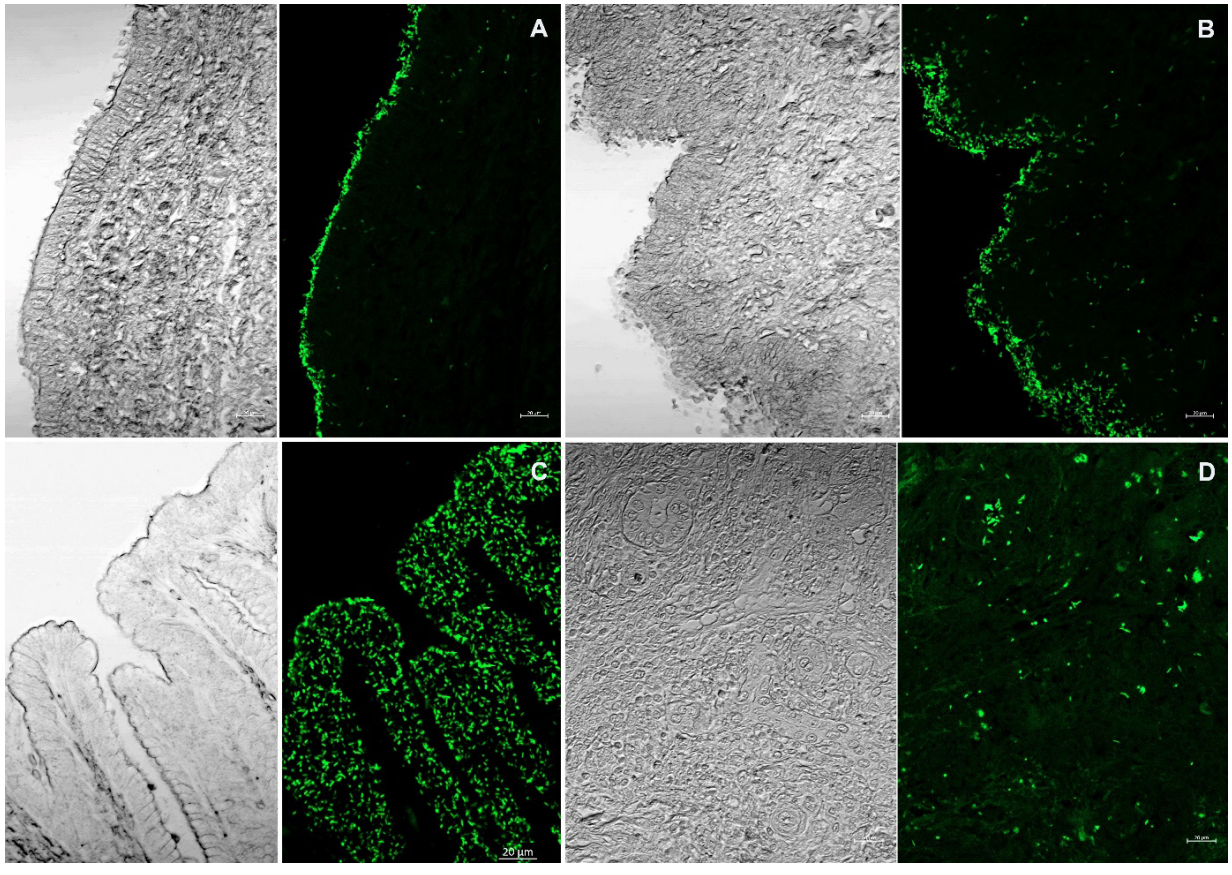

Figure 1 In situ adherence of *Helicobacter pylori*. Adhesion of *H. pylori* on normal (A), precancerous (B), and cancerous bile ducts (D). Bright and fluorescence dark field counterparts of each histologic type are shown. C = control staining on gastric epithelium. Scale bar = 20 µm.

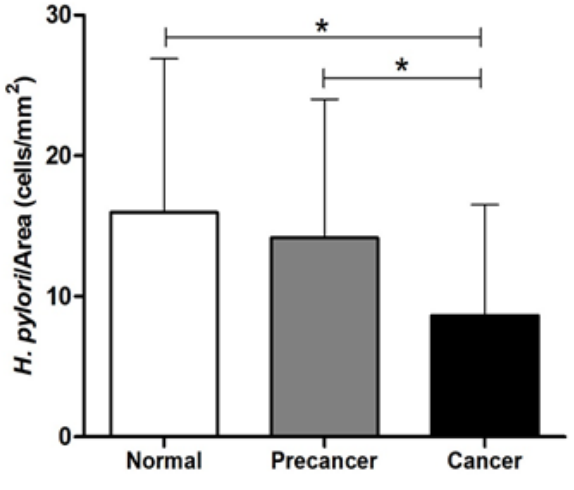

Figure 2 Number of *Helicobacter pylori* adhesion in each histologic type. Significantly higher numbers of *H. pylori* were found in non-tumorous normal and precancerous biliary epithelium than those in cancerous CCA tissue (p-value < 0.001). Precancer = pre-cancerous.

Helicobacter pylori adhesion to biliary cells via sialyl-Lewis X

To investigate specific receptors for *H. pylori* on the bile duct epithelium, H69 cholangiocytes were pretreated with WGA or UEA I lectins prior to adhesion with FITC-labelled bacteria. The results revealed that the number of *H. pylori* adhesion on H69 cells was significantly decreased after blocking with WGA (p-value < 0.05) but not with UEA I p-value > 0.05) (Figure 3A). We further investigated the role of sialyl-Lewis X receptor in *H. pylori* - cholangiocyte interaction by pretreating with different concentrations of sialyl-Lewis X antibody. The results showed a significant decreasing number of *H. pylori* adhesion correlated with the increasing dilution of sialyl-Lewis X (Figure 3 B, C, D), which implicates the essential role of sialyl-Lewis X in cholangiocyte-bacteria interaction.

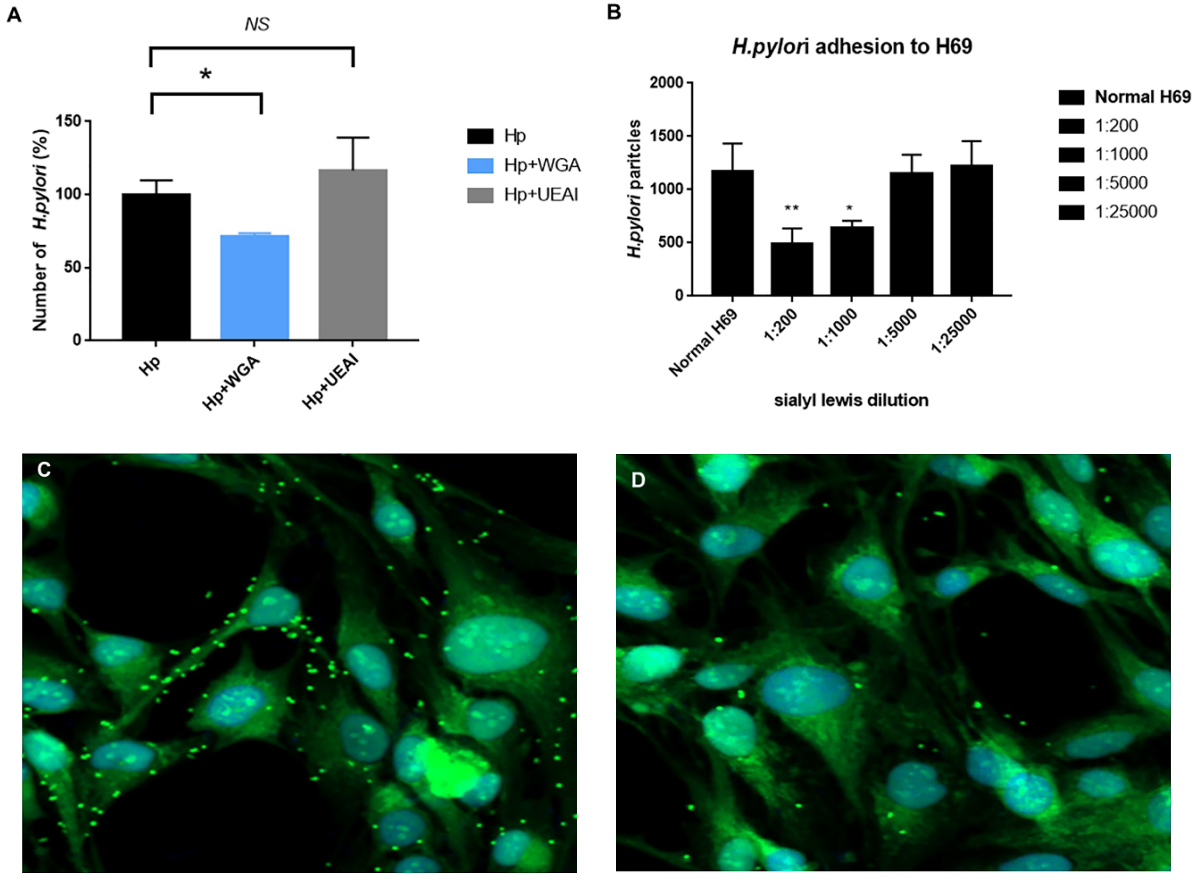

Figure 3 *Helicobacter pylori* adhesion to biliary cells via sialyl-Lewis X. Inhibition assays of *H. pylori* adhesion by WGA and UEA I lectins (A) and sialyl-Lewis X (B) showing a significant reduction of bacterial adhesion for WGA and sialyl-Lewis X but not UEA I. In addition, the adhesion reduction was in a dose-dependent manner for sialyl-Lewis X (B). Representative pictures of bacterial adhesion by confocal microscopy on control H69 cells (C) and those blocked with 1:200 sialyl-Lewis X antibody (D).

Discussion

There have been increasing evidence that *H. pylori* co-infected with *O. viverrini* are involved in the pathogenesis of opisthorchiasis, specifically periductal fibrosis both in an experimental animal model[22] and human study[4] implicating in CCA development[5]. Given that the liver fluke harbors *H. pylori*[3] in its gut and tegument[22]; upon reaching the bile ducts, the *H. pylori* has to bind to the host epithelium before colonization and induces tissue damage. Several major adhesins essential for colonization and infection establishment has been described in the gastric epithelium[13, 16, 23]. Here, for the first time, we reported the adhesion of *H. pylori* on human normal, precancerous and cancerous bile duct epithelium and the adherence to the cholangiocytes were via sialic acid-binding adhesins.

Tissue adhesion of *H. pylori* has been reported in several tissue types including epithelium of gastric tissue, esophageal submucosal glands with less binding extent in intestinal epithelium[17]. In addition, *H. pylori* does not bind to any epithelial cell populations represented in kidney, cervix, endometrium, or squamous cells[17]. No report on *H. pylori* tissue adhesion in the bile duct epithelium has been described. Our team reported adhesion of *H. pylori* to malignant biliary cell lines (KKU-100) and KKU-M156[9]. Here we demonstrated that *H. pylori* can bind to the biliary epithelium and may elicit cascades of signaling activation downstream leading to disease pathogenesis[10-12]. The higher adhesion rates to non-tumorous normal biliary epithelium than those in pre-cancerous or CCA tissue may be from the difference in *H. pylori* receptor expression in different tissue gradings. More detailed study is warranted.

Sialic acid-binding adhesin (SabA) recognizes sialyl-Lewis A and X glycan antigens[13]. SabA, one of *H. pylori* adhesin molecules, has been identified by the retagging technique based on its affinity for sialyl-Lewis X[24]. Our study showed that the bacterial adhesion on H69 cholangiocytes was significantly inhibited by blocking with sialyl-Lewis X antibody. Moreover, *H.pylori* adhesion to the H69 cells was also inhibited by WGA but not UEA I. WGA from *Triticum vulgar* non-enzymatically binds to N-acetyl-D-glucosamine and sialic acid residues of glycoproteins and glycolipids including those from *H. pylori*[25]. WGA has been described in human normal bile duct epithelium and CCA tissue[18]. UEA I is specific for a-L-fucose which is not or variably bound to normal bile duct epithelium[18, 19]. Therefore, blocking with the lectin UEA I but not WGA did not affect the adhesion of *H. pylori* on the H69 cholangiocytes even though it was slightly increased but it was not significantly different compared to controls *(p*-value > 0.05). Blocking with WGA and UEA I lectins is cost effective and has been used in several adhesion applications[26-28].

These results altogether suggest that sialyl-Lewis X might be a candidate receptor for *H. pylori* in the biliary epithelium. The interaction between the bacterium adhesins and the host cell surface receptor is involved in the initial stages of colonization. Adherence of bacteria to host cell receptors triggers cellular changes, signal transduction cascades leading to inflammation following the release of virulent factors[29], cell morphology change, EMT and cell transformation or may be reminiscent of the modified appearance of carcinoma cells after exposure *H. pylori* such as the hummingbird phenotype[30, 31].

Conclusion

Our study showed that *H. pylori* can bind to the biliary cells via sialyl-Lewis X receptor and may elicit the colonization on bile duct epithelial cells prior trigger pathogenesis in the hepatobiliary system.

Take home messages

Our study provides basis of host-pathogen interaction at initial stage in *H. pylori* infection of the biliary system. Further in-depth study on host-pathogen interactions is warranted.

Conflicts of interest

The authors declare no conflict of interest.

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One-minute seated push-up test: an alternative physical strength and endurance test in community-dwelling older individuals

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KEYWORDS
Elderly;
Push-up;
Mobility measures;
Sit-to-stand test;
Step test.

ABSTRACT

The available strength and endurance measures commonly involve lower limb functions, whilst the impairments in older people mainly occur in the lower limbs. Therefore, the existing measures may limit clinical application in these individuals. Based on the effects of global physiological changes throughout the body, the researchers hypothesized that the upper limb function can be used as an alternative clinical measure to reflect functional strength and endurance of older people. This cross-sectional study assessed the correlation between the outcome of 1-minute seated push-up test (1minSPUT) and standard measures to reflect functional strength and endurance, including the five times sit-to-stand test (FTSST) and the two-minute step test (2MST), among 67 community-dwelling older adults. Participants with an average age of 75 years were interviewed and assessed for their demographics and the ability to perform the 1minSPUT, FTSST, and 2MST. The findings indicated significant correlation between the 1minSPUT and the FTSST (r_s = -0.492 to -0.537, p-value < 0.05), and the 2MST (r_s = 0.388 to 0.441, p-value < 0.05) for total and separately for male and female participants. The findings suggest the use of 1minSPUT, a practical measure that can be done in a limited area, as an alternative measure to reflect functional strength and endurance in older individuals.

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Introduction

Maximal physiological components, i.e., muscle strength and endurance, are necessary for the continuation of independence in older adults[1,2]. Therefore, the ability to assess, promote and monitor muscular strength and endurance in various clinical and home-based settings is crucial to maximize independence of these individuals who are the fastest growing segment of the country and the world[3]. This issue is also especially important in a current era of healthcare paradigm-shift toward an increased demand for effective standard home healthcare and community-based rehabilitation services[4].

However, the existing simple and practical mobility measures for muscle strength and endurance are commonly involved lower limb functions, such as the five times sit-to-stand test (FTSST)[5], the two-minute step test (2MST)[6,7], and 6-minute walk test[8]. Such measures limit clinical application of the tests for many older individuals because age-related physiological decline is occurred predominantly in the lower body[9,10]. Evidence suggested that many older individuals suffer from lower limb pain and mobility limitation (57% to 95%)[11]. Based on the effects of global physiological changes throughout the body[12,13], the researchers believed that the exploration for a practical measure involving upper limb functions may offer an alternative measure that can be used to screen and monitor functional alteration over time for these individuals.

Previously, the maximum number of push-up repetitions in one minute, as the so-called a 1-minute seated push-up test (1minSPUT), has been applied to measure upper body strength and endurance in young adults[14]. This ability requires the upper limb and trunk muscles to increase muscle force and joint toque to lift the body up from the floor against the body weight[15,16]. The ability of continuous working within a minute also needs muscular and functional endurance to complete the test. With the effects of global physiological changes throughout the body, therefore, the researchers hypothesized that the 1minSPUT can be used as an alternative clinical measure to reflect functional strength and endurance in older people. Nonetheless, the gender-based differences in anatomy and physiology can affect the rate and magnitude of strength and endurance that develop in the muscle and central nervous system for male and female individuals[17,18]. Therefore, this study assessed the correlation between the outcome of 1minSPUT and standard mobility measures to reflect functional strength and endurance, namely FTSST and 2MST, among community-dwelling older adults. The data were analyzed for total participants and separately for male and female participants.

Materials and methods

Study design and participants

This cross-sectional study involved community-dwelling individuals, aged 65 years and older. The inclusion criteria were a body mass index between 18.5 and 29.9 kg/m^2, and the ability of understanding the command used in this study. The exclusion criteria were any signs and symptoms that might affect participation in the study, including no be able to independently perform the test without walking device, uncontrolled medical conditions (e.g., hypertension or heart disease), pain in the musculoskeletal system that might affect outcomes of the study such as rotator cuff injury, history of shoulder and upper limb problems, or pain in the lower limbs that limited ability to perform a 1minSPUT and standard mobility measures with a pain score of more than 5 out of 10 on a visual analog scale. All participants signed written informed consent forms that were approved by the Institutional Ethics Committee for Human Research (HE611600). The estimated minimum number of sample size was 67 participants when sets $R_0 = 0.0$ and R_1 from a pilot study of 0.335 with 90% power of test and an alpha value of 0.05[19].

Research protocols

The eligible participants were interviewed and assessed for their demographics, including age, gender, height, bodyweight, vital signs, underlying diseases, and walking device used as needed. Then the participants were assessed for the outcomes of the study, including 1minSPUT,

FTSST, and 2MST, by an experience assessor in a random order. During the tests, participants could take a period of rest between the tests and the trials as required (or at least 30s) in order to minimize learning effects and fatigue that might occur due to sequences of the tests. Participants were fastened with a lightweight safety belt around their waist in order for the assessor to provide efficient assistance as needed. Details of the tests were as follows.

1minSPUT: The test was executed using standard clinical push-up boards while participant were in a ring sitting position, and placing their hands on the push-up boards at slightly anterior toward their hips (Figure 1A). Then participants performed maximal seated push-up repetitions in a minute. In each repetition, participants pushed both hands against the devices, lifted the body from the floor with slightly bending the trunk forward while depressed both scapulars (Figure 1B), and then bended the elbows to sit down on the floor. Participants were also informed to minimize the use of lower limbs in the test[20]. Before and after the tests, the participants were given a session of warm-up and stretching to reduce the risk of musculoskeletal injury that may occur after completing the test. During the test, the participants could take a period of rest as needed without stopping time, and continued the test as soon as they could or terminated the test if they were unable to do further.

Figure 1 Position while assessing a 1-minute seated push-up test
(A) Starting position with clinical push-up broads.
(B) Position while lifting the body up from the floor during the test.

2MST: The test is an excellent test-retest reliability (intraclass correlation coefficients [ICC] = 0.90) with good concurrent validity with the one-mile walking time (r = 0.73)[7]. Thus it is recommended as a tool for measuring physical endurance in a small area. The participants raised their knee to a mid-thigh level, i.e., the mid distance between the iliac crest and patella of the participants, marking on the wall. The total number of stepping in place, i.e., the number of the right knee reached the target level, in two minute over one trial was recorded[6].

FTSST: The FTSST is a good test-retest reliability (ICC = 0.81) to reflect functional lower extremity muscle strength and dynamic balance control while changing from a sitting to standing positions[21]. Participants were timed the five chair-rise cycles in the fastest and safest possible manner without using the arms. The average time required over the three trials was recorded[22].

Statistical analysis

Descriptive statistics were used to describe the participants' characteristics and findings of the study. The continuous data between male

and female participants were compared using the independent samples t-test for normal distribution variables and Mann-Whitney U test for the non-normal distribution variables. In addition, Chi-squared test was utilized to determine the significant differences of the categorical variables. The Spearman's rank correlation (r_s) was used to analyze the correlation between outcomes of 1minSPUT and standard measures (the FTSST and 2MST). A correlation level was interpreted as very low or negligible (0.00 to 0.30), low (0.30 to 0.50), moderate (0.50 to 0.70), high or strong (0.70 to 0.90), and excellent (0.90 to 1.00)[23]. The closer the correlation coefficient approach to 1, regardless of direction, the stronger is the existing association indicating a linear relationship between the data of SPUTs and standard measures[24]. A level of statistical significance was set at *p*-value < 0.05.

Results

Sixty-seven individuals (31 females) with the average age of approximately 75 years completed the study. Most participants were well-functioning with normal body mass index, and able to perform daily activities independently without mobility devices (*n* = 63, 94%, Table 1). Approximately half of the participants had controlled underlying diseases (ranged 1 to 3 types/participant), including hypertension, diabetes mellitus, hyperlipidemia, and/or gouty arthritis (Table 1). There were no significant differences in demographics between male and female participants (*p*-value > 0.05, Table 1). However, male participants had the number of 2MST significantly greater than that of female individuals (*p*-value < 0.05, Table 1).

Table 1 Personal data and outcomes of the study of total, male and female participants

Variable	Total (n = 67)	Male (n=36)	Female (n=31)	*p*-value
Age[a]: years[*]	75.0 ± 6.6 (73.4 – 76.6)	75.8 ± 6.4 (73.6 – 77.8)	74.3 ± 6.9 (71.7 – 76.1)	0.348
Body mass index[b]: kg/m^2[*]	23.0 ± 3.0 (22.3 – 23.7)	22.5 ± 3.3 (21.4 – 23.7)	23.5 ± 2.6 (22.8 – 24.6)	0.105
Underlying disease[⸸c]: n (%)	32 (47.8)	18 (50.0)	14 (45.2)	0.196
Daily walking device[c]: Cane [n (%)]	4 (6.0)	1 (2.8)	3 (9.7)	0.235
2MST[b]: times[*]	55.7 ± 14.7 (52.1 – 59.3)	59.9 ± 12.7 (55.9 – 64.0)	50.7 ± 15.6 (44.6 – 56.4)	0.012
FTSST[a]: s[*]	12.6 ± 2.9 (12.2 – 13.5)	12.6 ± 2.9 (11.7 – 13.6)	13.2 ± 2.9 (12.3 – 14.3)	0.249
1minSPUT[b]: times[*]	29.3 ± 1.1 (27.6 – 31.1)	30.9 ± 6.6 (28.7 – 33.1)	27.5 ± 7.4 (25.2 – 30.5)	0.075

Note: [*] The data are presented by mean (SD) and (95% confidence interval), and the data between male and female participants were compared [a]using the independent samples *t* test for normal dis tribution variables, [b] using the Mann-Whitney U test non normal distribution variables, and [c] the data are presented using number (%), and comparison between male and female participants using the *Chi* square test.

[⸸] Underlying disease, including hypertension, diabetes mellitus, hyperlipidemia, gout, heart failure, chronic kidney disease, asthma, and osteoarthritis.

Abbreviation: FTSST, five times sit-to-stand test; 2MST, two-minute step test.

Figure 2 illustrates the correlation between outcomes of the 1minSPUT, and FTSST and 2MST when analysed for total participants and separately for male and female participants. The outcomes of the 1minSPUT showed negative low-to-moderate correlation with the FTSST (r_s = -0.492 to -0.590, *p*-value < 0.01, Figure 2A), and positive correlation with the 2MST (r_s = 0.412 to 0.469, *p*-value < 0.05, Figure 2B).

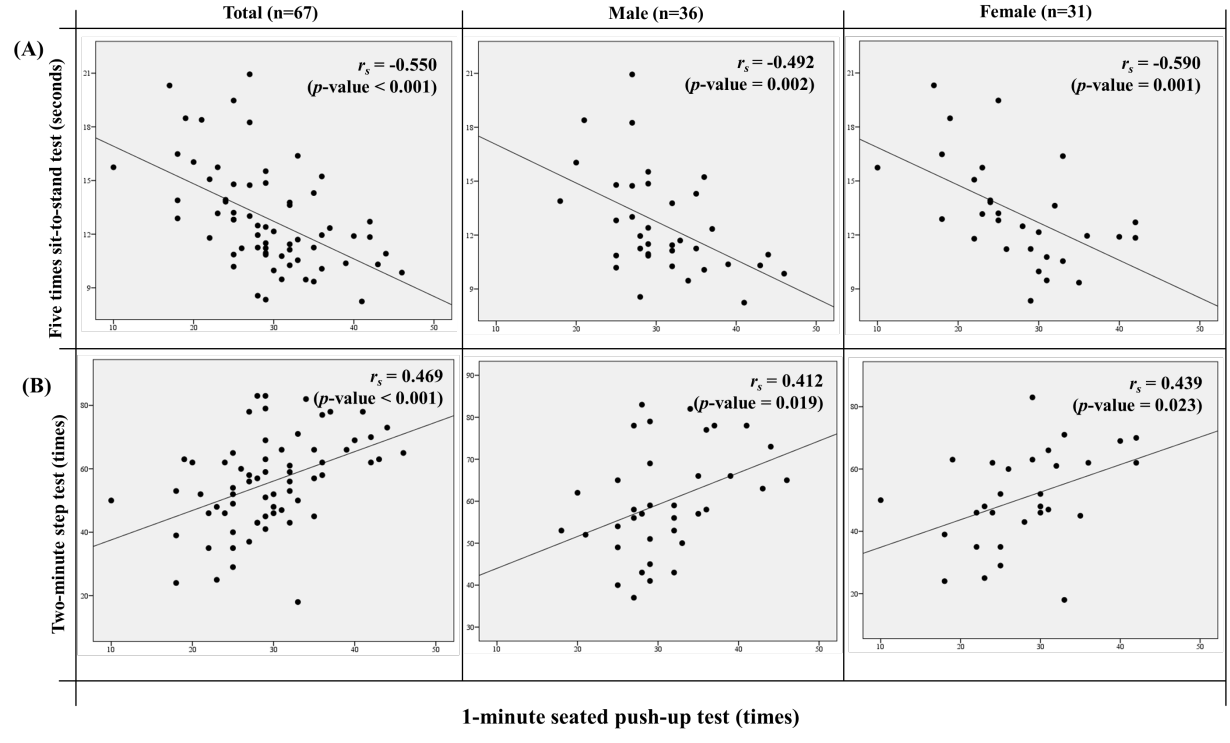

Figure 2 The correlation between a 1-minute seated push up tests and standard measures, including
(A) Five times sit-to-stand test
(B) Two-minute step test

Discussion

With the impairments occurring predominantly in the lower body, this study assessed the ability of the upper limb mobility measure, namely a 1minSPUT, to be used as an alternative measure to reflect functional strength and endurance of community-dwelling older individuals. The findings indicated significant correlation between outcomes of 1minSPUT, and the FTSST and 2MST (r_s = 0.412 to -0.590, *p*-value < 0.05, Figure 2) among community-dwelling older adults in both males and females.

The findings reflect characteristics of a 1minSPUT and global physiological change of the human body systems[13,25]. The ability of continuous lifting the body up from the floor by both hands in a minute requires significant muscle force and joint toque of the upper limb and upper trunk muscles[25]. In each attempt, participants needed muscle mass and muscle strength to adequately generate upper limb loading greater than 80% of the body weight[26]. The involvement of the small muscles in the upper extremities also increased cardiovascular stress that required oxygen uptake and respiratory control greater than the tasks involving large muscle groups of the lower extremities at any given absolute power output[27,28]. Moreover, the upper extremity muscles also have relatively small blood vessels, resulting in less capillary supply and limited oxidative capacity that facilitates cardiovascular stress, autonomic cardiac responses, perceived exertion, and early onset of muscle

fatigue as compared to lower extremity muscles[29]. Then the effects of global physiological alteration occurring throughout the human body enabled outcomes of the test involving upper limb muscles to reflect data of the test involving lower limb muscles[13]. Consequently, the ability to continuously lift the body up from the floor in a minute significantly correlated to the FTSST and the 2MST, in both male and female individuals (r_s = 0.412 to -0.590, p-value < 0.05, Figure 2).

However, the inversed directions of the correlation found with standard measures reflect characteristics of the tests. The longer the duration used to complete the FTSST reflects individuals with impaired lower limb muscle strength[21,30]. On the contrary, the higher the number of stepping in place and push up repetitions infers to those with good ability in the 2MST and 1minSPUT[31]. As a result, the outcomes of 1minSPUT showed negative correlation with those of the FTSST (Figure 2A), but positive correlation with 2MST (Figure 2B). However, the low-to-moderate correlation found between the 1minSPUT and both standard measures may reflect distinct characteristics of the test involving upper limbs that performed in sitting (1minSPUT) and the tests involving lower limbs that executed in standing (FTSST and 2MST). In addition, the study found that male participants had the number of 2MST significantly greater than that of female individuals (p-value < 0.05, Table 1). The results of this study are likely based on the fundamental characteristics of male participants who have comparatively greater physical ability, strength and endurance than female[32].

The findings suggest the use of 1minSPUT as an alternative measure to screen and monitor muscle strength and endurance of older individuals, particularly those with lower limb impairments. Nonetheless, there are some noteworthy limitations of the study. Without existing evidence using a 1minSPUTs in older individuals, this study was conducted cross-sectionally in well-functioning older individuals with a body mass index of less than 30 kg/m^2 (average data of 23.0 kg/m^2) using a fixed size of standard clinical push up boards. The findings may limit generalizability in older individuals with frailty and obesity. In addition, when considering characteristics of a 1minSPUT, outcomes of the test may be able to reflect other aspects crucially for older individuals. Therefore, a further study may be conducted in frailty individuals, and explore additional issues relating to SPUTs and older individuals, such as participant's height, elbow flexion angle, body compositions, balance ability and independence.

Conclusion

The present findings suggest the use of a 1minSPUT as an alternative measure to reflect functional strength and endurance of community-dwelling older individuals. Such practical measure may be useful in those with lower limb deficits, and/or having area and equipment limitation. The findings may help to promote the standard and effective community-based rehabilitation and home healthcare services, particularly in this era of limited hospital access.

Take home messages

A 1minSPUT may be applied as an alternative measure to reflect functional strength and endurance in older individuals, particularly in those with lower limb limitation.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgement

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Perception and impairments of female community dwellers with knee osteoarthritis who have not sought treatment or lost follow-ups

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KEYWORDS
Knee osteoarthritis;
Perception;
Rehabilitation;
Knee pain;
Physical Therapy.

ABSTRACT

Knee osteoarthritis (OA) is expected to increase in the future because of increasing life expectancy. However, the perception of the condition and clinical characteristics of symptomatic knee OA among Thai female community dwellers is not known. The primary objective of this study was to explore the perception of knee OA among participants who lost their follow-ups or had not sought health professional consultation regarding their condition. The secondary objective was to compare knee OA-related problems between those with and without the perceived need for physical therapy (PT). Ninety-four female community dwellers with symptomatic knee OA were enrolled in this study. They were divided into two groups based on their perceived need for PT management. The Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales, knee range of motion (ROM), and knee muscle strength were compared. Their perception of OA was determined using a structured questionnaire. The results showed that around half of the participants perceived that knee OA was associated with aging or degenerative change. Approximately 80% of the participants lost their follow-ups due to perceived ineffective medical care, preference for self-care management, and barriers associated with transportation services. The most important factor for the perceived need for PT management was pain severity. Pain improvement was the expected outcome if they had a chance to receive PT management. KOOS-Pain, KOOS-Symptoms, KOOS-Function in Daily Living, KOOS-Sport and Recreation, and knee flexion ROM were significantly different between groups with and without the perceived need for PT (p-value < 0.05). Patient perception was an important factor for knee OA management. Those who needed rehabilitation had more debilitating problems than those who did not need rehabilitation, confirming that patients tend to consult health professionals when symptoms are severe.

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Introduction

Knee osteoarthritis (OA) is perceptibly heterogeneous with a variety of clinical features, biochemical and genetic characteristics, as well as responses to treatment[1,2]. The prevalence of knee OA increases with age and more frequently affects women than men, considering the estrogen deficiency in postmenopausal women[3]. Moreover, the differences in cartilage thickness and lower extremity alignment between genders are related with the higher prevalence, worse symptoms, and greater disability in women than men[3]. Joint structural change in knee OA is associated with pain, which worsens during motion and relieves at rest[4]. Aside from pain, reduced range of motion (ROM) and muscle weakness are also present. Limitation in knee flexion ROM was found to be associated with osteophytes, joint space narrowing, bony enlargement, and pain or crepitus during knee flexion[5]. The degree of impaired ROM was also associated with activity limitation[6]. Decreased strength of both the quadriceps and hamstrings muscles was observed in patients with knee OA[7] and correlated with impaired physical function, specifically ambulation including walking, squatting, and stair climbing[8].

Although knee OA is apparently a debilitating condition, research has shown that many individuals with symptomatic knee OA have not sought medical treatment[9]. Community studies have shown that only 15-50% of older adults with knee pain have sought medical attention[9]. Several reasons were mentioned; for instance, ineffective medical care, use of self-coping strategies, and lack of information about the disease[10]. The decision to seek medical consultation was linked to the chronicity of the knee problem, experiences with health care services, as well as perceptions of the aging and degenerative process, beliefs about treatments and their effectiveness, and perceived seriousness of the condition[11]. A study in Australia has found that individuals with hip or knee OA had encountered significant challenges in treatment accessibility, and the challenges were largely associated with health care professionals, health systems, and financial factors[12].

Osteoarthritis is expected to increase in the future because of increasing life expectancy. Nonsurgical procedures, including physical therapy consultation, are currently the standard practice. However, the escalating cost of health care and the burden for health-care providers for pain and disability management have become important issues[13]. With the reported large prevalence of knee OA in Thailand (34.5-45.6%)[14], the physical therapy caseload for this condition is increasing. Self-care with professional guidance in the community, especially among individuals with early-stage knee OA management, is recommended. Physical therapists could play an important role in screening and providing reassurance and clear advice about movement and behavioral adjustments as well as the value of exercise in controlling symptoms. Still, the personal beliefs of the patients would shape the patients' attitudes and behaviors about how to manage their pain[15].

The perception of the condition and clinical features of symptomatic knee OA among female Thai community dwellers is not known. Therefore, this study aimed to explore the perception regarding knee OA in participants who had not consulted health professionals regarding their condition or missed their follow-ups. The reasons and factors influencing the decisions to seek treatment and rehabilitation were the issues of interest. Their perceived need for rehabilitation and the expected outcome improvements if they had a chance to undergo a rehabilitation program were also determined. The comparisons of disability and impairment variables related to knee OA between those with and without the perceived need for rehabilitation were then undertaken.

Materials and methods

Study design

This study was a cross-sectional survey, carried out in Thai communities. The protocol of this study was approved by the Walailak University Human Research Ethics Committee (WUEC-19-010-01).

Participants

Two hundred sixty-two female community dwellers with knee OA were interested in

participating in the study. They were included in this study if their symptoms met the American College of Rheumatology (ACR) clinical criteria for knee OA[16], having knee pain for at least 12 months, having pain intensity of at least two in a 10-point scale within 48 hours, and having never received physical therapy (PT) management and rehabilitation program. Participants were excluded if they had pain intensity of more than two in a 10-point scale in other joints of the lower limbs, had severe lower back pain, used pain medication within 48 hours, received lower extremity joint replacement, had surgery in the back and lower extremities, or underwent treatments for knee OA by health professionals within a year. The exclusion criteria considered the conditions that might influence the rating of the difficulty levels of activity performance. All participants provided written informed consent prior to data collection. Finally, 94 participants were enrolled in this study. They were also divided into two subgroups for the secondary analysis based on their answer to a yes/no question asking about the need for rehabilitation for their knee OA condition (Figure 1).

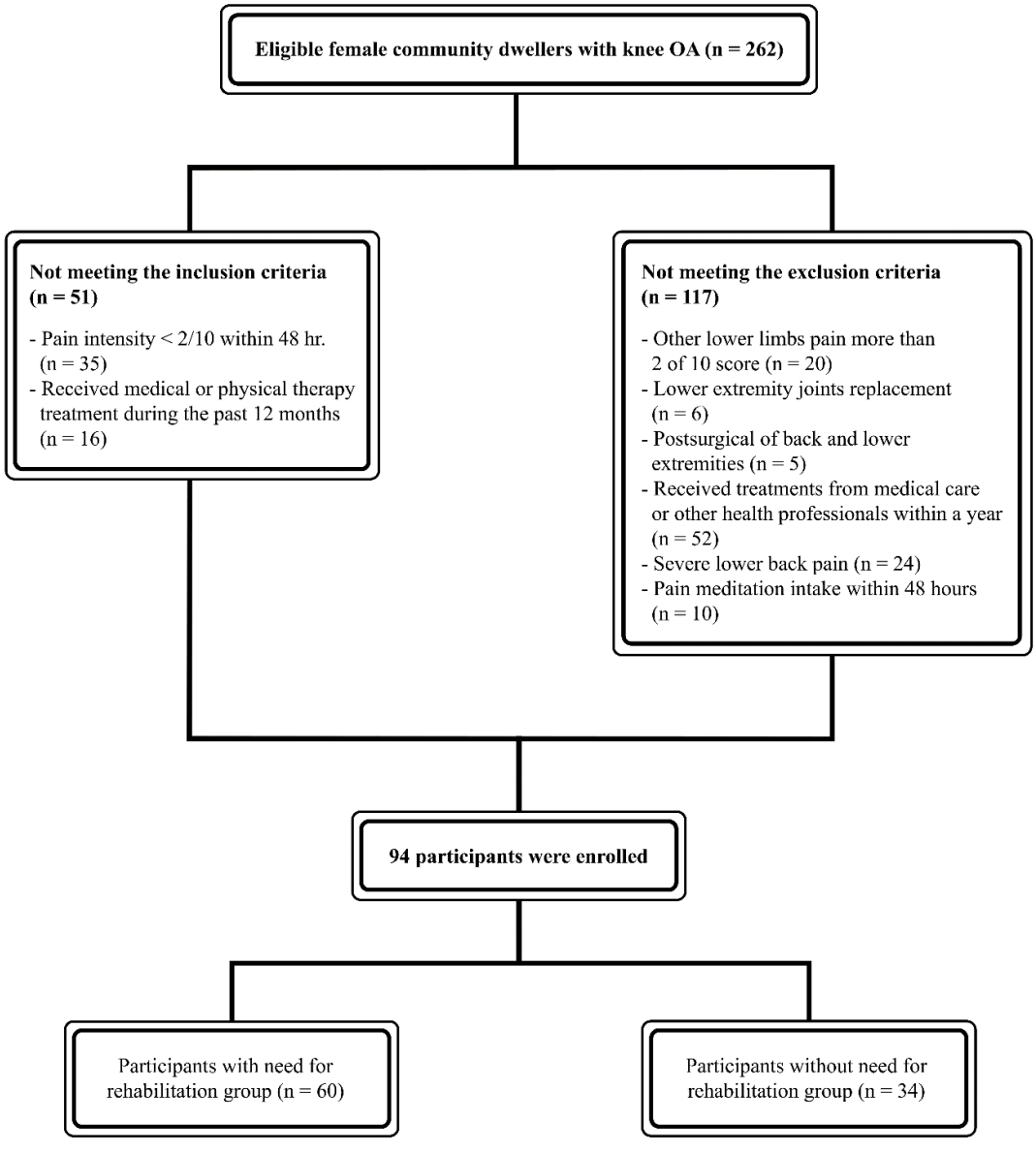

Figure 1 Participant recruitment

Procedures

The participants were interviewed regarding their demographic information (age, height, and weight), duration of knee pain, current pain intensity, and worst pain during the last 48 hours. Knee OA perception was determined through an interview using a structured questionnaire. The issues explored that contributed to the reason(s) towards a delay in seeking medical care or missing follow-ups included the following: need for rehabilitation, perceived cause(s) of knee pain, factors influencing the decision to seek physical therapists, and expected outcome if they had a chance to undergo a rehabilitation program. The disability and impairments including the Knee Injury and Osteoarthritis Outcome Score (KOOS), knee muscle strength, and knee ROM were also assessed.

KOOS (Thai version; www.koos.nu) was used to determine the multidimensional disability in five domains: pain, other symptoms, function in daily living (ADL), function in sport and recreation (Sport/Rec), and knee-related quality of life (QOL). A five-point Likert scale was used for standardized answer options, with 100 as the highest total score for each section (0 = extreme problem; 100 = no problem). Thai KOOS illustrated an acceptable reliability and validity among Thai people with knee OA[17].

A physical therapist with 10 years of experience in treating patients with musculoskeletal conditions, especially knee disorders, performed the objective examination for both muscle strength and knee ROM. The test-retest reliability of ICC > 0.85 for each measurement was confirmed. The maximum isometric strengths of both the knee flexor and extensor muscles were measured by a hand-held dynamometer (JT-AA104, PowerTrack MMT; JTECH Medical Industries, Midvale, UT, USA). The testing procedures and positions were performed according to standardized protocols[18]. The starting position of the strength test was in a sitting position with the knee flexed 90 degrees. Participants were asked to perform isometric contraction against the dynamometer. The average value of three trials was used for data analysis.

Passive knee flexion and extension ROMs were assessed using a goniometer. Participants were tested in a supine position. The fulcrum of the goniometer was centered over the lateral epicondyle of the femur. The stationary arm of the goniometer was placed along the lateral femur, with the greater trochanter as the reference point; and the moving arm was aligned with the lateral aspect of the leg, with the head of the fibula and the lateral malleolus as the reference points[19].

Statistical analysis

Statistical analysis was performed using SPSS version 18 for Windows (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov goodness-of-fit test was used to test the distribution of data. Continuous data are presented as mean ± standard deviation. Nonparametric data are presented as median (interquartile range, 25th-75th percentile). Nominal and categorical data are presented as percentages.

The groups were determined by the participants' answer about the perceived need for rehabilitation for their current knee OA condition. To compare the demographic data, the KOOS subscales, knee muscle strength and knee ROM between groups, independent t-test, or Mann-Whitney U-test was used depending on the characteristic of the variables and the distribution of data.

The sample size in this study was calculated based on the formula from the study of Pourhoseingholi, et al [20]. The expected pain solving of 6% was used in this formula based on the study by Bedson, et al [21]. The 5% substitution was also considered in case of missing data. Finally, 94 subjects were needed for this study.

Results

There was a total of 94 participants enrolled in this study. Their characteristics including age, BMI, duration of knee pain, current pain intensity, worst pain during the last 48 hours for both groups, and need for rehabilitation are presented in Table 1. BMI and duration of knee pain were significantly different between the groups.

Table 1 Participants' characteristics

Variable	Need rehabilitation (n = 60)			Not-need rehabilitation (n = 34)			95% CI	*p-value*
	Mean ± SD	Median	IQR	Mean ± SD	Median	IQR		
Age (years)	64.7 ± 9.1			66.6 ± 8.7			-1.89,5.72	0.319[a]
BMI (kg/m^2)	26.5 ± 4.0			24.9 ± 3.0			-3.14,-0.03	0.046[a*]
Duration of knee pain (years)		4	2-6		3	1-5		0.044[b*]
Current pain intensity (NRS)		1	0-3		0	0-2		0.254[b]
The worst pain intensity during the last 48 hr. (NRS)		7	4-8		5.5	4-7.3		0.106[b]

Note: [a] Independent t-test, [b] Mann-Whitney U-test, [*] *p*-value < 0.05. BMI, Body Mass Index; SD, standard deviation; IQR, interquartile range; CI, Confidence Interval; NRS, numeric rating scale

There were less participants who had never sought medical care for knee osteoarthritis (OA) or knee pain (18.09%) compared with those who used to receive treatments from health professionals but lost follow-ups (81.91%). The participants who never received professional care reported that the reasons included inconvenient transportation (9.58%) and preference for self-care management (8.51%). Those who did not go back for medical follow-ups gave the reasons of preference for self-care management (38.29%), perceived ineffective medical treatment (32.98%), and transportation inconvenience (10.64%). There were 60 participants (63.83%) who responded that they needed a rehabilitation program for their knee OA, while 34 participants (36.17%) reported that they did not need rehabilitation.

The participants' perception of the causes of knee OA and the factors influencing decision making for knee OA management are reported in Table 2. Most of the participants perceived that their knee OA was due to aging or degenerative change, whereas approximately one in 10 perceived that knee OA was related to previous knee injury (secondary OA). Moreover, pain severity was the most common influencing factor for deciding to undergo a rehabilitation program. If given the chance to receive rehabilitation, most of the participants expected pain reduction after treatment.

Table 2 Knee osteoarthritis perception

Perception	Overall (n = 94)		Need for rehabilitation (n = 60)		No need for rehabilitation (n = 34)	
	n	%	n	%	n	%
Causes of knee pain						
- Aging/ degenerative change	50	53.2	34	56.7	16	47.1
- Previous prolonged vigorous activity/ excessive loading of the knee	35	37.2	22	36.7	13	38.2
- Previous knee injury	9	9.6	4	6.6	5	14.7
Factors influencing the decision to seek treatment and rehabilitation for knee OA						
- Severity of knee pain	41	43.6	28	46.7	13	38.2
- Activity limitation	20	21.3	11	18.3	9	26.5
- Both severity of knee pain together with activity limitation	15	16.0	14	23.3	1	2.9
- Transportation service barriers	18	19.1	7	11.7	11	32.4
Expected outcome improvements if they had a chance to undergo a rehabilitation program for their current knee pain						
- Pain relief	88	93.6	58	96.7	30	88.2
- Improved ability to perform activities	16	17.0	14	23.3	2	5.9
- No expectation	4	4.3	1	1.7	3	8.8

For the secondary analysis, the disability and impairments related to knee OA were compared between participants who needed and did not need rehabilitation. Five variables including KOOS-Pain, KOOS-Symptoms, KOOS-ADL, KOOS-Sport/Rec, and passive knee flexion ROM were significantly different between groups (p-value < 0.05), but the KOOS-QOL, passive knee extension ROM, knee extensor muscle strength, and knee flexor muscle strength were not significantly different. For all domains of KOOS, the scores of the group that needed rehabilitation were lower than the scores of the group that did not need rehabilitation. The results are presented in Table 3.

Table 3 Comparisons of knee OA-related problems between participants who needed and did not need rehabilitation

Variables	Need for rehabilitation (n = 60)			No need for rehabilitation (n = 34)			95% CI	*p*-value
	Mean ± SD	Median	IQR	Mean ± SD	Median	IQR		
KOOS-Pain		56.0	47.0-68.5		69.0	56.0-81.5		0.001[a*]
KOOS-Symptoms		62.5	50-71		77.0	67.0-86.0		0.001 [a *]
KOOS-Function in Daily Living		77.0	68.0-88.0		87.5	74.5-94.8		0.015 [a *]
KOOS-Sports/Rec		22.5	15.0-45.0		35.0	25.0-65.0		0.012 [a *]
KOOS-QOL		50.0	38.0-56.0		50.0	42.5-72.0		0.084 [a]
Knee flexion PROM (degree)		133.0	124.0-138.0		137.5	131.8-142.5		0.019 [a *]
Knee flexor strength (lb)		20.0	18.0-23.3		20.5	17.5-25.1		0.705 [a]
Knee extension PROM (degree)	9.0 ± 5.3			9.1 ± 5.4			-2.16, 2.37	0.927[b]
Knee extensor strength (lb)	32.9 ± 8.8			33.4 ± 10.0			-3.38, 4.48	0.783 [b]

Notes: [a] Mann-Whitney U-test, [b] Independent t-test, [*] *p*-value < 0.05. KOOS, Knee Injury and Osteoarthritis Outcome Score; SD, standard deviation; PROM, passive range of motion; IQR, interquartile range

Discussion

This study explored the perception of knee OA among participants who had not consulted health professionals regarding their condition or lost their follow-ups. Their perceived need for rehabilitation was also determined. The results revealed that approximately four in five participants in this study had once sought medical treatment but their follow-ups for more than a year. The reasons included preference for self-care management, perception that medical treatment was ineffective, and barriers associated with transportation service. To support this group, effective self-coping strategies according to the evidence of home- and community-based exercises under professional supervision might be encouraged[22]. Further research is needed for investigating the effectiveness of self-care management and professional management approaches in this population. The issue of transportation service barriers should also be addressed.

Although having knee symptoms, some participants in this study had never sought medical treatment. A study on the prevalence of knee OA in the southern part of Sweden showed that one in three participants consulted physicians for knee OA or knee pain, and the influencing factors were inefficient OA care and self-coping[9]. Similar to our participants, previous studies have reported that aging patients perceived chronic joint pain and other symptoms of OA as a part of normal aging[23]. These patients were more likely to seek medical consultation when symptoms were acute and severe along with the problems of sleep disturbance and mobility[23].

The key finding of this study was that participants, who had not consulted health professionals regarding their condition lost their follow-ups, perceived that knee OA was associated with aging. The severity of pain was the most important concern for their decision to seek treatment and rehabilitation. Also, pain reduction was the key expected outcome if treatment was received. Two-thirds of them would want to receive rehabilitation for their present condition. The group that needed rehabilitation also had significantly greater pain level and symptoms, and greater limitations in daily and sport/recreation activities reflected by the KOOS subscales. These results implied that those with greater pain and perceived disability were more likely to consider seeking medical assistance. This group also had a significantly longer duration of knee pain compared with those who did not need rehabilitation. The duration and progression of knee OA were known to increase the severity of symptoms[24], which resulted in the need for a rehabilitation program. Knee pain was the key feature of knee OA, which is used by the ACR clinical criteria as the first criterion for diagnosing knee OA[16]. However, health-seeking behavior was also highly affected by the perception of the problem, concern, and expectation from treatment[25].

Another impairment found to be different between groups was knee flexion limitation. As reduced ROM is a sign of OA, people with knee OA demonstrated less knee flexion ROM than healthy controls[4]. Limitation in knee flexion ROM could result in the decline of functional performance[26]. Therefore, progressive knee OA might reduce both knee flexion ROM and physical function. Impaired joint motion might influence the functions causing these participants to consider the need for rehabilitation. Previous studies have demonstrated the deficits in both knee extensor and knee flexor strength in patients with knee OA[27]. In contrast, there was no significant difference in the strength of both muscles between groups in this study. However, the strength of the knee flexor and extensor muscles of the participants in both groups was less than the normative data from a previous study[28]. Remarkably, the participants in this study also did not perceive strength to be an important outcome in the decision to undergo a rehabilitation program. This might be because muscle weakness was not directly felt, i.e. individuals with knee OA might simply perceive this problem during some demanding activities such as walking.

Interestingly, the participants who reported not needing rehabilitation in this study had disability and impairments related to knee OA, although the severity was less than that of those

who needed rehabilitation. This might be due to the heterogenous characteristics of knee OA regarding different phenotypes[29]. The pathology of knee OA could result in different impairments and the difficulty to perform activities. Moreover, the participants who reported not needing rehabilitation had a KOOS-ADL score of 87.5 out of 100. This lower score also did not reach the minimal detectable change of KOOS-ADL (15.4) in knee OA[30]. For this group, screening programs can help identify those with risk factors and progressive signs of knee OA, and initial preventive strategies can be applied. The comorbidities which would occur later should also be addressed.

Physical therapists and health professionals in the primary care settings should play a role, especially in knee OA patients in the community who do not have the opportunity to consult with health professionals. However, therapies should be considered according to individualized patient needs and preferences. Professional advice with reassurance and clear instructions about the appropriate methods and value of exercises in controlling knee OA symptoms is recommended as an appropriate strategy for knee OA management[15].

This study had some limitations. The level of education of the participants was not investigated in this study, which might have been a factor that would have a large influence on knee OA perception and health service accessibility. Moreover, the perception of other environmental factors included in the ICF core set for OA (i.e. products or substances for personal consumption, immediate family, and individual attitude of health professionals) should be further investigated. According to the quantitative design, we could not explain the participants' perspective in further detail. Hence, a mixed method of qualitative and quantitative study should be performed. In addition, to emphasize our expectation about the importance of patient perception on knee OA, future research should evaluate the effectiveness of educational intervention on patient perception and self-coping strategies.

Conclusion

In conclusion, the results of this study revealed the important perception of patients who had missed follow-ups or never received any treatment from health professionals. The influencing factors for decision making in seeking rehabilitation and the expected outcome of treatment were also made known. Moreover, participants who needed rehabilitation demonstrated high levels of pain and other symptoms, greater activity limitation, and more limitation of passive knee flexion ROM than those who did not need rehabilitation. This implied that the high severity of symptoms seemed to prompt the patients to seek treatment. The results of this study can be used as preliminary data for the management of knee OA in communities. The education of symptoms and problems related to knee functions should be self-monitored, and appropriate self-coping management should be encouraged.

Take home messages

Patient perception was an important factor for knee OA management. Participants who needed rehabilitation had more severe problems than those who did not need rehabilitation, confirming that patients tend to consult health professionals when symptoms are severe. The results can be used as preliminary data for the management of knee OA.

Conflict of interest

The authors declare no conflict of interest.

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Cross-cultural adaptation and psychometric properties of the Thai version of the Neurophysiology of Pain Questionnaire in individuals with chronic low back pain

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KEYWORDS
Pain neurophysiology; Chronic low back pain; Cross-cultural adaptation; Reliability; Validity.

ABSTRACT
Pain neurophysiology knowledge is hypothesized to influence pain beliefs and physical performance in individuals with chronic low back pain (LBP). Valid and reliable measures of such knowledge are important to evaluate the pain treatment on this domain as well as to understand its role in both physical and psychological functions of individuals with chronic pain. This study aimed to culturally adapt the revised Neurophysiology of Pain Questionnaire into Thai (T-rNPQ), using the Functional Assessment of Chronic Illness Therapy translation methodology, and to evaluate its reliability and validity. Two hundred sixty-three individuals with chronic LBP completed the T-rNPQ and seven health and function domains of Thai versions of the Patient-Reported Outcomes Measurement Information System-29. Forty-five lecturers in musculoskeletal physical therapy completed the T-rNPQ. A subset of 95 individuals with chronic LBP completed the T-rNPQ again after an interval of seven to 15 days. Internal consistency for the total score and two subscales that emerged in the current analyses showed marked variability (Cronbach's alphas = 0.82, 0.82, and 0.63). Test-retest reliability was poor to good (ICC's$_{(2,1)}$ = 0.71, 0.40, and 0.65). Known-groups and discriminant construct validity of the T-rNPQ total score and subscale scores were satisfactory. The findings indicate that the T-rNPQ measures two knowledge domains, i.e., 'Neurophysiology Knowledge' and 'Pain means Harm'. The psychometric property assessment of the T-rNPQ indicated that using the scale in Thai individuals with chronic LBP should be undertaken with discretion.

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Introduction

Chronic low back pain (LBP) is one of the most common chronic musculoskeletal pain problems worldwide[1]. Only one-third of individuals who have an episode of LBP have been found to fully recover within a year of the episode[2]. Chronic LBP is known to be associated with low productivity, absenteeism, psychological stress (in both the person with LBP and their families), and significant costs to individuals and society[3,4].

The experience and impact of chronic pain is known to be influenced by a number of personal factors[5], including maladaptive beliefs about pain[6]. These beliefs include the idea that "hurt is a signal of harm" (i.e., if it hurts, something must be seriously injured), that "pain is a signal to stop what you are doing" (i.e., if an activity results in pain, you should stop before you injure yourself), and that "rest is the best medicine" (i.e., pain is a signal for you to rest to recuperate your body)[7]. Treatments that target maladaptive beliefs about pain and reducing fear-avoidance behaviors have been shown to be effective for the management of catastrophizing, fear of movement, improve self-efficacy, and persistent pain states[8].

Clinical practice guidelines for LBP have recommended education, exercise, and psychological therapies as the first-line treatment[9]. Pain neurophysiology education (PNE) is an educational therapy usually provided by physical therapists. It is also a treatment that specifically targets knowledge about pain for change, with the hypothesis that as people understand more about the neurophysiology and meaning of pain, they are less likely to catastrophizing about and be disabled by that pain[10]. Consistent with these ideas, PNE has been shown to increase knowledge about pain neurophysiology in individuals with chronic pain[11], and also to result in moderate-effect reductions in kinesiophobia and pain catastrophizing, with no identified harms or negative side-effects in individuals with chronic musculoskeletal pain[12,13]. A recent systematic review confirms the efficacy of multimodal approaches to chronic pain treatment, including PNE, for increasing compliance with exercise therapy and positive outcomes at long-term follow-up in individuals with chronic LBP[14].

In order to determine the extent to which PNE influences pain knowledge, as well as the extent to which such change mediates the beneficial effects of PNE and other treatments that target pain beliefs, it is necessary to be able to assess pain knowledge. The Neurophysiology of Pain Questionnaire (NPQ) was designed to do just that. The original NPQ contained 19 items[15] and assesses an individual's level of knowledge about the neurophysiology of pain. The NPQ was later been revised to contain 12 items (rNPQ) and considered as a unidimensional scale[16]. To date, the rNPQ has been translated and cross-culturally validated into French[17], Brazilian Portuguese[18], and German[19]. Although, the rNPQ is generally thought to be unidimensional, its dimensionality of the scale has been shown to vary, i.e., 2-4 dimensions[17,19]. Internal consistency has been found to be satisfactory in the original English version (Pearson Separation Index = 0.82)[16]. However, the internal consistency of the rNPQ was found to be unacceptable in the French version[17] and the German version [19] (Cronbach's alphas = 0.30 and 0.52, respectively).

The availability of valid and reliable translations of the rNPQ is necessary to be able to determine the extent to which pain knowledge plays a similar role to outcome across individuals who speak different languages and live in different countries. This study aimed to cross-culturally adapt and translate the rNPQ into Thai version (T-rNPQ) as well as to evaluate its psychometric properties (i.e., dimensionality, internal consistency, test-retest reliability, ceiling and floor effects, known-groups validity, and discriminant validity).

Materials and methods

Study design

The study was conducted in two phases. In the first phase, a cross-cultural adaptation of the rNPQ into Thai using the Functional Assessment of Chronic Illness Therapy (FACIT) translation methodology was conducted. In the second phase, the psychometric properties of the translated rNPQ were evaluated. The study was approved by the University Human Ethics Committee (COA No. 240/2020). All participants provided signed informed consent.

Phase 1: Cross-cultural translation and adaptation

The FACIT translation methodology was used to develop the culturally appropriate translation of the rNPQ[20], which was chosen as it also included the original developer in the quality review instead of an optional process found in other methods. This would help improve a consistency in the content and face validity between English and Thai versions of a questionnaire. There are 11 steps in the FACIT translation methodology, including forward translation, reconciliation, back-translation, back-translation review/quality control, independent reviews, pre-finalization review, finalization process, harmonization and quality assurance, formatting and proofreading, cognitive testing and linguistic validation, and evaluation of the participants' comments and finalization of translation. Detailed descriptions of the FACIT translation methodology are published elsewhere[20].

Phase 2: Evaluation of the reliability and validity of the TrNPQ

Participants

Two groups of participants provided data to evaluate the psychometric properties of the T-rNPQ. The first group was recruited from large public hospitals and government offices in the Bangkok metropolitan area from August 2020 through April 2021. Inclusion criteria included those aged 18 years or older, being able to read and speak Thai, and having chronic LBP (defined as "a back pain problem that has persisted at least three months and has resulted in pain on at least half the days in the past six months")[21]. The low back region was defined as the space between the lower posterior margin of the rib cage and the horizontal gluteal fold[21]. Exclusion criteria included having serious medical conditions or complications that might interfere with the participant's ability to respond to the study questionnaires (such as vision or reading impairments during data collection). The second group was Thai-speaking lecturers with at least five years of experience in a field of musculoskeletal physical therapy from 10 universities in Thailand.

Procedures

The researcher provided participants in both groups with an online questionnaire link, which was distributed to participants via email. Participants firstly completed written informed consent followed by a questionnaire asking about demographics and the T-rNPQ items. The participants with chronic LBP then completed the Thai version of Patient-Reported Outcomes Measurement Information System-29 (T-PROMIS-29): Physical Activity, Anxiety, Depression, Fatigue, Sleep Disturbance, Ability to Participate in Social Roles and Activities, and Pain interference[22]. We believed that the T-rNPQ (pain neurophysiology knowledge) assessed different characteristics from the T-PROMIS-29 (health-related quality of life), which would allow us to evaluate the discriminant validity of the T-rNPQ. All seven domains of the T-PROMIS-29 were assessed with scales ranging from 1 to 4 items. Respondents were asked to indicate the frequency that they experienced what was described with each item in the past seven days using 5-point Likert scales. Except for items assessing physical function, that were rated based on the present time. Pain intensity was assessed with a single item asking respondents to rate the magnitude of their pain in the past week on a 0 ("No pain") to 10 ("Worst imaginable pain") numerical scale. The T-PROMIS-29 scale scores were transformed into T-scores (mean 50 and SD 10) according to the PROMIS adult profile instrument guideline (http://www.healthmeasures.net). The direction of PROMIS scales is with respect to the scales name; higher scores indicate more of the domain assessed. The Thai version of the PROMIS-29 has been shown to provide valid and reliable measures of the domains it assesses, with good to excellent internal consistency (i.e., Cronbach's alpha coefficients ranging from 0.84 to 0.94) and moderate to good test re-test reliability, ICC's $_{(2,1)}$ coefficient ranging from 0.57 to 0.74[22].

The T-rNPQ contains 12 questions that are answered with "True," "False," or "Undecided." The overall T-rNPQ score is the sum of correct responses, and so can range from 0 to 12. A higher score indicates a greater understanding of the biological mechanisms that underpin chronic pain.

To assess the test-retest reliability of the T-rNPQ, participants with chronic LBP were asked to complete the T-rNPQ again at least seven days after the initial completion.

Statistical analysis

All analyses were performed using SPSS version 22.0 for Windows. A Shapiro-Wilk test verified the normal distribution for all parameters. Quantitative variables that were normally distributed were expressed as mean ± standard deviation (SD), and quantitative variables that were not normally distributed were expressed as median (percentile 25, percentile 75). The level of significance was set at 0.05.

Dimensionality

The dimensionality of the T-rNPQ questionnaire was tested by conducting an exploratory principal component analysis (PCA), using the scree test to determine the number of underlying components assessed by the measure (eigenvalues of > 1). Varimax rotation was applied, and the items with a factor loading of 0.30 or greater for a given factor were used to indicate that an item loaded on the factor(s) that emerged[23].

Internal consistency

Internal consistency for the T-rNPQ was calculated using Cronbach's alpha. Cronbach's alpha values that were 0.70 or greater were used to determine that the scale's internal consistency was acceptable[24].

Reliability

For test-retest reliability, we computed the intraclass correlation coefficient ($ICC_{(2,1)}$ for individuals with chronic LBP[25]. ICC values less than 0.50 indicate poor reliability, values between 0.50 and 0.75 indicate moderate reliability, values between 0.75 and 0.90 indicate good reliability, and values greater than 0.90 indicate excellent reliability[26]. The $SEM_{test\text{-}retest}$, which is a measure of the standard error of measurement, was calculated as $\sqrt{(\sigma^2_{\text{time}} + \sigma^2_{\text{residual}})}$[27]. The minimal detectable change at 95 percent confidence ($MDC_{95\%}$), which indicates the minimal change score to be confident at the 95% level that the change is not due to measurement error, was calculated by $MDC_{95\%}$ = square root of 2 multiplied by $SEM_{test\text{-}retest}$ and 1.96[25,27].

Ceiling and floor effects

Ceiling and floor effects were evaluated by calculating the percentages of the responses of the highest and the lowest possible scores achieved by respondents. Rates greater than 15% for the highest and the lowest scores indicated ceiling and floor effects, respectively[28].

Known-groups validity

The known-groups validity, by comparing the T-rNPQ scores from the 263 individuals with chronic LBP and 45 lecturers in a field of musculoskeletal physical therapy. If the T-rNPQ scale was valid, we hypothesized that the scores obtained from lecturers in a field of musculoskeletal physical therapy would be significantly higher than those obtained from individuals with chronic LBP. As the T-rNPQ scores of both groups were not normally distributed, a Mann–Whitney test was used for this analysis.

Discriminant validity

The discriminant validity, by computing Spearman's rank correlation coefficients between the T-rNPQ and seven health and function domains of the T-PROMIS-29 scales. We hypothesized that if the T-rNPQ scale (or scales, if the planned factor analysis indicated that the measures assess more than one domain of knowledge) was valid, weak associations between the T-rNPQ and the T-PROMIS-29 measures of these domains would be found.

Results

Cross-cultural translation and adaptation

The cross-cultural translation and adaptation of the rNPQ into a Thai version was deemed to be understandable and culturally appropriate, except for one item; that is, the item stating that "Nerves adapt by increasing their resting level of excitement." The sentence contained the word "resting" and was difficult to understand in the Thai language. After discussions within the translation committee and with the developer of the rNPQ, it was decided to delete this word, and the item was modified to be "Nerves adapt by increasing their sensitization to stimuli."

Participants

Eight hundred and fifty individuals with chronic LBP were screened for eligibility and 587 of these did not meet the study inclusion and exclusion criteria which left 263 participants (Table 1). The majority of individuals with chronic LBP were middle-aged women and worked full time, reporting an average pain intensity of 5. Seventy lecturers were invited to participate, and 45 agreed to do so. The majority of lecturers were middle-aged women and had experience in a field of musculoskeletal physical therapy for an average of 10 years, ranging from 5 to 27 years.

Table 1 Demographic and characteristics of participants

Characteristic	N (%)	Mean (SD)
Individuals with chronic LBP (n=263)		
Age (in years)		40.7 (11.7)
Sex		
Women	161 (61)	
Men	102 (39)	
Weight (self-reported), kg		67.1 (16.2)
Height (self-reported), cm		162.9 (8.5)
Employment status		
Working full time	247 (94)	
Unemployment	16 (6)	
Pain intensity (1-10)		5.0 (2.1)
Educational level		
Primary school	10 (4)	
Secondary school	9 (3)	
High school	41 (15)	
University	203 (78)	
T-rNPQ (0-12)		3.7 (2.1)
T-PROMIS (T-scores)		
Physical Function		43.7 (8.0)
Anxiety		57.2 (8.7)
Depression		50.3 (9.5)
Fatigue		53.4 (7.8)
Sleep Disturbance		51.3 (6.8)
Ability to Participate in Social Roles and Activities		51.6 (8.1)
Pain Interference		57.1 (6.2)
Lecturers in musculoskeletal physical therapy (n=45)		
Age (in years)		42.4 (6.6)
Sex		
Women	36 (80)	
Men	9 (20)	
Work duration (in years)		14.1 (9.2)
Experience in a field of musculoskeletal physical therapy		10 (6.8)
T-rNPQ (0-12)		6.9 (1.9)

Note: LBP, Low back pain.

Dimensionality

An exploratory factor analysis using data from the 263 participants with LBP pain followed by varimax rotation was used to test the dimensionality of the T-rNPQ. The result of Bartlett's test of sphericity indicated that the correlation matrix was not random, x^2 (66, *N*=263) = 806.7, *p*-value < 0.001, the Kaiser-Meyer-Olkin statistic was 0.84, indicating that there were a sufficient number of correlated items in the matrix to conduct the EFA. All individual measures of sampling adequacy values were greater than 0.30. A scree test suggested two meaningful factors with eigenvalues of more than 1 (46% of the total variance); factor 1 (eigenvalue 4.04), and factor 2 (eigenvalue 1.46). We, therefore, concluded that the T-rNPQ items assess two distinct underlying components (Spearman's rho between the two components = 0.07, *p*-value = 0.24). The former represents responses of the neurological system (which we labeled "Neurophysiology Knowledge") to pain and the latter represents injury and pain perception (which we labeled "Pain means Harm"). The component loadings for the T-rNPQ are presented in Table 2. As could be seen, only one item (item 11) had an item-total correlation less than 0.40.

Table 2 Factor loading for twelve T-rNPQ items

Item number	Item	Factor loading	
		Neurophysiology Knowledge	Pain means Harm
3	Special nerves in your spinal cord convey 'danger' messages to your brain	**0.86**	0.09
12	When you are injured, special receptors convey the danger message to your spinal cord	**0.78**	0.02
9	Descending neurons are always inhibitory	**0.74**	0.06
6	Nerves adapt by increasing their resting level of excitement.	**0.68**	0.16
5	The brain decides when you will experience pain.	**0.57**	0.24
10	When you injure yourself, the environment that you are in will not affect the amount of pain you experience, as long as the injury is exactly the same.	**0.55**	0.33
1	When part of your body is injured, special pain receptors convey the pain message to your brain.	**0.52**	0.19
11	It is possible to have pain and not know about it.	**0.38**	0.20
4	Pain occurs whenever you are injured.	0.11	**0.76**
2	Worse injuries always result in worse pain	0.16	**0.72**
8	Pain only occurs when you are injured or at risk of being injured.	0.14	**0.63**
7	Chronic pain means that an injury hasn't healed properly.	0.12	**0.54**

Internal consistency

Given the results of the factor analysis suggesting that the T-rNPQ assesses two distinct pain neurophysiology knowledge domains, we examined the internal consistency of the T-rNPQ total score as well as the two subscale scores. The total score IC was acceptable (Cronbach's alpha = 0.82) for the total score, for the Neurophysiology Knowledge score (Cronbach's alpha = 0.82), but unacceptable for the Pain means Harm scale (Cronbach's alpha = 0.63) in the group of individuals with chronic LBP.

Neither the ceiling nor floor effect of the T-rNPQ total score or the Neurophysiology Knowledge subscale was observed. However, floor effect was found for the Pain means Harm scale in the group of individuals with chronic LBP (53%).

Test-retest reliability

With at least 7-day apart (range = 7 to 15 days; average = 10 days), 95 individuals with chronic LBP returned completed T-rNPQs. The $ICC_{(2,1)}$ value indicated poor to moderate test-retest reliability for the chronic LBP group (Table 3).

Table 3 Mean (standard deviation) and test-retest reliability coefficients of the T-rNPQ scores at the first and second session

	1st session	2nd session	$ICC_{(2,1)}$ (95%CI)	$SEM_{test-retest}$	$MDC_{95\%}$
Individuals with chronic LBP (n=95)					
T-rNPQ total score	3.5 (2.2)	3.7 (1.9)	0.71 (0.57-0.81)	1.10	3.04
Neurophysiology Knowledge	3.2 (1.8)	3.0 (1.6)	0.40 (0.10-0.60)	1.31	3.62
Pain means Harm	0.7 (1.0)	0.5 (0.9)	0.65 (0.47-0.76)	0.56	1.55

Note: ICC, Intraclass correlation coefficient; MDC, Minimal detectable change; SEM, Standard error of measurement; LBP, Low back pain.

Known-groups validity

For the T-rNPQ, a Mann-Whitney test revealed a significantly higher T-rNPQ total score in the group of lecturers (Mdn = 7, 6.0 – 8.0) than the group of individuals with chronic LBP (Mdn = 4, 2.0 – 5.0) (*p*-value < 0.001). The items that had more than 50% of lecturers answered incorrectly were items 1, 2, 4, 7, and 11. The items that had more than 50% of individuals with chronic LBP answered incorrectly were items 1-3 and 9-12.

For "Neurophysiology Knowledge" factor, a Mann-Whitney test revealed a significantly higher Neurophysiology Knowledge subscale score in the group of lecturers (Mdn = 5, 4.0 – 6.0) than the group of individuals with chronic LBP (Mdn = 3, 1.0 – 4.0) (*p*-value < 0.001)

For "Pain means Harm" factor, a Mann-Whitney test revealed a significantly higher Pain means Harm subscale score in the group of lecturers (Mdn = 2, 1.0 – 3.0) than the group of individuals with chronic LBP (Mdn = 1, 0.0 – 2.0) (*p*-value < 0.001).

Discriminant validity

Non-significant and little correlations were found between the total score and its subscale scores of the T-rNPQ and the T-PROMIS-29 scores (Table 4).

Table 4 Spearman correlation coefficients between the T-rNPQ and the validity criteria measure (n=263)

Measures	T-rNPQ total score	Neurophysiology Knowledge	Pain means Harm
T-PROMIS-29			
• Physical Function	-0.06	-0.09	-0.05
• Anxiety	0.10	0.05	-0.01
• Depression	0.05	0.03	-0.01
• Fatigue	0.03	0.05	0.06
• Sleep disturbance	0.07	0.02	0.07
• Ability to Participate in Social Roles and Activities	-0.02	-0.11	-0.01
• Pain Interference	0.01	0.13	0.02

Discussion

In this study, the English version of the rNPQ was successfully translated into a Thai version, in which most parts were deemed to have cultural equivalence except one item. The change required for the single item was semantic (i.e., changing "Nerves adapt by increasing their resting level of excitement" to "Nerves adapt by increasing their sensitization to stimuli"). The results indicated that the T-rNPQ assessed two underlying constructs and showed marked variability internal consistency and test-retest reliability. It had acceptable known-groups and discriminant validity for use in Thai individuals with chronic LBP.

The exploratory factor analysis of the T-rNPQ generated two factors: one for the Neurophysiology Knowledge and the other for the Pain means Harm. This result is in contrast to the original English version of the rNPQ that was proposed the 12 items version of the NPQ after a Rasch analysis, claiming that this 12 items version had superior psychometric properties, and considering it is a unidimensional scale. The present result was in line with previous studies of the adapted scale in other languages, although the number of and the items in the factors differed between studies[17,19]. The separate scoring on both subscales provides important information justifying a change to the subscale structure of the test. However, we assume that the two subscales found in this study ('Neurophysiology Knowledge' and 'Pain means Harm') have much more significance in identifying patients with problematic pain neurophysiology knowledge and beliefs, which will probably strongly influence their future behavior. Future validation studies are needed to confirm our findings using a confirmatory factor analysis, which is a more sophisticated method. As all previous studies did not report the psychometric properties of the rNPQ for each factor, thus this study used the total score to compare with the previous studies.

An acceptable internal consistency for the T-rNPQ total score for the individuals chronic LBP is similar to that reported for the original English version with Pearson Separation Index (a Rasch analysis equivalent of Cronbach's alpha that can be interpreted similarly) (Pearson Separation Index = 0.82)[16]. The value in the present study is higher than those reported in the other adaptation versions, including the French (Cronbach's alpha = 0.30)[17], Brazilian Portuguese version (Cronbach's alpha = 0.63)[18], and German (Cronbach's alpha = 0.52)[19]. The Pain means Harm subscale demonstrated an inadequate internal consistency (Cronbach's alpha = 0.63). The reason for the low level of Cronbach's alpha of the Pain means Harm subscale is perhaps nature of the true/false format and could be susceptible to guessing[16].

No floor or ceiling effect was observed for the T-rNPQ total score. The findings are consistent with those reported for individuals with chronic

spinal pain using the English version[16], the French version[17], and the German version[19]. These results suggest that the T-rNPQ total score would be appropriate for assessing pain neurophysiology knowledge. However, the floor effect as high as 53% found in the Pain means Harm subscale in the group of individuals with chronic LBP would urge therapists to improve knowledge regarding injury and pain perception in this group so that it may have an impact on their pain condition.

The moderate test-retest reliability of the T-rNPQ total score and the Pain means Harm subscale in the individuals with chronic LBP (ICC = 0.71 and 0.65, respectively) with an average of 10 days apart. The measurement time longer than that of Demoulin et al. (2017) with seven days apart, report poor retest reliability (ICC = 0.48) for the 12 items[17]. However, the present result was lower than the English version (ICC = 0.97) that studied in the group of individuals with spinal pain before receiving pain neurophysiology education[16] and lower than the German version (ICC = 0.97) that studied in the group of individuals with chronic non-specific spinal pain[19]. The time window between the measurement times was 2-5 days[16] and 10 days[19]. Demoulin et al. (2017) postulated that short intervals would allow participants to remember their previous answers and would result in less variation in their repeated responses. Regarding the Neurophysiology Knowledge subscale, poor reliability coefficients was found[17]. This study is the first study to propose that the T-rNPQ consisted of two factors, i.e., the Neurophysiology Knowledge and the Pain means Harm factors. It is unclear why the Neurophysiology Knowledge subscale possessed poor reliability coefficients. Further studies are required to confirm our findings and to improve on test-retest reliability of the Neurophysiology Knowledge subscale.

The results indicated that the T-rNPQ total score and its subscale scores had satisfactory known-groups validity which supports those reported for the total score in French, German, and Brazilian Portuguese versions[17-19]. The consistent results across all adaptations provide evidence that the rNPQ can separate those with higher and lower levels of pain neurophysiology knowledge. Interestingly, more than 50% of the lecturers answered three from four questions (items 2, 7, and 8) in the Pain means Harm subscale incorrectly. This finding suggests that they should improve their knowledge in respect to injury and pain perception, although they had a good understanding of the responses of the neurological system to pain.

The results showed that level of pain neurophysiology knowledge, assessed by the T-rNPQ total score and its subscale scores, are conceptually not related to health-related quality of life measured by the T-PROMIS-29, supporting the discriminant validity of T-rNPQ. The findings of this study are consistent with a previous adaptation study showing non-significant low correlations between the pain neurophysiology knowledge and Physical, Psychic domain of the 12-Item Short-Form Health Survey; between the rNPQ and Hannover Functional Questionnaire Backache[19]. The fact that the correlation of the T-rNPQ total score and its subscale scores is very poor indicates that these measure independent parameters of the same construct. Additionally, the role of pain neurophysiology knowledge in both physical and psychological functions of individuals with chronic pain did not find in this current study.

A number of limitations of the present study should be noted and considered when interpreting the results. First, participants were limited to individuals with chronic LBP who lived in Bangkok, Thailand. The geography of participants reflects several aspects of sample, including culture, language, some demographic characteristics (e.g. occupation, education level, financial status). Thus, generalization of the findings to other individuals with LBP or other health conditions as well as healthy individuals should be made with caution. Second, the use of a convenience sample restricts the external validity of this study. Thus, generalization of the results from this study to other chronic LBP populations should be made with caution. Future studies may consider random sampling approaches to recruit study participants from community settings. Third, both internal consistency and test-retest reliability for the group of lecturers were not assessed. With the limitation of time and resources, only 45 lecturers

in musculoskeletal physical therapy from universities in Thailand participated in this study. This sample size was inadequate to assess these types of reliability and to perform an exploratory factor analysis of the T-rNPQ in the group of lecturers. A study with a larger sample size is needed to assess the internal consistency and test-retest reliability as well as to confirm the two factors found in the group of individuals with chronic LBP and the known-groups validity of the T-rNPQ found in the present study. Last, we did not evaluate the responsiveness analysis and the minimum important change scores for the T-rNPQ. Future studies might consider the assessment of responsiveness to change and minimum important change scores to be able to better interpret the change of the T-rNPQ total score and its subscale scores after the intervention to target the pain neurophysiology knowledge in individuals with chronic LBP.

Conclusion

Despite the study's limitations, the findings provide important initial support for the cultural appropriateness and recommend assessing and discriminating the level of pain neurophysiology knowledge between the individuals with chronic LBP and lecturers in musculoskeletal physical therapy in Thailand. However, the interpretation of the results of the T-rNPQ version must be taken with caution due to the absence of robust psychometric properties of the instrument. Additional research would be useful that replicates the current findings in samples of individuals with different chronic pain conditions, that evaluates the sensitivity of the T-rNPQ to treatment which is designed to change pain neurophysiology knowledge, and that identifies cut-offs that would be useful for identifying patients with chronic pain who might most benefit from treatment. Despite this, the measure may be useful for cross-cultural research evaluating the role that pain neurophysiology knowledge may play and may be used in both clinical treatment and research settings for evaluating the pain neurophysiology knowledge in adjustment to chronic pain.

Take home messages

The findings indicate that the Thai version of the Neurophysiology of Pain Questionnaire measures two knowledge domains, i.e., 'Neurophysiology Knowledge' and 'Pain means Harm'. The psychometric property assessment of the T-rNPQ indicated that using the scale in Thai individuals with chronic LBP should be undertaken with discretion.

Conflict of interest

The authors declare no conflict of interest.

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With respect to author contributions, P. Pasangkayo was involved in concept/research design, data collection, data analysis, and manuscript writing, and M.P. Jensen, R. Kanlayanaphotporn, and P. Janwantanakul were involved in concept/research design, data analysis, and manuscript writing. All authors read and approved the final manuscript.

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Supplementary

The FACIT translation methodology was used to develop the culturally appropriate translation of the revised Neurophysiology of Pain Questionnaire (rNPQ) (Eremenco, Cella and Arnold, 2005). There are 11 steps in the FACIT translation methodology, as described below.

1. Forward translation

The rNPQ was initially translated into Thai by two independent professional translators, who were native Thai speakers (both were from the Language Institute of University). They were asked to use simple and culturally appropriate language.

2. Reconciliation

A third native Thai speaker (one of the authors of the manuscript), who did not participate in the forward translation, evaluated the first two translated questionnaires and made an attempt to reconcile any discrepancies between the two translations to generate a third translation. The translator took notes to document his thinking behind the decisions made.

3. Back-translation

The reconciled Thai version of the rNPQ was then back-translated by a native English-speaking translator (a person from the Language Institute of University), who was also fluent in Thai. The back translator was not allowed access to, and had no knowledge of, the original English version. The translator was asked to translate using simple language that captured the key meaning of the items.

4. Back-translation review/quality control

A native English speaker who had experience in using the rNPQ in research (one of developers of English version of the rNPQ) performed a back-translation review. The goal of review was to evaluate the equivalence in the meaning of the English source and Thai translation. The Translation Project Manager (one of the authors of the manuscript), who was a health professional and a native Thai speaker, provided additional comments on any discrepancies between the back-translated and original versions. Both reviewers made suggestions regarding wording that might require changes to ensure equivalent meaning.

5. Independent reviews

Three native Thai speakers, who were healthcare professionals (three physical therapists), reviewed all information obtained from the preceding steps. The most appropriate translation for each item was selected or alternate translations were provided if the previous translations were found to be unacceptable.

6. Pre-finalization review

The Translation Project Manager (one of the authors of the manuscript) reviewed the translation recommended as a result of step 5, along with the reviewers' comments. The Translation Project Manager identified potential problems and made comments about the recommended translation to guide the Language Coordinator (one of the authors of the manuscript) in step 7.

7. Finalization process

The Language Coordinator (one of the authors of the manuscript), who was a health professional, with experience in the intent of the items and a native Thai speaker, determined the final translation. All of the preceding information were reviewed. The Language Coordinator provided explanations for the choice of final translation and performed the respective literal back-translation and more idiomatic back-translation for each item.

8. Harmonization and quality assurance

A native English speaker who was involved in the development of the rNPQ (one of developers of English version of the rNPQ) made a preliminary assessment of the accuracy and equivalence of the final translation by comparing the final back-translation with the source and verifying that documentation of the decision-making process was complete.

9. Formatting and proofreading

Formatting, typesetting, and proofreading of the rNPQ instructions and items of the final translation were checked for spelling and grammatical issues. Two proof-readers (two physical therapists) worked independently and reconciled the proofreading comments.

10. Cognitive testing and linguistic validation

The final version of the Thai version of the rNPQ (T-rNPQ) was pretested with 10 Thai individuals with chronic LBP. The goal was to ensure understandability and verify that the meaning of each item was equivalent to the English source after translation.

11. Evaluation of the participants' comments and finalization of translation

The Language Coordinator (one of the authors of the manuscript) compiled and summarized comments from step 10 (back-translated into English) and proposed any final changes in the translation. The native English speaker (one of developers of English version of the rNPQ) who was involved in the development of the rNPQ conducted a final quality review and the translation was finalized.

Reference

Eremenco SL, Cella D, Arnold BJ. A comprehensive method for the translation and cross-cultural validation of health status questionnaires. Eval Health Prof 2005; 28: 212-32.

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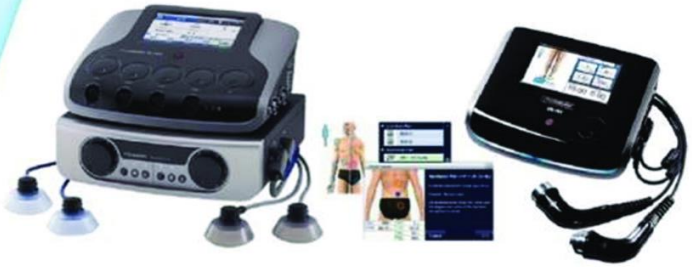

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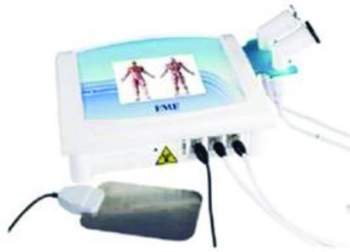

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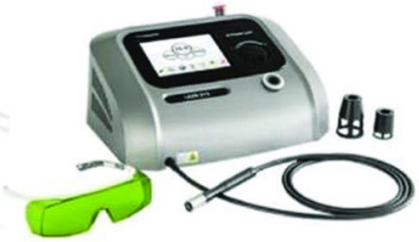

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