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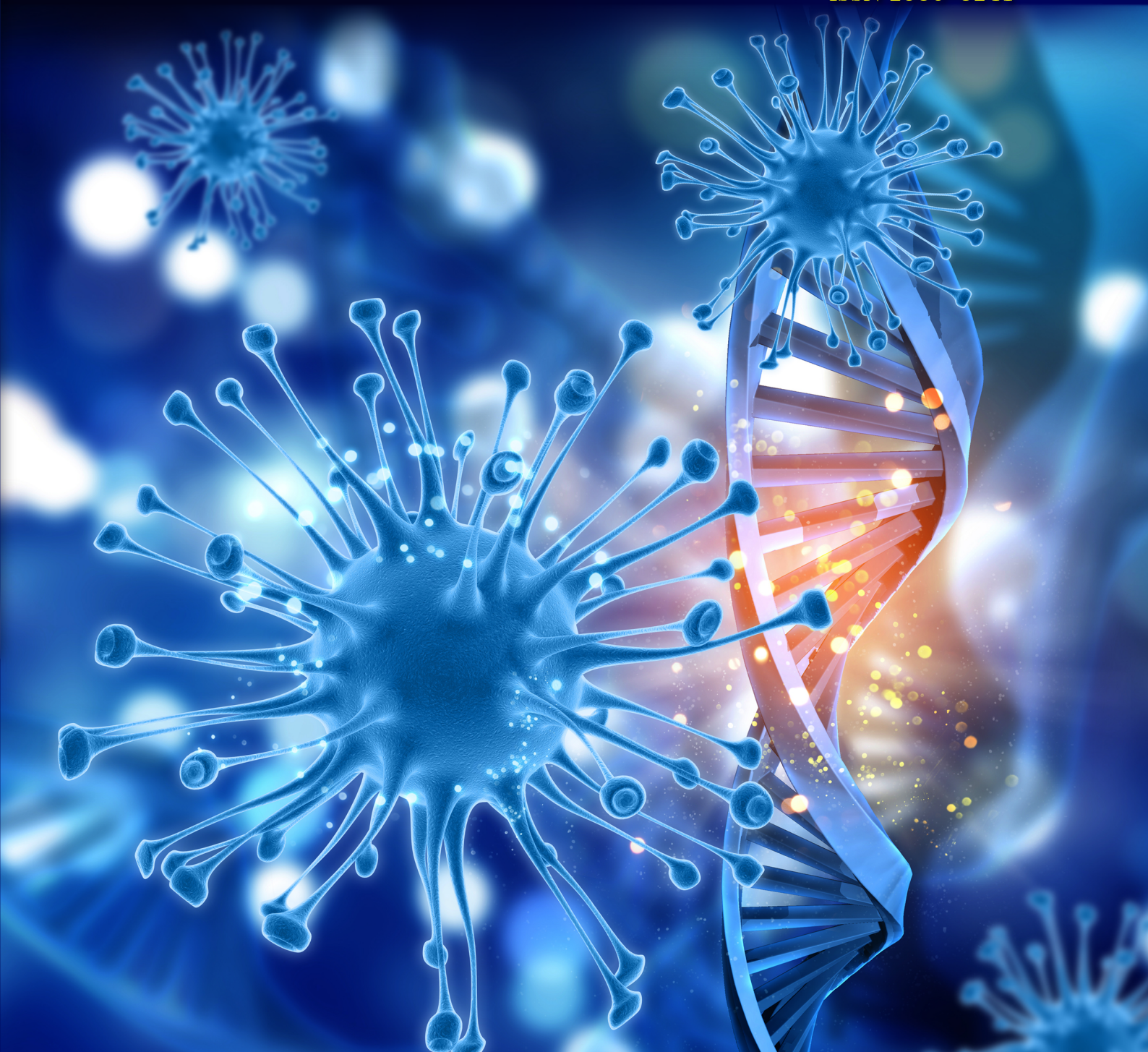

Introduction

The Journal of Southeast Asian Medical Research is a peer-reviewed journal with printing every 6 months. The main goal of this collaboration project is to distribute new knowledge in medical sciences to medical communities and scientists, as well as encouraging scientific collaborations within Southeast Asia and also other nations around the world. The journal publishes original research in the medical sciences: clinical and basic. We welcome original articles from across the world. The editorial board consists of international experts in various fields of medicine, ranging from internal medicine to a variety of surgeries. The full text of the journal is available online at http://www.jseamed.org

It is our aim to publish the most up-to-date and useful research information in medical sciences. In Southeast Asia, there are some unique problems in health care and diseases, such as tropical diseases, and it is crucial that health professionals can access, share and exchange knowledge promptly. In this region, there is still a gap of knowledge in health sciences that needs to be closed by scientific research, which we are hoping to close after this collaboration project. We hope that the journal will fulfill the objectives and will provide benefit to all, both medical practitioners and researchers alike.

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A.Original Article

CUTOFF VALUE OF TWO-POINT DISCRIMINATION DISTANCES IN CARPAL TUNNEL SYNDROME

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Abstract

Background: Two-point discrimination test (2PD) represents large sensor fiber, which is more sensitive than smaller fiber to detect abnormality in carpal tunnel syndrome (CTS). Few studies have focused in 2PD to diagnose CTS.

Objective: The study aimed to establish the cutoff value of 2PD to determine CTS.

Methods: A descriptive diagnostic study was conducted at the Outpatient Department of Rehabilitation Medicine, Phramongkutklao Hospital. Participants who were suspected of having CTS were included in the study. All participants performed the 2PD test at the thumb, index finger and middle finger. The nerve conduction studies were performed and definitive diagnosis of CTS was based on the results. Data were analyzed using the receiver operation coefficient curve.

Results: Of 48 participants (total of 95 hands), CTS was diagnosed in 85 hands (89.5%). Additionally, of all CTS hands, severity was mild degree in 17 hands (28.4%), moderate degree in 31 hands (32.6%) and severe degree in 37 hands (39%). The optimum cutoff values were >4 mm having the sensitivities of 75.3, 68.2 and 68.2% while the specificities were 80, 90 and 90%, respectively, for the thumb, index finger and middle finger. The areas under curve were 0.826, 0.833 and 0.823, respectively.

Conclusion: The participants with more than 4 mm of 2PD at the thumb, index finger and middle finger had high probability of having CTS.

Keywords: Two-point discrimination test, Carpal tunnel syndrome, Sensory testing

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Introduction

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy. [1, 2] Classic clinical characteristics of CTS include numbness and tingling along the median sensory distribution and weakness or atrophy of the thenar muscle. Most patients reported nocturnal pain. Diagnosis of CTS involves a combination of several physical examinations and electrophysiological data obtained from nerve conduction study (NCS) of the median nerve. [3-6] NCS provides excellent validity and reliability and is accepted as the gold standard for diagnosing CTS. [7-9]

Most patients report sensory symptoms in early stage of CTS[6] Larger sensory fiber is more sensitive than smaller fiber to detect abnormality.[10] Two-point discrimination (2PD) is the most widely-used and reliable test.[11, 12] Despite many studies evaluating the validity and reliability of 2PD, the cutoff point to diagnose CTS using this pragmatic test remains unclear. [13-18] This study aimed to establish the cutoff value of the 2PD test to determine CTS.

Methods

Population

This study recruited Thai patients who were suspected of having CTS and were sent to the Rehabilitation Department, Phramongkutklao Hospital. Eligible patients aged 20 to 80 years having at least one of the following signs and symptoms were recruited in the study:[19] 1) numbness or tingling of the hand(s) at rest, 2) numbness or tingling sensation of the hand(s) during light activity, 3) flicking of the hand(s) that improves numbness or tingling or 4) weakness of the hand(s). Participants, receiving a diagnosis of peripheral neuropathy, experiencing altered consciousness, cervical radiculopathy or rheumatic diseases including bone fracture, steroid injection or hand(s) surgery, were excluded. Participants signed consent forms to participate in the study. The study protocol was approved by the Institutional Review Board of the *Royal Thai Army Medical Department* (IRBRTA 016/2560).

Sample size determination

The sample size was calculated based on the sensitivity and prevalence from the study of Ziswiler HR. et al, [20] and MacDermid JC. et al. [16, 17] The sample size totaled 92 hands with suspected CTS to provide 5% type-I error and 10% type-II error.

Two-Point Discrimination

Basic characteristic data were obtained. Patients were asked to sit relaxed and place the affected hand on the bed. After closing their eyes, the Touch Test® Two-point discriminator **(Figure 1)** was used set perpendicular to the tip of the thumb, index and middle fingers. The examiner started with 2 mm and increased by 1 mm until patients discriminated 2 points and recorded the distance.[21] An intraining physiatrist resident obtained all basic characteristic data and the 2PD test. The 2PD test was conducted before performing the nerve conduction study.

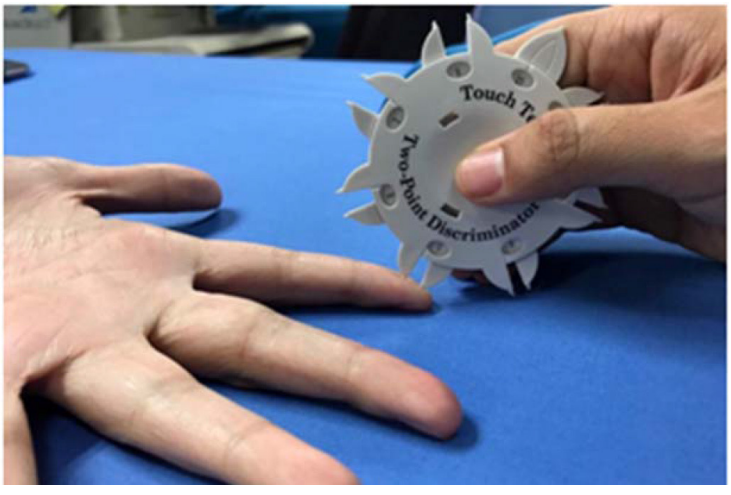

Figure 1. Touch Test® Two-point discriminator

Table 1. Electrodiagnosis classification of CTS

	no CTS	**Mild CTS**	**Moderate CTS**	**Severe CTS**
sensory latency	normal	prolonged	prolonged	prolonged or absent
sensory amplitude	normal	normal	normal	low or absent
motor latency	normal	normal	prolonged	prolonged or absent
motor amplitude	normal	normal	normal	low or absent

Table 2. Sensitivity, specificity, and predictive value of each cutoff value of the thumb

Criterion (mm)	Sensitivity	95% CI	Specificity	95% CI	PPV	NPV
Thumb						
>2	97.65	91.8 - 99.7	10	0.3 - 44.5	90.2	33
>3	89.41	80.8 - 95.0	30	6.7 - 65.2	91.6	25
>4	75.29	64.7 - 84.0	80	44.4 - 97.5	97	27
>5	55.29	44.1 - 66.1	100	69.2 - 100.0	100	20.8
>13	0	0.0 - 4.2	100	69.2 - 100.0		10.5
Index finger						
> 2	96.47	90.0 - 99.3	10	0.3 - 44.5	90.1	25
> 3	83.53	73.9 - 90.7	70	34.8 - 93.3	95.9	33
> 4	68.24	57.2 - 77.9	90	55.5 - 99.7	98.3	25
> 5	51.76	40.7 - 62.7	90	55.5 - 99.7	97.8	18
> 6	36.47	26.3 - 47.6	100	69.2 - 100.0	100.0	15.6
>13	0	0.0 - 4.2	100	69.2 - 100.0		10.5
Middle finger						
> 2	95.29	88.4 - 98.7	0	0.0 - 30.8	89	0
> 3	83.53	73.9 - 90.7	60	26.2 - 87.8	94.7	30
> 4	68.24	57.2 - 77.9	90	55.5 - 99.7	98.3	25
> 5	52.94	41.8 - 63.9	100	69.2 - 100.0	100.0	20
> 14	0	0.0 - 4.2	100	69.2 - 100.0		10.5

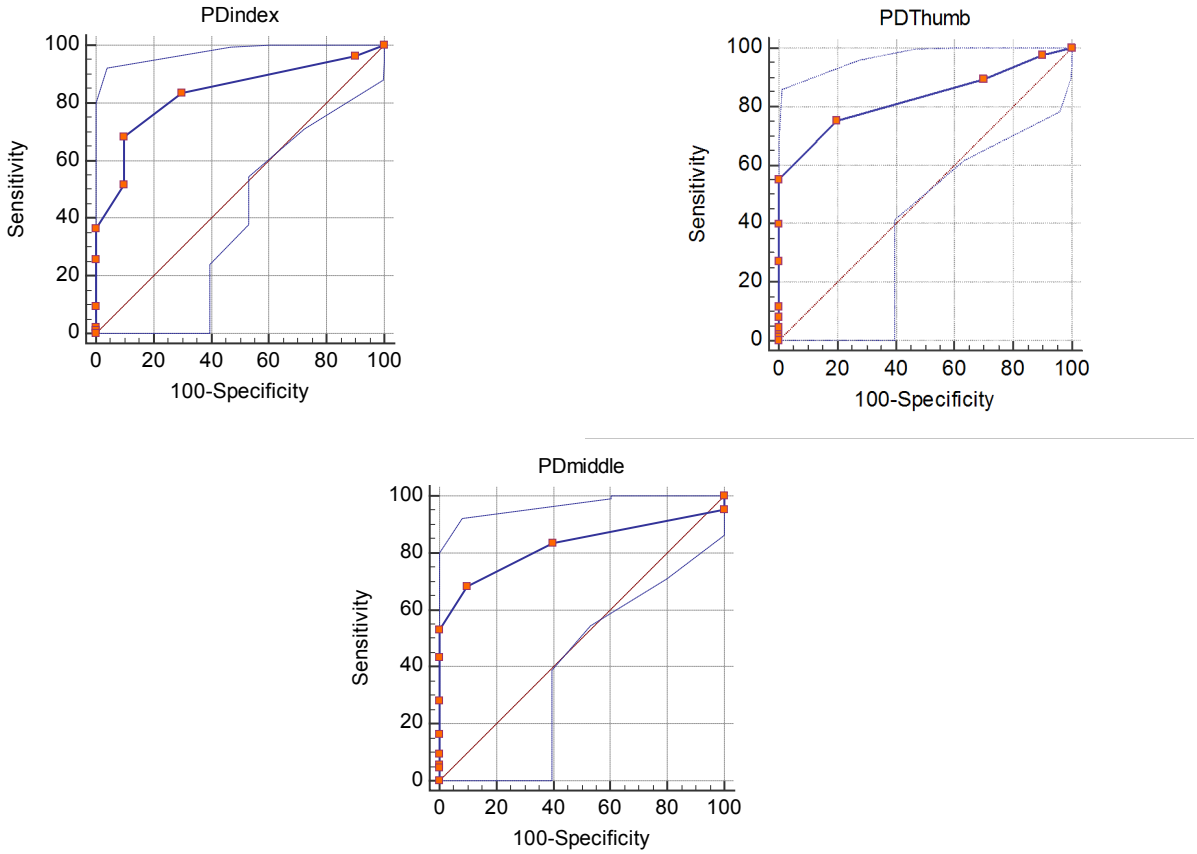

Figure 2. Receiver Operation Coefficient (ROC) curve of the 2PD test of each finger

Nerve conduction studies

A single physiatrist who was blinded to the 2PD results performed NCS on the same day of 2PD. A standard electrodiagnosis machine (Medelec Synergy T5EP model, Oxford Instruments, Oxfordshire, UK) was used. Sensory NCS was performed at the 14-cm antidromic sensory median and ulnar nerve[22, 23] for peak latency and amplitude. Normal values for the median nerve were 3.6 ms and 10 μV, respectively. Motor NCS was performed at 8-cm orthodromic median and ulnar nerve to determine distal motor latencies, amplitude and nerve conduction velocity. Normal values were 4.2 ms and 5 mV, respectively. The NCS results were classified in four groups: none, mild, moderate and severe CTS. [24]

Statistical analysis

The overall diagnostic value of 2PD was evaluated by the area under the receiver operator characteristics (ROC) curve using MedCalc Statistic Software, Version 18.2.1. The data was analyzed for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) across a range of the 2PD from 2 mm in 1 mm incremention. Spearman's rank correlation coefficient was used to assess the relationship between 2PD and CTS severity.

Results

The 2PD was positively correlated with severity of CTS with r = 0.48, r = 0.51, r = 0.49 in the thumb, index, and middle fingers, respectively. Of the 95 hands (48 participants), most were female (77.1%) with mean age of 57.8±12.2 years. The number of patients presenting bilateral, left hand and right hand symptoms were 52.1, 29.9 and 25.0%, respectively. Diabetes Mellitus was noted in 16.7%, and CTS was diagnosed in 85 hands (89.47%). Of all 85 hands with CTS 28.4 (17 hands), 32.6 (31 hands) and 38.9% (37 hands) were documented as mild, moderate, and severe CTS, respectively. According to the ROC curve, a >4 mm 2PD could be used as the best cutoff value between the sensitivity and specificity for the thumb (75.3%, 80%), index (68. 2%, 90%), and middle (68.2%, 90%) fingers. In addition, 4 mm cutoff value showed PPV 97 to 98.3% and NPV 25 to 27%. **(Table 2 and Figure 2)**

Discussion

The 2PD test and CTS severity exhibited moderate positive correlation. This result correlated with a related study by Elfar et al. [22] who reported r = 0.48. This is the first study to determine the cutoff value of 2PD in diagnosing CTS. However, the cutoff value in this prospective study differed from related studies[18, 25]. Elfar et al. evaluated 2PD in 40 CTS hands and reported a mean 2PD value of the middle finger as 6.07 mm. Diagnostic value and cutoff point from ROC were not reported in that study. However, race and nationality may have affected the 2PD test result. Regarding nerve injury of the upper extremity, Vorawanthanachai et al. recommended >4 mm to diagnose ulnar neuropathy at the elbow.[26] The cutoff value in this study was similar to that of Wolny et al.[27], reporting mean 2PD in the index and middle fingers as 4.75±1.33 and 3.83±0.85, respectively.

The 2PD test has high sensitivity and specificity. Using 4 mm cutoff point provided the highest sensitivity (75.3%) in the thumb and the greatest specificity in the index and middle fingers (90%). These results resembled those of a study of other provocative tests in Thailand. Khanittanuphong reported the modified phalen test had a sensitivity of 70%, and the carpal compression test had a specificity of 85% to diagnose CTS.[28]

The 2PD test could be used in addition to standard physical examination to diagnose CTS because this test did not provoke uncomfortable symptoms in patients. However, the 2PD test was unable to grade severity of CTS.

Interestingly, the 2PD at the index finger increased the sensitivity to 83.5% but the specificity reduced to 70% when the cutoff point changed to 3 mm. The sensitivity and specificity of 3 mm had more power to rule out CTS.

A review article published by Macdermid et al. reported low sensitivity (24%) and high specificity (95%) of the 2PD at the cutoff value of 5 mm.[29] The cutoff value was equal to the present study while the diagnostic values differed. However, among those published articles from 1984 to 1992, the gold standard of diagnosis and electrodiagnosis machine differed from that of the present.

In this study, 2PD and NCS were conducted on the same day. The physical examiner and electromyographer were blinded to each other's results. This study evaluated patients suspected of having CTS with few nonCTS patients for comparison. Thus, selection bias also affected NPV and PPV in this study. Additionally, a lack of test-retest reliability and interpersonal reliability might have posed an important limitation. The force of testing 2PD by single examiner might have been unstable.

Conclusion

Patients with symptoms of CTS, having 2PD test result >4 mm of the first 3 digits had a high probability of CTS. The severity of CTS might not be determined by 2PD test.

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EFFECT OF RENAL SPECIFIC ORAL NUTRITION (ONCE RENAL) ON DIETARY INTAKE AND SERUM ELECTROLYTES IN CHRONIC KIDNEY DISEASE STAGE IV

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Abstract

Background and Objective: Low nutritional intake is common in advanced chronic kidney disease (CKD) and poses a direct risk for malnutrition. Our study evaluated the effects of a renal specific oral nutrition (ONCE Renal) supplement concerning nutritional status, minerals and electrolytes among patients with stage IV CKD.

Methods: A total of 32 patients with CKD with an estimated glomerular filtration rate 16-29 mL/min/1.73 m^2, well-nourished subjects and anticipated good compliance with the diet received the ONCE Renal diet instead of 1 meal daily for 30 days. Dietary protein and energy intake, body compositions, and serum concentrations of urea, creatinine, calcium, magnesium, phosphate and albumin were assessed at baseline, and at 30 days. A dietary intake by three-day food record was also evaluated by a registered dietitian.

Results: At the end of 30 days, significant improvements in energy, fat, fiber and magnesium intake by dietary interview were noted. In addition, the patients also increased body weight and body mass index after supplement. No significant changes in renal function, serum electrolytes, calcium, phosphorus, magnesium concentration and other nutritional markers including serum albumin, body compositions and protein equivalence of total nitrogen appearance were observed during study. The compliance with the ONCE Renal diet was good among enrolled patients and no adverse reactions were found.

Conclusion: Renal specific oral diet supplement can improve energy intake, body weight and maintain serum electrolyte concentrations among patients with stage IV CKD.

Keywords: Renal specific oral nutrition, Low protein diet supplement, Chronic kidney disease, Serum electrolytes, Nutritional status

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INTRODUCTION

Malnutrition and chronic inflammatory state are common among patients with advanced chronic kidney disease (CKD) and are associated with increased hospitalization and mortality rates.[1, 2] Strong relationships exist among malnutrition, inflammation and atherosclerosis in CKD. The major causes of malnutrition in CKD include reduced food intake and appetite due to effects of uremia, reduced absorption of nutrients, metabolic acidosis, increased protein loss from chronic inflammation and oxidative stress.[3, 4]

Suboptimal dietary intake and resting energy expenditure is increased among patients with advanced CKD and hemodialysis with severe hyperparathyroidism.[5-7] Therefore, these populations are susceptible to insufficient energy intake with energy intakes below 30 kcal/kg/day.[8] Oral nutritional supplementation is one of treatment options in these populations. Specific renal diets, designed to increase caloric and fiber intake without high protein, electrolytes and mineral load, are expected to improve energy intake and nutrition status without significant electrolyte abnormality.

Early evaluation and intervention concerning dietary intake may help to prevent malnutrition and CKD progression before and after commencing renal replacement therapy. Currently, dietary supplements among patients with advanced CKD can be challenging to health care teams and patients. Most patients with advanced CKD and undergoing hemodialysis have lower than normal dietary energy intake, and oral nutrition supplements are further needed to achieve intake recommendations.[9,10] Currently, no consensus guidelines exist on the specific type of oral nutrition supplements and dietary approaches mentioned and strong evidence remains lacking.[11] This study aimed to determine the effects of a renal specific oral nutrition (ONCE Renal) diet on biochemical intake, calcium, magnesium, phosphate metabolism, nutrition markers and compliance with the prescribed diet among patients with advanced CKD for 30 days.

MATERIALS AND METHODS

Our prospective interventional study was conducted at Phramongkutklao Hospital, Bangkok, Thailand, from August to December 2018. All patients were recruited from the outpatient center, examined by the same physician and counseled by the same registered dietitian during the study. This project was approved by the *institutional review board* of the *Royal Thai Army Medical Department* (S005h/61) and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from participants.

Inclusion criteria for subjects with CKD aged 18 to 75 years was estimated glomerular filtration rate (eGFR) of 15 to 29 mL/min/1.73 m^2 (stages 4 CKD) and those who had <10% change in GFR within 3 months, well-nourished subjects (Subjective Global Assessment score A/B and serum albumin ≥3.5 g/dL) and consented to participate in the study. Patients with CKD with active malignancy, severe heart, lung or liver disease, chronic HIV, hepatitis B virus or hepatitis C virus infection, malnourished conditions defined as a loss of ≥5% body weight over the past 3 months or serum albumin concentration <3.5 g/dL were excluded from the study.

Baseline information including age and sex of participants was obtained. All participants were interviewed, physically examined, and investigated for underlying medical illness. Weight was measured using a weighing scale and height was measured using a stadiometer to the nearest centimeter with subjects before and after treatment. The body mass index (BMI) was calculated using the formula: Weight/$(Height)^2$ (kg/m^2). Casual systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a standard mercury sphygmomanometer applied on the same arm after a 10-minute rest in the sitting position.

About 7 mL of venous blood after an 8-hour fast was obtained from patients to perform biochemical tests including fasting plasma concentrations of blood urea nitrogen (BUN), creatinine, electrolytes, calcium, phosphorus, magnesium and albumin before and after treatment. All participants performed self-directed 24-hour urine collections for protein, sodium, potassium, magnesium and chloride. Serum and urine creatinine samples were analyzed using the enzymatic method. GFR, using the CKD-EPI equation based on serum creatinine, was calculated.

Table 1. Contents of the ONCE Renal Supplement

Macronutrient	**1 serving or 76 g (360 kcal)**
Caloric Distribution of Macronutrients (%)	
- Protein	8%
- Carbohydrate	52%
- Fat	40%
Source	
Protein	7.19 g
1. Casein	3.595 (50%)
2. Soy protein isolate	3.595 (50%)
Carbohydrate	48.25 g (fiber 2.99 g)
1. Maltodextrin	31.3 (64.88%)
2. Isomaltulose	9.97 (20.66%)
3. Fructose	3.99 (8.27%)
4. Fibersol	1.99 (4.13%)
5. Fructooligosaccharides	1.00 (2.06%)
Fat	15.95 g
1. Canola oil	6.98 (43.74%)
2. High oleic safflower oil	2.99 (18.77%)
3. Medium chain triglycerides oil	5.98 (37.49%)
Micronutrient	
Vitamins & Minerals	
Vitamin A (mcg RE)	67.43
Vitamin D (IU)	15.20
Vitamin C (mg)	36.27
Calcium, mg	143.6
Phosphorus, mg	143.6
Magnesium, mg	39.06
Potassium, mg	197.4
Sodium, mg	132.8
Carnitine, mg	99.71
Others	As Thai RDI recommendation

Body composition was evaluated using direct segmental multi-frequency bioelectrical impedance analysis (DSM-BIA, In-Body (720) body compositions analyzer). The spectrum of electrical frequencies was used to predict the body composition, total fat mass, intracellular (ICW) and extracellular water (ECW) compartments of the total body water (TBW) in the various body segments. Body composition was assessed at baseline and at the end of the study period.

Dietary Intervention

All participants were provided 360-kcal sachets of ONCE Renal supplement containing 7.19 g of proteins, 48.25 g of carbohydrate with fiber 2.99 g, 15.95 g of fat, 143.6 mg of calcium, 143.6 mg of phosphorus, 197.4 mg of potassium and 132.8 mg of sodium (Table 1) instead of 1 meal daily for 30 days. Additional 30 ONCE Renal supplement sachets were provided at first visits, and empty sachets were collected to determine compliance.

All participants kept a 3-day food record and underwent dietary interviews by a registered dietitian, before and after the study period. Nutrient composition of the diets was analyzed using the standard national food database program (Inmucal Version 3.2). Daily protein intake was determined using the calculated protein equivalence of total nitrogen appearance (PNA).

Statistical Analysis

Data were analyzed using the statistical package for social sciences (SPSS), Version 16.0 (SPSS, Chicago, IL, USA). Continuous variables were presented as means and standard deviation and discrete variables were presented as percentages. Comparisons against the baseline measurements were evaluated using the paired *t*-test while *P* values <0.05 were considered significant.

RESULTS

We reviewed the eligibility criteria of 62 patients, and 32 patients were recruited during the period of study, consisting of 15 men and 17 women with mean age 66.4± 11.9 years. Hypertension (84.4%), dyslipidemia (81.3%) and type 2 diabetes (33.3%) were common comorbid diseases. Baseline participant characteristics are shown in **Table 2**.

Table 2. Characteristics of the study population

Characteristics	**N=32**
Men (N, %)	15 (46.9%)
Age (yr)	66.4± 11.9
Height (cm)	161.0±8.9
Body weight (kg)	66.4±13.6
Body mass index (kg/cm^2)	25.5±3.5
Blood urea nitrogen (mg/dL)	34.6±11.7
Serum creatinine (mg/dL)	2.6±0.6
Estimated glomerular filtration rate (mL/min/1.73 m^2)	22.1±6.0
Serum albumin (g/dL)	4.4±0.3
Comorbid disease (N, %)	
- Diabetes mellitus	11 (33.3%)
- Hypertension	27 (84.4%)
- Gout	8 (24.2%)
- Dyslipidemia	26 (81.3%)

Values presented as n (%) and mean±SD.

Table 3. Dietary intake with three-day food record at baseline and the end of one month follow-up

Per day	Nutritional Recommendation in CKD stage III-IV	Baseline	End	Mean Change (95%CI)	*p*-value
Energy (kcal)	-	1292.9±392.6	1462.3±281.1	169.4 (57.1 to 281.7)	0.004
Energy (kcal/kg/day)	30-35	19.8±6.1	22.5±5.3	2.7 (0.9 to 4.5)	0.005
Protein (g)	-	49.2±15.1	47.4±15.9	-1.8 (-4.2 to 7.7)	0.551
Protein (g/kg/day)	0.6-0.8	0.7±0.2	0.7±0.3	0.02 (-0.1 to 0.1)	0.595
Carbohydrate (g)	-	190.4±56.4	201.7±45.1	11.3 (-4.5 to 23.7)	0.114
Fat (g)	Saturated fat <7% Trans fat <1%	40.7±14.9	50.9±15.2	10.1 (4.9 to 14.3)	<0.001
Fiber (g)	25-38	8.8±3.2	11.0±3.7	2.2 (0.8 to 3.2)	<0.001
Sodium (mg)	<2,300	2331.1±1016.7	2112.6±1278.1	207.4 (-297.9 to 712.7)	0.409
Potassium (mg)	<1,500 with hyperkalemia	1242.6±537.7	1219.9±353.9	29.6 (-143.9 to 203.2)	0.730
Calcium (mg)	-	372.7±171.2	415.5±198.0	49.1(-123.7 to 25.6)	0.190
Phosphorus (mg)	<800-1,000 with hyperphosphatemia	518.9± 227.1	600.2±188.3	81.2 (-167.4 to 5.1)	0.064
Magnesium (mg)	-	56.5±45.9	80.6± 26.3	25.0 (10.4 to 39.7)	0.001

Values presented as Mean±SD. and Mean change (95%CI). p-value corresponds to Paired t-test.

Table 4. Comparison of two regular meals per day without the ONCE renal supplement at aseline and at the end of study

Per day	Baseline	End	Mean Change (95%CI)	*p*-value
Energy (Kcal)	900.8 ± 287.7	923.2 ± 287.6	22.3 (-104.8, 60.2)	0.585
Energy (kcal/kg/day)	13.9 ± 4.8	13.9 ± 4.1	0.05 (-12.9, 1.2)	0.935
Protein (g)	38.1 ± 19.9	41.5 ± 23.9	3.3 (-7.7, 1.1)	0.133
Protein (g/kg/day)	0.8 ± 0.3	0.6 ± 0.3	0.04 (-0.1, 0.02)	0.229
Carbohydrate (g)	126.4 ± 55.1	120.7 ± 49.4	-5.6 (-7.2, 18.5)	0.378
Fat (g)	26.6 ± 10.3	30.3 ± 14.1	3.67 (-8.2, 0.8)	0.106

Values presented as Mean±SD. and Mean change (95%CI). p-value corresponds to Paired t-test.

Energy and Nutrient Intake

Table 3 shows the mean values for estimated energy and nutrient intake at baseline and at week 4. A significant increase in energy intake from 19.8±6.1 to 22.5±5.3 kcal/kg/day (p=0.005), fat intake from 40.7±14.9 to 50.9±15.2 g/day (p<0.001) and fiber intake from 8.8±3.2 to 11.0±3.7 g/day (p<0.001) were observed during the study. No significant change was found in dietary protein, carbohydrate, sodium, potassium, calcium and phosphorus intake after intervention except significant increase in magnesium intake [25.0 (95% CI 10.4 to 39.7) g/day, p=0.001]. We also determined that energy and nutrient intake from regular food (2 meals daily) was similar at baseline and at the end of the study **(Table 4)**.

Table 5. Nutritional, electrolyte, mineral and renal parameters at baseline and at the end of four-week follow-up

Variables	Baseline	End	Mean Change (95%CI)	*p*-value
Nutrition parameters and body compositions				
Body weight (kg)	66.4±13.6	66.9±13.3	0.45 (0.74 to 0.84)	0.021
Body mass index (kg/cm2)	25.5±3.5	25.6±3.4	0.17 (0.22 to 0.32)	0.026
Serum albumin (g/dL)	4.4±0.3	4.5±0.3	0.03 (-0.12 to 0.65)	0.557
Percentage of total body water (%)	46.9±5.9	46.7±5.5	-0.25 (-0.42 to 0.90)	0.453
Percentage of body fat (%)	30.4±8.2	30.8±7.6	0.39 (-1.48 to 0.70)	0.466
Muscle mass (kg)	43.9±10.8	42.6±10.5	-1.36 (-1.38 to 4.10)	0.319
Bone mass (kg)	3.2±3.7	3.2±3.8	0.01 (-0.09 to 0.66)	0.748
Protein equivalence of total nitrogen appearance (g/kg/day)	0.7±0.2	0.7±0.2	-0.06 (-0.01 to 0.12)	0.095
Renal function, serum electrolytes and minerals				
Blood urea nitrogen (mg/dL)	34.6±11.7	34.3±11.3	-0.34 (-1.64 to 2.33)	0.726
Serum creatinine (mg/dL)	2.6±0.6	2.5±0.6	-0.07 (-0.15 to 0.01)	0.109
Estimated glomerular filtration rate (mL/min/1.73 m^2)	22.1±6.0	22.9±6.3	0.77 (-2.56 to 1.02)	0.387
Sodium (mEq/L)	137.5±22.6	140.9±1.7	3.46 (-11.50 to 4.58)	0.387
Potassium (mEq/L)	4.6±0.4	4.5±0.5	-0.09 (-0.05 to 0.24)	0.193
Bicarbonate (mg/dL)	23.8±2.5	24.3±2.6	0.55 (-1.34 to 0.25)	0.171
Calcium (mg/dL)	9.4±0.5	9.3±0.4	-0.02 (-0.11 to 0.16)	0.718
Phosphorus (mg/dL)	3.7±0.5	3.7±0.5	0.03 (-0.18 to 0.13)	0.701
Magnesium (mg/dL)	2.8±3.6	2.2±0.2	-0.65 (-0.66 to 1.96)	0.316
24-hr urine protein, electrolytes and minerals				
Protein (g/day)	0.9±1.1	1.0±1.3	0.06 (-0.22 to 0.10)	0.472
Sodium (mEq/day)	90.4±36.2	97.7±67.1	7.37 (-31.04 to 16.30)	0.530
Potassium (mEq/day)	17.3±7.3	17.3±7.3	-0.01 (-2.76 to 277)	0.998
Magnesium (mEq/day)	3.8±1.8	3.9±1.7	0.05 (-0.62 to 0.51)	0.858
Chloride (mEq/day)	71.4±34.7	78.7±71.5	7.33 (-34.23 to 16.57)	0.582

Values presented as Mean±SD. and Mean change (95%CI). p-value corresponds to Paired t-test.

Nutrition and body compositions

A significant increase in body weight with a mean difference of 0.45 (95% CI 0.74 to 0.84, *p*=0.021) kg and BMI with a mean difference of 0.17 (95% CI 0.22 to 0.32, *p*=0.026) kg/cm^2 were observed after 30 days. No significant changes in serum albumin, PNA and body compositions were found at the study endpoint **(Table 5)**.

Serum and Urine Biochemical Measurement

At the end of the study, the treatment did not significantly change the concentrations of renal function, serum sodium, potassium, bicarbonate, calcium, phosphorus, and magnesium. No significant differences were observed in 24-hour urine protein, electrolytes and minerals before and after treatment. During the study, no serious complications were observed especially electrolyte disturbances and fluid overload. At the study's completion, patient compliance, receiving the ONCE Renal supplementation on schedule, was 99.7%

Discussion

The results of our study showed that the daily use of a 360-kcal ONCE renal supplement for 30 days improved energy, fat, fiber, and body weight among patients with stage IV CKD, indicating

that the use of these supplement had beneficial effects on dietary nutrient intake without short term electrolytes disturbance.

Loss of appetite, poor food intake, anorexia and vomiting are more common symptoms among patients with advanced CKD; hence, predisposing them to malnutrition. Several studies have indicated that minimum calorie requirements were not met among patients with advanced |CKD, despite dietary nutritional counseling.[8] Enriched nutritional supplements might improve dietary intake and malnutrition. However, limited evidence exists pertaining to the impact of nutritional supplementation in preventing malnutrition and improving quality of life among patients with CKD and undergoing dialysis.[12, 13] Most clinical guidelines preferred oral nutritional supplements as first line treatment to increase caloric and protein dietary intake at 25 to 30 kcal/kg/day and 0.55 to 0.6 g/kg/day in advanced CKD.[14, 15] Our study indicated that the ONCE Renal diet significantly improved energy and fiber intake and maintained nutritional markers among patients with advanced CKD. This study was consistent with results found in other studies and a systematic review demonstrating effectiveness of renal dietary intervention for patients with advanced CKD and dialysis populations.[16-20] Studies are limited concerning the efficacy of specific renal supplement in a long term study and among significantly malnourished patients with CKD .

Medical nutrition therapy by a registered dietitian experienced in predialysis CKD improved nutrition-related biomarkers,[21], but energy and dietary component targets may be difficult to achieve with dietary counseling alone.[22] An additional benefit of the ONCE Renal supplement is the low amount of protein (7.2 g/360 kcal), sodium ((132 mg/360 kcal), phosphate (143 mg/360 kcal), potassium (197 mg/360 kcal) and magnesium (39 mg/360 kcal) content. As a consequence, serum potassium, magnesium and phosphate did not increase after treatment, which was of significant benefit to patients. Moreover, our study indicated that the ONCE Renal diet supplement instead of 1 regular meal could achieve the therapeutic targets of dietary intake with an average dietary sodium intake of 2.1 g/day, average 24-hour urine sodium of 98 mEq/day, average dietary potassium intake of 1.2 g/day, average 24-hour urine potassium of 17 mEq/day, average dietary phosphorus intake of 0.6 g/day and average dietary magnesium intake of 80 mg/day in addition to dietary counseling. The ONCE Renal supplement did not increase risk of electrolyte abnormality among patients with advanced CKD.

Inadequate energy and excess protein intake were correlated with worsening renal function in CKD[23] and ensuring compliance is the main target for effective nutritional intervention.[24] Related studies have shown that about 40 to 50% of patients with CKD follow the recommended diets.[25, 26] In contrast to our study, compliance was very good; 99% of patients complied with the ONCE Renal supplementation for 30 days, improving an average additional caloric intake with low amount of protein (7.2 g/360 kcal). The high percentage of compliance may reflect the type of patient selection in our study in that they received the intervention based on their excellent reputation for nutritional management. Therefore, the ONCE Renal diet was convenient for educated patients with CKD unable to choose an appropriate low protein renal diet to maintain adequate energy intake. However, patient compliance was limited by the relatively short period of follow-up.

The study had a few limitations. First, the study design was not randomized or placebo-controlled. Second, the INMUCAL program could not represent all micronutrients completely, especially magnesium (validity 36.3%).[28] Therefore, the amount of magnesium was shown lower than usual diets. Furthermore, the study was conducted in an outpatient clinic setting, and a 3-day dietary recall was used to estimate food intake. The validity of this method could be questioned because the day-to-day food intake may have varied, and it may not be representative of a usual diet.

In conclusion, the results provided some beneficial effects of a renal-specific oral nutritional support combined with nutritional counseling among patients with advanced CKD. The ONCE Renal diet improved energy, fiber and magnesium intake without significant short term abnormal electrolyte disturbance. This intervention might require larger studies in other groups of patients with CKD with longer duration of the ONCE Renal supplement.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Individual clinical data used to support the findings of this study are available from the corresponding author upon request.

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COMPARISON BETWEEN IMAGE-FREE ROBOTIC ASSISTED AND CONVENTIONAL TOTAL KNEE ARTHROPLASTY: POSTOPERATIVE CT ASSESSMENT OF ALIGNMENT

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Abstract

Background: Navio Surgical System, a newer-generation robotic technology, is an image-free robotic-assisted total knee arthroplasty (TKA) offering several advantages over older versions, including CT scan, the potential to dynamically assess soft tissue over a range of motion and the ability to use haptic control in bone preparation.

Objective: The study aimed to compare the accuracy of component alignment between image-free robotic-assisted and conventional TKA.

Methods: Forty patients were randomly assigned to two groups, 20 image-free robotic-assisted and 20 conventional TKA. The primary outcome was prosthetic alignment including mechanical axis alignment, epicondylar axis alignment and posterior tibial slope. The secondary outcomes included postoperative blood loss and operative time.

Results: Significant difference were found in the postoperative mechanical axis between the image-free robotic group and the conventional group (1.15°±1° vs. 1.88°±1.19° deviated from neutral mechanical alignment, $p = 0.043$). There was significant difference in femoral rotational alignment between groups (1.00°±0.75° vs. 2.33°±0.96° deviated from the epicondylar axis, $p<0.001$). The mean posterior tibial slope did not significantly differ (3.89°±1.66° vs. 4.12°±1.37°, $p=0.639$). The operative time in the image-free robotic group was significantly longer than that of the conventional group (102.80 ± 11.18 min vs. 62.90 ± 3.28 min, $p <0.001$). Total blood loss in the image-free robotic group was significantly higher than conventional group (2.24±0.49 g/dl vs. 1.64±0.68 g/dl, $p = 0.001$).

Conclusion: Image-free robotic-assisted TKA constituted a surgical procedure which could provide better accuracy in prosthetic alignment in both mechanical axis and rotational axis compared with conventional TKA. However, the image-free robotic assisted TKA involved higher blood loss and longer operative time.

Keywords: Image-free robotic-assisted TKA, Robotic knee surgery, NAVIO, Mechanical axis alignment, Rotational axis alignment

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Introduction

Total knee arthroplasty (TKA) is a standard treatment for pain relief and restoration of joint function in the advanced arthritic knee. Studies for conventional TKA have revealed some mechanical axis outliers[1-4] affecting patient satisfaction and implant longevity;[5-8] the mechanical axis exceeding ± 3° varus/valgus deviation has been reported with abnormal force, aseptic loosening and poor long-term outcomes.[9-10] Femoral component rotational malalignment has been associated with anterior knee pain, patella-femoral maltracking and ligament balancing problems.[11-13] To improve the accuracy of component alignment, computer-assisted and robotic systems have been developed for TKA. Robotic-assisted TKA increases the accuracy of component position[14-16] and has reported only 0 to 2% of mechanical axis outliers.[14, 16-20] However, the previous generation of robotic systems were costlier and showed nonsignificant differences in clinical outcomes compared with conventional techniques.[16, 18, 20-22] Newer-generation robotic technology (Navio Surgical System) produces an image-free robotic-assisted TKA offering several advantages over older versions including CT scan, the potential to dynamically assess soft tissue over a range of motion and the ability to use haptic control in bone preparation. This novel technology has been used in unicompartmental knee arthroplasty (UKA) for several years and demonstrated superior outcomes over conventional techniques.[23] Recently, it has been approved by the US Food and Drug Administration to use in TKA. No previous clinical study of this technology used for TKA has been conducted, so a well-designed clinical trial is required to investigate its efficacy. The study aimed to compare the accuracy of component alignment between image-free robotic -assisted (Navio Surgical System) and conventional TKA.

Methods

Primary osteo-arthritis knee patients undergoing total knee arthroplasty at Phramongkutklao Hospital from August 2018 to June 2019 were recruited to the study. Forty patients were previously prospectively randomized in two groups (20 image-free robotic-assisted and 20 conventional TKAs). Patients with an instrument extended into the knee, metal device that could cause CT scatter, deformity greater than 15 degrees of varus, valgus or flexion contracture, previous ipsilateral distal femoral or high tibial osteotomies, inflammatory arthritis, ankylosis of the hip joint on the side to be treated or previous patellectomy were excluded from the study. All patients were assigned to one of the two groups (1:1), group 1 was treated with image-free robotic-assisted TKA using the Navio Surgical System (Smith & Nephew Inc.), while group 2 was treated using conventional manual implantation. In both groups, we used the standard medial parapatellar approach and the same prosthesis (legion posterior stabilized knee, Smith & Nephew, Memphis, TN, USA). The operation was performed by a single surgeon experienced in knee replacement surgery over 25 years.

Surgical technique

Image 1. 3D-model of the patient's cartilage and bone was captured using direct surface mapping by surgical probe, eliminating the need of pre-operative CT scan.

The Navio Surgical System was used in the image-free robotic assisted surgery group. Planning of implant position and bone resection were determined intra-operatively without need of pre-operative CT scan. After tracker fixation and landmark registration, range of motion and laxity mapping were performed. Anatomy of the femoral condyle and tibial plateau were mapped by painting the surfaces with an optical probe. A virtual model of the knee was thus created as shown in **Image 1**. Planning for component size, position, alignment and amount of bone removal were determined intra-operatively by the surgeon. Degenerative bone and cartilage were removed using the handheld sculptor as shown in **Image 2.** The system continuously tracked the position of the patient's lower limb and the

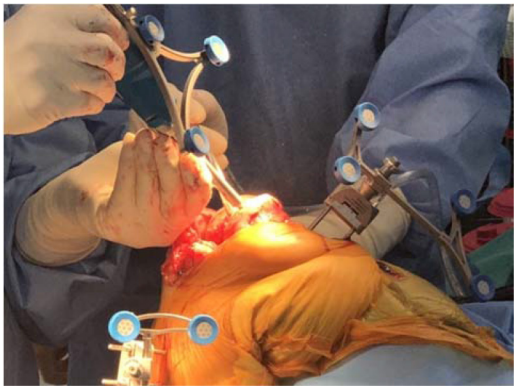

Image 2. NAVIO™ handheld burring technology removed only the bone determined by the surgeon's plan. Bone removal was seen on the NAVIO screen in real-time allowing the surgeon to continuously assess patient anatomy.

progress of bone resection using a navigation system camera.

For the conventional group, we performed the proximal tibial cut with an extramedullary guide, perpendicular to the mechanical axis and 3° posterior slope. Then an intramedullary guide was used with 5°valgus resection cut of the distal femur and external rotation was set at 3°-5° related to the posterior condyle of the femur (combined measurement and gap techniques). The patella was resurfaced in both groups. All patients received tranexamic acid 10 mg/kg, one dose after start anesthesia and one dose before skin closure with no suction drain used in all cases. The operative times were also recorded. We also collected total blood loss calculated using hemoglobin change between pre-operative period and postoperative day 4. At 6 weeks postoperative, all patients received a weight bearing radiograph of the hip-knee-ankle and CT scan of the knee.

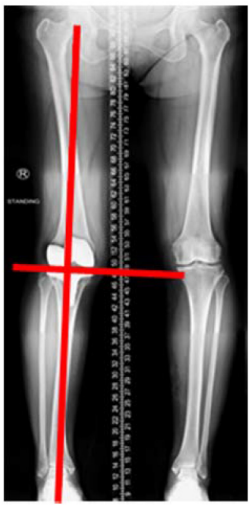

Image 3. Postoperative weight bearing radiograph was used for mechanical axis alignment measurement.

The results were evaluated by two adult reconstruction hip & knee fellows unassociated with the treatment. Inter-observer reliability was analyzed using interclass correlation coefficient. The measurement used to determine component coronal alignment was the mechanical axis from the center of the femoral head to the center of the talus **(Image 3)**. The accepted normal range of the mechanical axis did not exceed ± 3 degrees of varus/valgus deviation. For the rotational alignment, we used the epicondylar axis, line connecting the medial epicondylar sulcus and the lateral epicondylar prominence, based on the technique described by Berger et al.[24-26] **(Image 4)** The posterior tibial slope as also assessed. The chi-square test, independent t-test, Mann-Whitney U test and Fisher's exact test were used to compare baseline characteristics between groups. The analysis was performed using SPSS Software, Version 24. This study was approved by the Institutional Review Board of the Royal Thai Army Medical Department and all patients provided written informed consent.

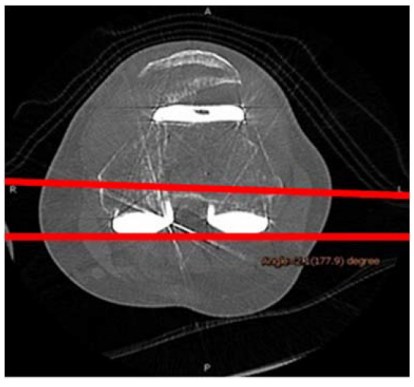

Image 4. Postoperative CT scan used for rotational axis alignment measurement.

Table 1. Demographic characteristics of enrolled participants

	Robotic gr. N=20	Conventional gr. N=20	*p*-value
Age	67.75±8.69	70.95±5.74	0.178
Sex			1.000
Male	2 (10.00%)	3 (15.00%)	
Female	18 (90.00%)	17 (85.00%)	
Body mass index (kg/m^2)	28.8±4.22	26.61±2.92	0.054

Table 2. Comparative results of component alignment, operative time and hemoglobin change

	Robotic group		Conventional group		*p*-value
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Mechanical axis	1.15° ± 1	0.8° (-1.2°-4.7°)	1.88° ± 1.19	-0.95° (-4.2°-2.8°)	0.043*
Rotational axis	1.00° ± 0.75	0.70° (-1.6°-3.1°)	2.33° ± 0.96	2.15° (-2.8° -4.9°)	<0.001*
Posterior slope	3.89° ± 1.66	3.5° (1.2- 7)	4.12° ± 1.37	4° (2°- 7°)	0.639
Operative time (min)	102.80±11.18	101 (81-126)	62.90 ± 3.28	62.5 (58-69)	<0.001*
Hemoglobin change (g/dl)	2.24 ± 0.49	2.3(1.6-3.5)	1.64 ± 0.68	1.7 (0.5-3.3)	<0.001*

Mechanical axis: Negative values stand for varus; positive values stand for valgus.
Rotational alignment: Negative values stand for internal rotation; positive values stand for external rotation.
Posterior slope: Negative values stand for anterior slope; positive values stand for posterior slope.
* Statistically significant difference

Results

No significant difference was found between groups regarding mean age of patients, sex and BMI as shown in **Table 1.**

Significant differences were found in the postoperative mechanical axis between the image-free robotic group [mean 1.15°±1° deviated from the neutral mechanical alignment (range, varus 1.2° to valgus 4.7°)] and the conventional group [mean 1.88° deviated from neutral mechanical alignment (range, varus 4.2° to valgus 2.8°), p = 0.043]. One patient (5%) in the image-free robotic group and three patients (15%) in the conventional group had mechanical axis outliers (error > ± 3°), but without statistically significant difference between groups (p = 0.605). **(Table 2) (Figure 1)** Significant differences were found in the femoral rotation alignment between the image-free robotic group [mean 1.00°±0.75° deviated from the epicondylar axis (range, internal

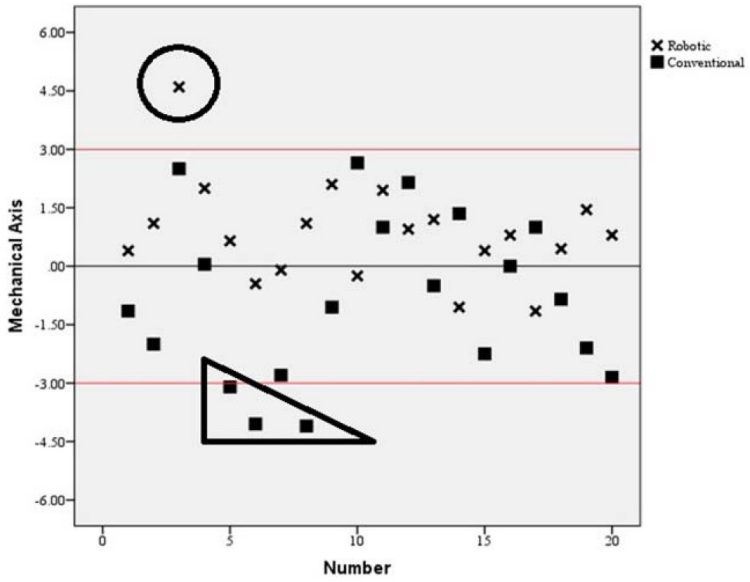

Figure 1. Graphic representation of postoperative mechanical axis comparing between the image-free robotic group and the conventional group (accepted alignment was ±3° varus/valgus deviation). Negative values stand for varus & positive values stand for valgus.

rotation 1.6° to external rotation 3.1°)] and the conventional group [mean 2.33°±0.96° deviated from the epicondylar axis (range, internal rotation 2.8° to external rotation 4.9°), $p<0.001$]. The mean posterior tibial slope showed no significant differences between both groups (3.89°±1.66° vs. 4.12°±1.37°, $p=0.639$). Significant differences were found in operative time between the image-free robotic and the conventional groups [102.80 ± 11.18 min (range, 81-126 min) vs. 62.90 ± 3.28 min (range, 58-69 min), respectively, $p<0.001$]. Mean difference time was 39.9 minutes. Mean hemoglobin change in the image-free robotic group was significantly higher than that of the conventional group [2.24±0.49 g/dl (range, 1.6-3.5 g/dl) vs. 1.64±0.68 g/dl (range, 0.5±3.3 g/dl), $p = 0.001$]. No significant differences were found in length of stay [3.30 days (range, 3-4 days) vs, 3.15 (range, 3-4 days), p=0.268] and presenting no postoperative complications such as wound infection, deep vein thrombosis or blood transfusion in both groups.

Discussion

The goal of primary TKA is to re-establish a normal mechanical axis. Conventional TKA which has been accepted as a standard treatment, performed by manual instrumentation and guided by intramedullary or extramedullary rods, as well as rotational guides that are not patient-specific. Despite continued improvement of manual instrumentation, postoperative component malalignment has still been reported. The mechanical axis of the limb in the coronal plane has been cited more than other alignment parameters.[9, 27] Jeffery et al.[28] reported outcomes after TKA among 115 patients with 24% rate of aseptic loosening when the mechanical axis exceed ± 3° valgus/varus deviation, but a rate of only 3% for the knee with an axis within 3° of neutral. The study showed that limb malalignment affected longevity of prosthesis; thus, the mechanical axis within 3° neutral in the coronal plain remains a reasonable target and should be considered as the standard treatment. Rotational alignment of the femoral component is also important because it can affect patellofemoral tracking, ligament balancing and causes anterior knee pain. Jenny JY, Boeri C et al.[29] reported mal-alignment of the femoral component up to 15° using conventional techniques. Computer and robotic-assisted technology were developed to improve the accuracy of alignment. Several studies had shown better alignment in the robotic group than in the conventional TKA. Song et al.[16] comparing the outcomes of robotic-assisted and conventional TKA in same patient, simultaneously. They found the outliers of postoperative leg alignment of the conventional side more than that of the robotic-assisted side (mechanical axis, coronal inclination of the femoral prosthesis and the sagittal inclination of the tibial prosthesis).

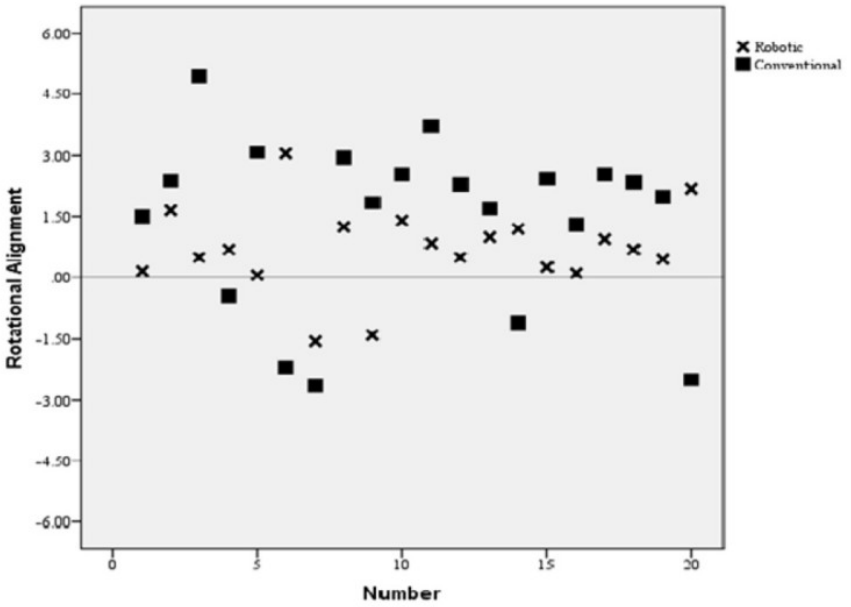

Figure 2. Graphic representation of postoperative rotational alignment comparing between the image-free robotic group and the conventional group. Negative values stand for internal rotation & positive values stand for external rotation.

Liow et al.[18] reported no mechanical axis outliers (> ± 3° from neutral) in 31 patients treated with roboticassisted TKA. The newer technology constitutes the Navio Surgical Systems, a robotic-assisted platform using CT-free technology for accurate implant sizing and positioning without the need of rods. While older generation robotic-assisted platforms require pre-operative CT scan, the Navio Surgical System works without them, meaning the patients are not exposed to the potentially harmful radiation.

In this study, we compared the newer technology image-free robotic-assisted TKA (Navio System) with conventional TKA. We found that the mean mechanical alignment and rotational alignment in the image-free robotic group was significantly closer to the mechanical axis and epicondylar axis than that of the conventional group **(Figures 1 and 2)**. The number of mechanical axis outliers was defined as an error of more than 3° varus or valgus deviation. In the robotic group only one outlier was observed (5%), and in conventional group three outliers were observed (15%), without significant difference **(Figure 1)**. These results were similar to one related study showing that the older version robotic assisted TKA exhibited greater accuracy of the component alignment than that of the conventional technique. Despite reducing the component malalignment in the robotic-assisted group, several studies have shown no difference in short term functional outcomes. The recent study of Liow et al.[30] reported a subtle improvement in patient QoL measurement in robotic-assisted TKA compared with conventional TKA at 2 years follow-up.

We observed that surgical wounds were longer in the image-free robotic group because the surgeon required more exposure for tracking fixation. The operative time and blood loss in image-free robotic group were significantly higher than that of the conventional group, probably from time consuming involving registration of the instrument and burring of bone. However, operative time and blood loss in the image-free robotic group decreased in the later case because the surgeon had gained more experience using the Navio Surgical System. Despite these issues, data demonstrated significant improvement of alignment, current disadvantages such as the need for the placement of tracking fixation, increased operating time, increased blood loss and higher overall cost that will have to be resolved in the future. Further randomized and multicenter randomized controlled trials might be required to evaluate the accuracy and clinical efficacy to support this technology. Cost effectiveness will need a long term study in which improved in component alignment could save operative cost or reduce late failure of prosthesis.

Conclusion

Image-free robotic-assisted TKA is a surgical procedure that provides better accuracy in prosthetic alignment in both mechanical axis and rotational axis compared with conventional TKA. However, the image-free robotic-assisted TKA had some disadvantages such as more blood loss, longer operative time and requiring more experience than conventional TKA

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RANDOMIZED DOUBLE-BLIND CONTROLLED TRIAL TO EVALUATE EFFICACY OF VITAMIN D SUPPLEMENTATION AMONG PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract

Objective/background: Patients with systemic lupus erythematosus (SLE) have a high prevalence of vitamin D deficiency. We aimed to assess the efficacy and safety of ergocalciferol combined with standard care among patients with SLE.

Methods: A randomized, double-blinded, placebo-controlled study was conducted among patients with SLE (N=104). The patients were randomized to receive either a higher dosage of ergocalciferol (100,000 IU of ergocalciferol weekly for 4 weeks followed by 40,000 IU of ergocalciferol weekly for 20 weeks, group A (N=52) or placebo (group B, N=52). All patients received 800 units of cholecalciferol daily for 24 weeks. Concurrent medications were adjusted as clinically required. We compared demographics, serum 25-Hydroxy vitamin D (25(OH) D) levels, SLE disease activity index (SLEDAI-2K) and treatment variables between the two groups. The outcomes were measured at baseline, 12 and 24 weeks follow-up. These outcomes included serum 25(OH) D, SLEDAI-2K, SLE flare event defined by an increase of SLEDAI-2K between 2 visits, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), urine protein creatinine ratio (UPCR), health assessment questionnaire (HAQ), the change of dosage of immunosuppressive drugs and glucocorticoids (GCS) and ergocalciferol related toxicity. Subgroup analyses were also undertaken among patients with lupus nephritis. Continuous variables between the 2 groups were compared using student's t-test whereas categorical groups were compared using the chi-square test.

Results: Of 104 patients, only 88 patients completed the study. Baseline characteristics between the 2 groups were similar. At 24 weeks, the mean ± standard difference (SD) of serum levels of 25(OH) D in group A was significantly higher than those in group B (41.2 ± 14.4 vs. 27.2 ± 10.1, $p < 0.001$). No difference was observed between groups A and B with respect to SLEDAI-2K, flare event, ESR, CRP and dosage of immunosuppressive drugs. However, at 12 and 24 weeks, the number of patients who could reduce GCS dosage in group A were significantly greater than group B (at 12 weeks, 39.6 vs. 17.6%, $p = 0.008$; at 24 weeks, 43.4 vs. 23.5%, $p = 0.013$). Subgroup analysis revealed no significant improvement of UPCR in group A compared with group B. Ergocalciferol related adverse reactions in both groups were similar. Serum calcium levels did not change within and between groups of treatment.

Conclusion: This study was inconclusive in demonstrating the efficacy of high dose ergocalciferol in controlling SLE disease activity. However, high dose ergocalciferol could be a safe adjunctive therapy that has a corticosteroid-sparing effect on patients with SLE.

Keywords: Vitamin D level, Systemic Lupus Erythematosus

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Introduction

Vitamin D is a secosteroid that carries a structure similar to a steroid. The main source of vitamin D is de novo synthesis in the skin through ultraviolet irradiation of 7 dehydrocholesterol. Vitamin D is related to mineral metabolism and skeletal health. Vitamin D enhances intestinal calcium, phosphate absorption stimulated osteoclast differentiation, calcium resorption from bone and promotes mineralization of bone matrix. [1, 2]

Over the last decade, several studies found vitamin D receptor (VDR) and vitamin D activating enzyme 1, α-hydroxylase (CYP27B1) expressed in many cell types especially cells of the immune system. Vitamin D deficiency has effects on innate and adaptive immune systems and possibly enhances the activity or occurrence of auto-immune disease. [3-6] It has been shown that 1, 25-dihydrovitamin D3 could inhibit dendritic cell maturation and expression of IFN-α gene among patients with Systemic Lupus Erythematosus (SLE).[7] A recent study also demonstrated patients with vitamin D-deficient SLE had higher serum IFN-α activity and B-cell activation compared with those patients with higher vitamin D levels.[8]

Several studies demonstrated a high prevalence of vitamin D deficiency among patients with SLE due to multiple risk factors such as sunlight avoidance, glucocorticoids and hydroxychloroquine exposure and chronic kidney disease.[9] Low serum vitamin D levels have been suspected as a risk factor in developing SLE, persistence of disease activity and increasing morbidity and mortality among patients with SLE (10-12). A recent study among Thai patients with SLE demonstrated a statistically significant inverse relationship between disease activity scores of SLE and serum levels of 25-hydroxyvitamin D and inverse relationship between urine creatinine ratio and serum levels of 25-hydroxyvitamin D. [13, 14] Two recent studies evaluating the efficacy of vitamin D supplementation among patients with SLE found that high dose vitamin D supplementation increased naive CD4+ T cells, Tregs and decreased effector Th1 and Th17 cells, memory B cells and anti-DNA antibodies. Another study also showed significantly improved levels of pro-inflammatory cytokines and hemostatic markers (fibrinogen, von Willebrand factor).[15, 16]

This study aimed to assess the efficacy and safety of high dose ergocalciferol combined with standard care among patients with SLE by measuring the level of 25-hydroxyvitamin D, an inflammatory marker, disease activity index, quality of life, adverse events and concurrent medications.

Methods

Study Design

A randomized double-blind controlled trial was conducted in the Rheumatic Department, Phramongkutklao Hospital. The study was approved by the Institutional Review Board of the Royal Thai Army Medical Department. All subjects provided informed consent and all procedures were performed under the ethics standard of the responsible committee on human experimentation. Following informed consent, eligibility criteria and clinical status were assessed at first visit.

Subjects were enrolled from November 2013 to January 2014. All subjects fulfilled at least 4 of the American College of Rheumatology (ACR) classification criteria for SLE, 1997. Inclusion criteria included patients with SLE at least 18 years of age. Female subjects were eligible to enter the study if they were not pregnant or nursing. All subjects had the ability to understand the requirements of the study to provide written informed consent and complied with the study protocol procedures. Subjects were excluded if they had other co-existing auto-immune diseases (except for secondary Sjogren's Syndrome), history of liver disease, history of renal stone, chronic inflammatory or infectious condition, active cancer or laboratory abnormality of the following conditions, i.e., serum creatinine >2.5 g/dl, serum calcium >10.5 mg/dl or serum 25 (OH) D <10 ng/ml.

All subjects and physicians were blinded to group assignment and treatment allocation. Subjects were randomized in 2 parallel groups, randomized by box of 4 using computer analysis at baseline of treatment. All subjects gave a detailed history and received a thorough physical examination. Clinical data recorded included disease duration, body mass index, medication use including mean daily dosage of corticosteroid, antimalarial and other immunosuppressive drugs. Subjects were randomized in 2 groups. The high dose (HD) group was assigned to receive 100,000 IU of

ergocalciferol weekly for 4 weeks followed by 40,000 IU of ergocalciferol weekly for 20 weeks. The placebo group received identical placebo 24 weeks and both groups received 800 units of cholecalciferol daily for 24 weeks. Both groups were allowed to adjust the dose of corticosteroid, antimalarial and immunosuppressive drugs followed by disease activity.

25 (OH) vitamin D level measurement and definitions

Serum samples for 25 (OH) vitamin D levels were obtained from all randomized subjects before administering ergocalciferol or placebo at the baseline visit and end of study (week 24). The 25 (OH) vitamin D level was measured using a chemiluminescence immunoassay. In accordance with the US Endocrine Society, vitamin D deficiency was defined as 25 (OH) vitamin D level of 20 ng/ml or less, vitamin D insufficiency as 21 to 29 ng/ml, and vitamin D sufficiency as 30 ng/ml or higher. [9, 16, 17] Biological markers and auto-antibodies measurements included complete blood count, erythrocyte sedimentation rate (ESR), blood urea nitrogen, creatinine, liver function test, serum calcium and phosphorus levels, C-reactive protein (CRP), autoantibodies levels (anti-dsDNA), C3, C4, lupus anticoagulant, serum anti-cardiolipin and B2glycoprotein. Urinary analysis included urine protein-creatinine ratio (UPCR). These biomarkers were measured at baseline and at weeks 12 and 24.

Disease activity assessments on SLE Disease activity index (SLEDAI) and SLE flare index were evaluated at baseline, weeks 12 and 24. Quality of life was evaluated at baseline and end of the study. Treatment-related adverse events reported by patients or observed by physicians were collected at every visit.

Efficacy endpoints and analysis

Primary efficacy endpoints included the change of inflammatory and disease activity markers (ESR, CRP, anti-dsDNA, C3, C4, lupus anticoagulant, serum anti-cardiolipin, B2glycoprotein) and disease activity index (SLEDAI, HAQ) at week 12 and the end of study. Secondary efficacy endpoints included the renal response in one patient with lupus nephritis at the end of the study. Lupus nephritis was determined by UPCR $\geq$0.5 and the renal response was determined by changes in proteinuria (UPCR below 0.5 and/or 25 to 50% reduced proteinuria) and the dose adjustment of prednisolone and other immunosuppressive drugs.

Statistical analysis

Data were analyzed using SPSS Software, Version 20. Values in the study were expressed as mean (SD), median (IQR) or number (percentage). Continuous variables between the 2 groups were compared using the student's t-test, and categorical groups were compared using the chi-square test. Statistical significance was defined as a 2-sided *p*-value of 0.05.

Results

The 104 eligible participants (91 woman, 13 men) were randomized in either high dose group (HD-groups, n=52) or placebo group (n=52). The mean age was 41.15 years in the high dose group and 43.67 years in the placebo group. Eighty-five patients (81%) completed the protocol at the end of 24 weeks of treatments.-

The demographic characteristics of study groups are depicted in **Table 1.** Baseline characteristics were similarly distributed between the 2 treatment groups except only hypertension was more common in the placebo group. Mean 25 (OH) D levels, inflammatory, disease activity marker, renal response of vitamin D supplement of the study population at baseline and 24 weeks of treatment are shown in **Table 2.**

Table1. Baseline characteristics of study participants according to treatment groups

	High dose group	Placebo group	*p*-value
Sex, female/male, (n, %)	48 (90.57%)	43 (84.31%)	0.386
Age, years, mean (SD)	41.15 (13.31)	43.67 (13.19)	0.336
BMI, kg/m2, mean (SD)	22.01(5.49)	22.59 (5.59)	0.533
DM (n, %)	7 (13.21%)	4 (7.84%)	0.374
HT (n, %)	18 (33.96%)	28 (54.90%)	0.032
DLD (n, %)	14 (26.42%)	22 (43.14%)	0.073
CAD (n, %)	3 (5.56%)	3 (5.58%)	0.961
Hypothyroid (n, %)	2 (3.77%)	0	0.161
APS (n, %)	4 (7.55%)	6 (11.76%)	0.466
Disease duration (months), median (IQR)	72 (24, 144)	120 (48, 228)	0.052
Vitamin D Supplement IU/day, median (IQR)	800 (800, 2857)	800 (600, 2875)	0.632
Drug calcium (mg), mean (SD)	1301.89 (512.72)	1264.71 (550.94)	1.0
Prednisolone (mg / day), median (IQR)	8.75 (5, 15)	5 (2.5, 10)	0.257
CQ (mg/day), mean (SD)	207.63 (65.16)	197.5 (73)	0.669
HCQ (mg/day), mean (SD)	180 (40.82)	193.8 (102.6)	0.538
Azathioprine (mg/day), mean (SD)	55.25 (26.73)	59.1 (23.1)	0.699
CYC iv (mg/month), mean (SD)	1000 (200)	800 (163.3)	0.203
Cyclosporin A (mg/day), mean (SD)	-	100	NA
MTX (mg/week), mean (SD)	6.25 (1.77)	-	NA
MMF (mg/day), mean (SD)	1416 (664.58)	1647 (852.2)	0.609
SLEDAI, median (IQR)	4.0 (2, 6)	4.0 (1, 4)	0.544
c3 (g/l), mean (SD)	0.81 (0.34)	0.83 (0.34)	0.757
c4 (g/l), mean (SD)	0.20 (0.13)	0.19 (0.11)	0.869
Anti-dsDNA (U/ml), median (IQR)	135 (25.9, 408.5)	142.25 (29.43, 472)	0.797
ESR (mm/hour), mean (SD)	49.17 (26.47)	41.89 (21.62)	0.150
CRP (mm/hour), median (IQR)	1.6 (0.6, 3)	1.4 (0.6, 3.3)	0.892
25 (OH) D (ng/ml), mean (SD)	27.99 (9.24)	25.92 (10.57)	0.288
Ca (mg/dl), mean (SD)	9.16 (0.49)	9.07 (0.52)	0.396
po4 (mg/dl), mean (SD)	3.68 (0.6)	3.57 (0.66)	0.359
Alb (mg/ml), mean (SD)	4.06 (0.4)	4.12 (0.5)	0.520
UPCR, mean (SD)	0.35 (0.65)	0.47 (0.99)	0.470
Cardiolipin (U/ml), median (IQR)	1.8 (0.85, 2.86)	1.3 (0.7, 3.6)	0.479
b2gly (U/ml), median (IQR)	9.2 (4.4, 14.25)	7.9 (4.5, 12)	0.734
HAQ, mean (SD)	64.42 (20.93)	68.12 (33.8)	0.502

DLD: dyslipidemia; CAD: coronary artery disease; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; CQ: chloroquine; HCQ: hydroxychloroquine; MTX: methotrexate; CYC: cyclophosphamide; MMF: mycophenolate mofetil; Alb: serum albumin; UPCR: urine protein-creatinine ratio; HAQ: health assessment questionnaire.

Table 2. Vitamin D status and inflammatory and disease activity markers at baseline and 24 weeks of treatment

	High dose group	Placebo group	*p*-value
Serum vitamin D (ng/ml) (mean, SD)			
Baseline	27.99 (9.24)	25.92 (10.57)	0.288
24 weeks	41.17 (14.44)	27.16 (10.12)	<0.001
Anti-dsDNA (U/ml), median (IQR)			
Baseline	135 (25.9, 408.5)	142.25 (29.43, 472)	0.797
24 weeks	164.80 (40.55, 321.0)	102.3 (42.5, 260)	0.706
C3 (g, l) (mean, SD)			
Baseline	0.81 (0.34)	0.83 (0.34)	0.757
24 weeks	0.96 (0.35)	0.92 (0.36)	0.606
C4 (g, l) (mean, SD)			
Baseline	0.20 (0.13)	0.19 (0.11)	0.869
24 weeks	0.20 (0.11)	0.27 (0.28)	0.166
ESR (mm, hr) (mean, SD)			
Baseline	49.17 (26.47)	41.89 (21.26)	0.150
24 weeks	45.55 (25.99)	39.17 (20.27)	0.219
CRP (mm, hr) (median) (IQR)			
Baseline	1.6 (0.6, 3)	1.4 (0.6, 3.3)	0.892
24 weeks	0.9 (0.5, 2.0)	1.4 (0.55, 2.9)	0.442
Cardiolipin (U/ml) (median) (IQR)			
Baseline	1.8 (0.85, 2.86)	1.3 (0.7, 3.6)	0.479
24 weeks	1.1 (0.8, 2.5)	1.7 (0.8, 2.6)	0.284
B2 glycoprotein (U/ml) (median) (IQR)			
Baseline	9.2 (4.4, 14.25)	7.9 (4.5, 12)	0.734
24 weeks	8.4 (4.6, 18.2)	8.1 (3, 14)	0.478
Subgroup of subjects with UPCR ≥ 0.5 at baseline	N=36	N=33	
UPCR (mean) (SD)			
UPCR at baseline	1.28 (1.07)	2.67 (1.29)	0.028
UPCR at 24 weeks	0.83 (0.82)	0.55 (0.65)	0.561
Renal response (N, %)			
25 % decreased UPCR or UPCR < 0.5 at 24 weeks	19(57.6%)	11 (30.6%)	0.024
50 % decreased UPCR or UPCR < 0.5 at 24 weeks	11(33.3%)	8 (22.2%)	0.302

UPCR: urine protein-creatinine ratio.

Vitamin D status

Vitamin D status of the HD-group at baseline was similar to the placebo group (27.99 ±9.24 vs. 25.92±10.57ng/ml, p=0.288). At baseline, a small number of patients in the HD-group had vitamin D deficiency (<20ng/ml) compared with the placebo group (20.75 vs. 33.33%, p=0.148). At the end of the study, mean 25 (OH) D levels of the HD-group were significantly higher than

those of the placebo group (41.2 ± 14.4 vs. 27.2 ± 10.1, $p < 0.001$). In addition, a significantly lower number of subjects in the HD group had vitamin D insufficiency than that of the placebo group (7.55 vs. 21.57%, P = 0.035) at 24 weeks of treatment.

Inflammatory and disease activity markers

Inflammatory and disease activity markers including anti-dsDNA, C3, C4, CRP, ESR, B2-glycoprotein and anti-cardiolipin were similar between the HD and placebo groups during the study. Subgroup analysis was performed among subjects with 25 (OH) D levels below 30ng/ml at baseline. No significantly improved inflammatory and disease activity markers were found between the two treatment groups (data not shown).

Subgroup of patients with lupus nephritis

In all, 17 patients presented lupus nephritis at baseline (HD-group, n=10 and placebo group, n=7). Renal response among patients with lupus nephritis at the end of the study between the two groups is shown in **Table 2.** At baseline, the mean level of UPCR in the HD-group was significantly lower than that of the placebo group (1.28±1.07 vs. 2.67±1.29, p= 0.028). At 24 weeks of treatment, no significant difference was observed in the mean level of UPCR between two groups (0.83±0.82 vs. 0.55±0.65). However, the number of subjects presenting lupus nephritis with 25% reduced UPCR or UPCR below 500 mg/day and the number of subjects with lupus nephritis with 50% reduced UPCR or UPCR below 500 mg/day did not significantly differ between two groups.

Disease activity index

Efficacies of vitamin D supplement are shown in **Table 3**. In this study, no significant improvement was shown in both disease activity indexes (SLEDAI, flare index) and quality of life determined using a health assessment questionnaire (HAQ) between the two study groups.

Table 3. Variations in SLEDAI score, HAQ score and number of patients (n, %) with an improved flare index in the HD-group compared with those of the placebo group, values are mean (SD), median (IQR)

SLEDAI Median (IQR)	High dose group	Placebo group	*p*-value
At baseline	4.0 (2, 6)	4.0 (1, 4)	0.544
At 12 weeks of treatment	2.0 (0, 4)	2.0 (0, 2)	0.880
At 24 weeks of treatment	0.0 (0, 4)	2.0 (0, 2)	0.101
HAQ (mean, SD)			
At baseline	64.42 (20.93)	68.12 (33.8)	0.502
At 24 weeks of treatment	60.04 (22.42)	58.09 (21.3)	0.672
SLE not flare (N, %)			
At 24 weeks of treatment	39 (73.6%)	42 (82.4%)	0.266

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; UPCR: urine protein-creatinine ratio; HAQ: health assessment questionnaire.

Vitamin D as steroid-sparing effect and effect on immunosuppressant

Significantly more subjects could reduce the dose of prednisolone in the HD group compared with the placebo group at 12 weeks until the end of the study (12 weeks; 43.75% vs. 18.75%, $p = 0.008$ and 24 weeks; 52.27% vs. 26.66%, $p = 0.024$) and at 6 months of treatment (52.27% vs. 26.66%, $p = 0.024$*). In addition, significant difference was found in the dose adjustment of immunosuppressive drugs between the two groups during the study. Data are shown in **Table 4**.

Table 4. Number of subjects with reduced prednisolone and immunosuppressive doses at 12 and 24 weeks of treatment.

The number of subjects with a reduced prednisolone dose	High dose group	Placebo group	*p*-value
At 12 weeks of treatment (n, %)	21 (39.62%)	9 (17.65%)	0.008
At 24 weeks of treatment (n, %)	23 (43.40%)	12 (23.53%)	0.013
The number of subjects with reduced immunosuppressive dose			
At 12 weeks of treatment (n, %)	2 (3.8%)	0	0.242
At 24 weeks of treatment (n, %)	4 (7.6%)	1 (2.0%)	0.203

Safety profile

One patient in the HD group withdrew from the study due to minor rash reaction and recovered after vitamin D discontinuation. One patient in the placebo group withdrew from the study due to weight gain. Serum calcium and phosphorus levels did not change within and between groups of treatment (data not shown).

Discussion

In the view of the potential beneficial effects of vitamin D on immunomodulation and high prevalence of vitamin D deficiency among patients with SLE [8, 10, 16, 18, 19], supplementation of vitamin D constitutes an important therapeutic strategy. Avoidance of sunlight, renal insufficiency, obesity, and use of medication such as glucocorticoids are major risk factors for vitamin D insufficiency in SLE. [14] This study showed the effect of high dose over low dose vitamin D supplementation on rising serum vitamin D levels among patients with SLE.

The immunomodulation of vitamin D is opposite that of the observed immunological aberrations among patients with SLE. A related study demonstrated that 1, 25-dihydroxy vitamin D and its analogs inhibited polyclonal and anti-dsDNA (IgG) production by stimulating peripheral blood mononuclear cells from patients with SLE. [20] Dihydroxy vitamin D3 has been shown to inhibit dendritic cell maturation and expression of the IFN-α gene (IFN signature) among patients with SLE.[1, 7, 25] A more recent study also demonstrated that vitamin D deficient patients with SLE had higher serum IFN-α activity and B-cell activation compared with those patients with higher vitamin D levels taken together. Strong evidence indicates that insufficient vitamin D may aggravate immunological abnormalities among patients with SLE.[8] Several studies have reported an inverse relationship exists between 25 (OH) D level and disease activity. [16, 21, 22] Abou-Raya et al. showed that high dose vitamin D supplementation provided a significant effect on the reducing autoantibodies levels (anti-sm, anti-dsDNA) and ESR with improved complement level and SLE-DAI score.[16] This study could not demonstrate improved inflammatory markers, immunological markers, disease activity or quality of life of patients with SLE. This could be explained by the small sample size, short duration of follow-up, a small number of patients with vitamin D deficiency and uncontrolled concurrent medications.-

Regarding the subgroup analysis of patients with lupus nephritis, this study found no significantly improved UPCR among patients receiving high dose of vitamin D supplementation. According to a recent study of Petri M el al., vitamin D supplementation among patients with SLE with low level 25 (OH) D (<40 ng/ml) and 20 ng/ml increase in 25 (OH) D level were associated with a 21% decrease in the odds of having a high disease activity score and 15% decrease in the odds of having clinically improved proteinuria. [23]This could be explained by the small number of patients with lupus nephritis as well as short duration of follow-up.

Interestingly, our study was the first to find a steroid-sparing effect of high-dose vitamin D supplementation. A significantly improved de-escalating of corticosteroid among patients receiving high dose vitamin D supplementation was observed, despite no differences in adjusting immunosuppressive agents. Two cross-sectional studies found an inverse relationship between levels of vitamin D and corticosteroid use (both

current dose and cumulative dose) which might have supported corticosteroid-sparing effects in our study (14, 24). However, a future study controlling the dosage of immunosuppression is needed to confirm these findings.

The long term use of vitamin D is not completely safe, concerning hypercalcemia, hyperphosphatemia and renal stones, but the risks are extremely low. Long term follow-up is needed to ensure sufficient levels of 25 (OH) D leads to clinically improved disease activity. Finally, we recommend a routine assessment of vitamin D levels and adequate supplementation of vitamin D among patients with SLE.

Conclusion

This study could not demonstrate the efficacy of high dose ergocalciferol in controlling SLE disease activity. However, high dose ergocalciferol could improve vitamin D levels back to normal and constitute a safe adjunctive therapy exhibiting a steroid-sparing effect among patients with SLE.

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Disclosures None

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SYNOVIAL HYPERTROPHY DETECTED USING ULTRASONOGRAM IN PRIMARY OSTEOARTHRITIC KNEES: PREVALENCE AND CORRELATION WITH RADIOGRAPHIC STAGING

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Abstract

Background: Treatment of primary osteoarthritic (OA) knee has changed in recent decades with a greater focus on synovitis as one cause of cartilage destruction and degeneration. Ultrasonography (US), a noninvasive, low cost and convenient procedure may be used for early detection and monitoring synovitis in primary OA knee. Somehow, the lack of data on the prevalence of synovial hypertrophy (SH) and its correlation to disease progression has precluded the use of US in clinical practice.

Objective: The study aimed to determine the prevalence of SH at each stage of the disease and its correlation to structural damage.

Methods: In all, 214 knees among 127 cases diagnosed as having primary OA knee were examined using US. The midline scanning technique of US was performed and synovial thickness at the suprapatellar pouch was observed. All knees were categorized according to the Kellgren-Lawrence radiographic staging (KL). The prevalence of SH in each KL with 2, 2.5 and 3 mm cutoff level were calculated. The correlation between synovial thickness and KL was also analyzed.

Results: The prevalence of SH with 2 mm cutoff level in KL I-IV was 38.8, 70.8, 66.6 and 91.1%, respectively. The prevalence of SH with 2.5 mm cutoff level in KL I-IV was 5.5, 37.5, 35.4 and 74.2%, respectively. The prevalence of SH with 3 mm cutoff level in KL I-IV was 0, 29.1, 20.8 and 56.4%, respectively. The overall prevalence with 2, 2.5 and 3 mm cut-off level was 72.2, 50.9 and 37.1%, respectively. Synovial thickness, measured in millimeters, correlated well with KL (p<0.01). The correlation of synovial thickness between each KL was also statistically significant (p<0.05) except those between KL II and KL III (p=0.98).

Conclusion: Synovial thickness at the suprapatellar pouch detected with midline scanning US reflected the degree of synovitis which correlated well with structural damage and could be used to monitor disease progression in primary OA knee.

Keywords: Synovial hypertrophy, Synovitis, Osteoarthritic knee, Radiographic staging, Ultrasonogram

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Introduction

For several decades, mainstay treatments of primary osteoarthritic (OA) knee were supportive until the end stage of disease in which the joint replacement was inevitable. As the disease progresses, the knee structure decays and the symptoms worsen.[1] Recently, the paradigm of conservative treatment has changed to prevent or delay disease progression by controlling synovitis of the joint.[2-13] However, the imaging modality to monitor the effectiveness of each treatment has not yet been agreed upon. Plain radiography is reflects only irreversible structural damage; thus, cannot be used for early detection. Magnetic resonance imaging study (MRI) is not a cost-effective choice to monitor disease progression in clinical settings. On the other hand, ultrasonogram (US), a noninvasive, low cost and convenient procedure can offer the benefit of early detection and monitor synovial hypertrophy (SH) with comparable accuracy to MRI.[14] Many studies conducted in the US in osteoarthritic knees reported a wide range of SH prevalences (14.5 to 99.7%), different cut-off levels of SH and different correlations with either radiographic staging or symptoms.[15-19] The study aimed to determine the prevalence of SH at each stage of disease and its correlation to structural damage.

US has been widely used in monitoring synovitis of inflammatory joint disease, usually performed by rheumatologists and radiologists.[15-20] Unfortunately, the archaic concept of pathophysiology in primary osteoarthritic knee, i.e., mechanical wear and tear, has long blinded orthopedic surgeons from the true culprit of cartilage destruction, i.e., subclinical synovitis; thus, the use of US in orthopedic practice is underrated.[4-13]

Another concern about US is the variety of techniques and operator dependency, rendering the reliability lower than it should be. The reliability of US in detecting structural abnormalities is low; however, when focusing on only inflammatory abnormalities, the agreement is high despite the experience of the sonographer.[21] Our secondary goal is to determine the reliability of a midline scanning US technique to detect SH at the suprapatellar pouch.

Methods

Study population

Patients, visiting the Outpatient Department, Orthopedics Division, Phramongkutklao Hospital and presenting the chief complaint of knee pain, were enrolled in this study from June 2018 to December 2018. This study was approved by the Research Ethics Committee of Phramongkutklao College of Medicine. All participants provided written informed consent.

The inclusion criteria comprised patients receiving a diagnosis of osteoarthritis on either side of the knees according to the ACR clinical classification criteria for knee osteoarthritis and having at least three of the following six items: age >50 years, morning stiffness <30 minutes, crepitus on knee motion, bony tenderness, bony enlargement and no palpable warmth.[22] The exclusion criteria comprised patients having a history contributing to secondary osteoarthritis, i.e., posttraumatic, postinfection, postsurgery, inflammatory joint disease, vasculitis or any connective tissue disorder.

Ultrasound Instrument

The GE Healthcare model LOGIQ® e, Preset: Musculoskeletal - knee in B-mode, 12L-RS Wide Band Linear Probe (12MHz) was used in this study.

Technique

The patient was placed in a supine position on the examination table, keeping his/her knee flexed but relaxed at 30°, one at a time. Midline scanning technique US was performed with a linear probe vertically applied at just proximal to the superior pole of the patella.[23, 24] The quadriceps were identified as a parallel line of muscle fibers originating from the superior pole of the patella and were tracked along the quadricep fiber proximally, but not farther than 1 to 2 finger breadth, in the supra-patella pouch. The suprapatellar prefemoral fat pad is just proximal to the anterior part of the femoral condyles. The heterogenous fatty streak confirms the fat pad and is used to differentiate from the synovium, the homogenous echoic layer of tissue overlying the fat pad. When a substantial amount of synovial effusion is encountered, the probe is compressed as much as possible to minimize effusion at the area of interest.[18, 23, 24] The thickest part of the synovium was measured in millimeters to one decimal. The measurements were repeated three times and the thickest value of the synovium was recorded.

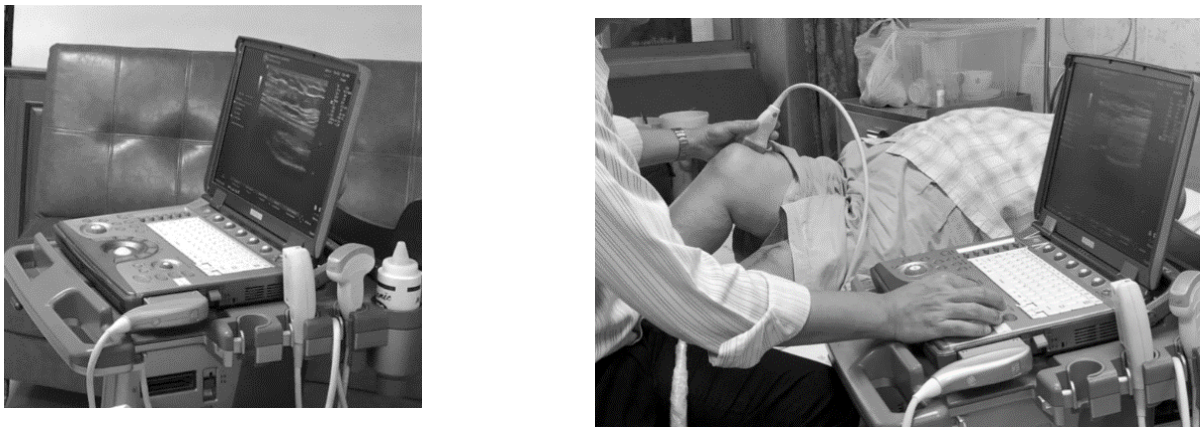

Image 1. Ultrasound machine, midline scanning technique with linear probe

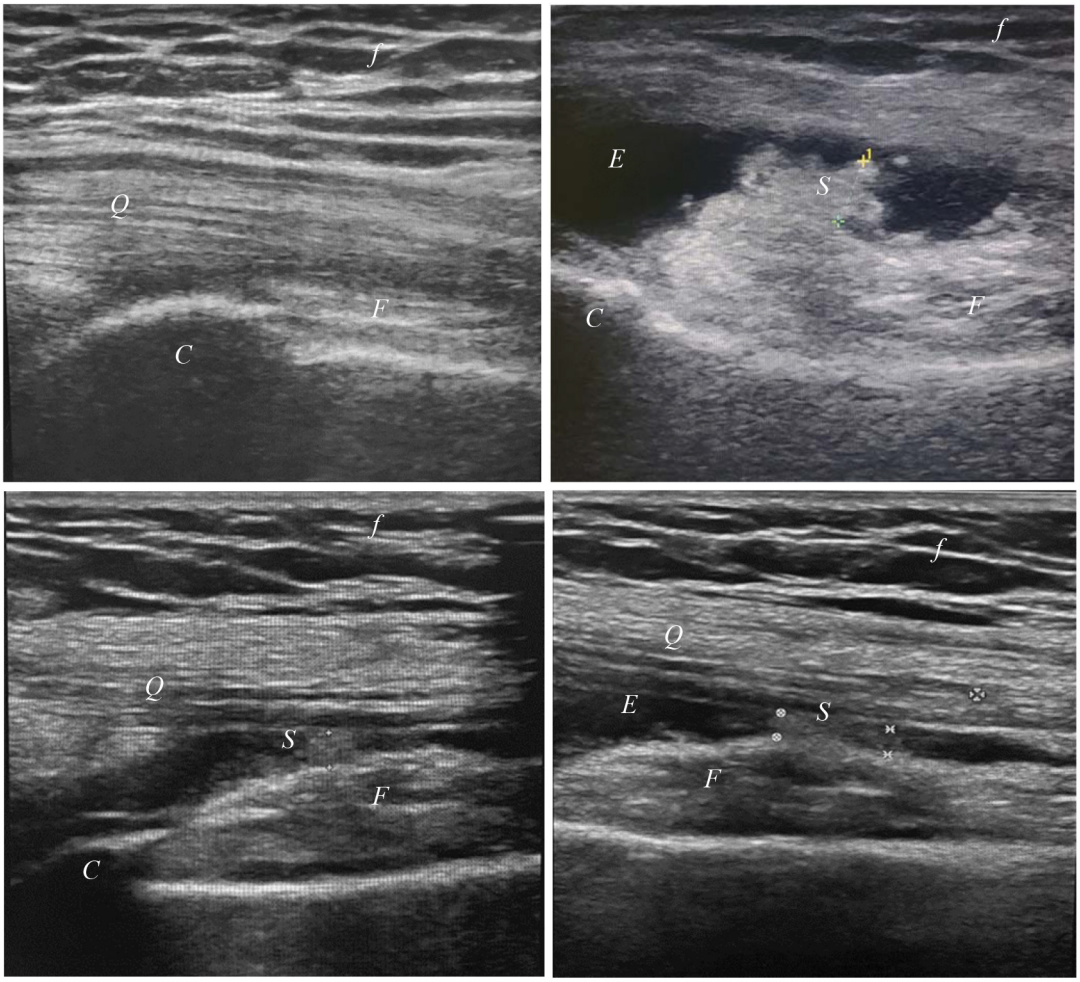

Image 2. Imaging and measuring
(f: subcutaneous fat, Q: quadriceps, F: prefemoral fat pad, S: synovium, C: femoral condyle, E: effusion)

Reliability of measuring synovial thickness

Under the same midline scanning technique, two sonographers, blinded to patients' history, physical examination and radiographic results, independently performed ultrasonogram in the same 10 OA knees. Intra and interobserver reliability were calculated using intraclass correlation coefficients (ICC) using the Shrout and Fleiss model (1979)

$$\frac{MS_R - MS_W}{MS_R + (k+1)MS_W}$$

Intra-observer reliability under the model of one-way random effects, absolute agreement and single rater [ICC(1,1)] were calculated using the formula below.

$$\frac{MS_R - MS_W}{MS_R}$$

Interobserver reliability under the model of one-way random effects, absolute agreement, multiple raters [ICC(1,k)] were calculated using the formula below.
MS_R = mean square for rows, MS_W = mean square for residual sources of variance, k = number of raters

Radiographic staging

The standing AP/lateral radiogram of knees was performed and classified under the Kellgren and Lawrence grading system (KL).[25]

Because the difference between KL grading of 0 and 1 is subtle and difficult to categorize, they were combined as KL grade 0-1.

blinding outcome assessors

Patients' history taking and physical examination were performed by an orthopedic surgeon in the screening room. When the patients' condition met the criteria, after being informed and agreeing to enroll in the study, they were sent to the US room, without any documents describing their history or physical examination. They were sent for radiogram only after their sonogram was completed. In this manner, the sonographers were blinded to the patients' history and radiographic results.

Statistical analysis

Prevalence was calculated with respect to different cutoff levels of SH at 2, 2.5 and 3 mm thickness. The correlation between synovial thickness (in mm) and KL was analyzed using One-way ANOVA and Scheffe post-hoc test. The prevalence of SH in each KL with 2, 2.5 and 3 cutoff levels was calculated. Synovial thickness more than 2 mm was identified as SH and calculated with Chi-square test to determine the relationship between SH and KL.

Results

Demographic data of enrolled participants

Age and sex of the patients in each KL grading were recorded as baseline characteristics as shown in **Table 2**.

Prevalence of synovial hypertrophy (SH)

The overall prevalence of SH with 2 mm cutoff was 72.2% and the prevalence among KL 0 to 4 were 38.8, 70.8, 66.6 and 91.1%, respectively. Using the 2.5 and 3 mm cutoff values, the prevalences were lower than those of the 2 mm (as shown in **Table 3**).

Table 1. Kellgren and Lawrence grading system (KL)

Kellgren and Lawrence grading system (KL)
Grade 0: No feature of osteoarthritis
Grade 1: Doubtful narrowing of joint space and possible osteophytic lipping
Grade 2: Definite osteophytes and possible narrowing of joint space
Grade 3: Moderate multiple osteophytes, definite narrowing of joint space, and some sclerosis and possible deformity of bone ends
Grade 4: Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends

Table 2. Demographic data of enrolled participants

	KL0-1	KL2	KL3	KL4	Total
Male	2	10	14	33	59
Female	15	14	34	92	155
Age	50-80	52-83	50-83	50-86	50-81
(mean)	(56)	(65.8)	(67.8)	(71.3)	(68.7)
Total	17	24	48	125	214
No statistical significance was found between all parameters					

Table 3. **Prevalence of SH using different cutoff levels**

cut-off level	KL 0-1	KL 2	KL 3	KL 4	Overall
2mm	38.8%	70.8%	66.6%	91.1%	72.2%
2.5mm	5.5%	37.5%	35.4%	74.2%	50.9%
3mm	0%	29.1%	20.8%	56.4%	37.1%

Correlation

Synovial thickness, measured in millimeters, was higher with more advance KL grading. Under one-way ANOVA analysis, synovial thickness was well-correlated with KL grading (p<0.01). Under the Scheffe posthoc test, the correlation of synovial thickness between each KL was also significant (p<0.05) except those between KL2 and KL3 (p=0.98).

Synovial hypertrophy (SH), i.e., synovial thickness of more than 2mm, is well-correlated with KL grading under the Chi-square test (p<0.01) These significances were also found at 2.5 and 3 mm cut-off levels.

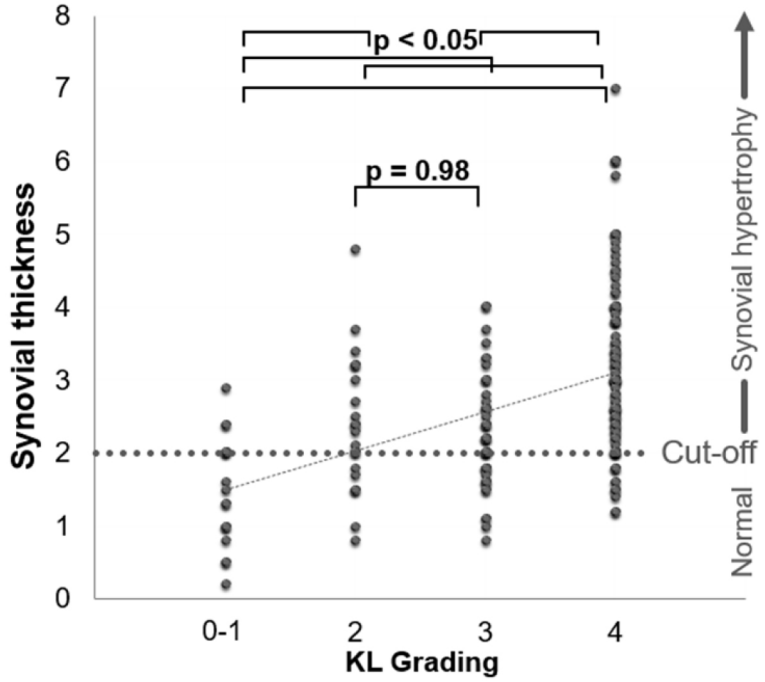

Figure 1. Correlation between synovial thickness and KL grading under one-way ANOVA

Table 4. Repeated measurement of synovial thickness under midline scanning technique performed by two independent sonographers.

	Rater1				Rater2			
	1st	2nd	3rd	Final	1st	2nd	3rd	Final
Knee 1	2.5	2.8	1.8	2.8	2	1.8	3.5	3.5
Knee 2	3.1	2.5	3.5	3.5	2.2	3	2.6	3
Knee 3	3	2.6	3	3	2.4	2	1.8	2.4
Knee 4	2.6	1.9	2	2.6	3	3.3	3.1	3.3
Knee 5	0.9	1.8	1.4	1.8	2.5	1.6	1	2.5
Knee 6	2.6	2.4	2	2.6	2.2	3.2	2.6	3.2
Knee 7	1.6	2	2.4	2.4	2.3	1.9	2.8	2.8
Knee 8	1.5	1.4	2	2	1	0.4	0.8	1
Knee 9	4.2	3.6	4.2	4.2	2.7	3.6	3.1	3.6
Knee 10	3	3.8	3.6	3.8	2.8	2.2	3.4	3.4

Inter- and Intra-observer reliability

After a period of practicing the same protocol of midline scanning technique of two sonographers, 10 random osteoarthritic knees were examined and repeated three times use of US in each knee and sonographers. The highest value of synovial thickness was concluded as the final value.

For Rater1, intra-observer reliability was good to excellent (ICC's: 0.79 (0.53–0.93) to 0.92 (0.77–0.98). For Rater2, intra-observer reliability was moderate to good (ICC's: 0.60 (0.22–0.86) to 0.82 (0.46–0.95).

Synovial thickness was observed with moderate to good inter-observer reliability (ICC's: 0.64 (0.02-0.89) to 0.78 (0.04-0.94). During this study, in terms of our experience, Rater1 had already performed sonogram under midline scanning technique over 200 cases compared with only 30 cases performed by Rater 2.

Discussion

Synovial thickness at the supra-patellar pouch, measured either in mm or percentage of SH, is well-correlated with radiographic staging. In advanced stage of osteoarthritic knees with severe structural damage, the synovium are thicker than early stages. These findings suggested that long standing synovitis in the joint may thicken the synovium over time. Thin synovium can be found in KL4 and may be the result of shrinkage under fibrotic processes. Further study is needed to prove this assumption.

The prevalence of SH varied with different cut-off levels; however, the 2 mm cut-off level was more sensitive in early stages of osteoarthritic knees with prevalence 38.8% in KL0 to 1. On the other hand, the synovial thickness of less than 2mm should be considered normal, to prevent overdiagnosis of SH with US.

In this study, the overall prevalence among each cut-off levels (37.1 to 72.2%) were within the range of related studies (22.1 to 82.5%)[15-19]

The correlation of SH to structural damage was similar to a majority of related studies [15-19] but distinct from some studies.[17,18] The different methods of collecting data may limit the comparison of result across studies.

The concern about operator dependency of US has long hindered a majority of orthopedics in trying or practicing US. Better than expectation, we found that the midline scanning technique for US was easy to perform with acceptable reliability and was easy to improve, even among inexperienced practitioners.

Conclusion

Plain radiograms could represent irreversible structural damage and are conventionally used as tools to classify stages of osteoarthritis. In this study, the more advanced the stage of osteoarthritic knees became, the higher prevalence of SH was observed. The trend of synovial thickness also increased at each stage; thus, correlating with structural damage. These findings suggest that long standing synovitis contributed to cartilage destruction. Similar to secondary osteoarthritis from inflammatory disease, primary osteoarthritis also presents inflammation, even to a much lesser degree, but prolonged enough to

thicken the synovium to a detectable range in US. Conservative treatment of primary osteoarthritic knee should aim to prevent structural damage of the cartilage by controlling the synovitis process. Treatment should not be halted until the synovitis is well-controlled, even when the symptoms are minimized by medication or activity reduction because the fluctuating pain did not correlate with the tedious progression of osteoarthritis, especially during early stage osteoarthritis, when structural damage has yet to occur. Salvaging the cartilage during early stage osteoarthritic knees is paramount.

Unfortunately, subclinical synovitis is subtle concerning physical examination alone, presently, and US may be the most practical method of monitoring synovitis. With any mode of treatment applied, US will also detect its effectiveness, rather than subjective pain. This study brings a new paradigm one step closer regarding osteoarthritic treatment - to delay or even prevent osteoarthritis against the sands of time.

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EVALUATION OF SPECIFIC ABSORPTION RATE AMONG PATIENTS USING 3 TESLA AND 1.5 TESLA MAGNETIC RESONANCE IMAGING MACHINES

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Abstract

Background: Specific Absorption Rate (SAR) is radiofrequency power delivered to tissue during a Magnetic Resonance Imaging (MRI) examination, expressed as watts per kg (W/kg). Radiofrequency power deposition results in increased heating of patient tissues; thus, the use of MRI has to be controlled to ensure patient safety.

Objective: The study aimed to evaluate SAR among patients using the 3 Tesla MRI (MRI 3T) and 1.5 Tesla MRI (MRI 1.5T) machines.

Methods: Data were obtained from patients who were examined using MRI 3T (1,159 patients, 8,225 series) and MRI 1.5T (1,423 patients, 8,605 series) machines. Age, body weight, SAR, repetition time (TR), type of radiofrequency (RF) pulse and anatomical region exposed were studied.

Results: Average SAR for all patients using the MRI 3T was lower than that of the MR 1.5T in every part (p <0.001) = 0.92 ± 0.57 W/Kg, 2.45 ± 1.01 W/Kg, accordingly. The SAR that the patients received using the spin echo technique revealed that T2 weighted image had lower SAR than T1 weighted image from both MRI 3T and MRI 1.5T (p < 0.001), 0.87 and 0.98 W/kg for MRI 3T, 2.20 and 2.83 W/kg for MRI 1.5T, respectively. For underweight patients, the lowest SAR was 0.89 W/Kg (MRI 3T) and 2.40 W/Kg (MRI 1.5T), respectively. Whereas, among overweight patients, the SAR was the highest at 0.97 W/Kg (MRI 3T) and 2.52 W/Kg (MRI 1.5T). For SAR categorized by the flip angle of the RF pulse, and patients evaluated by the MRI 3T, the study revealed that the group with the flip angle of the RF pulse <75 degrees had lower SAR than the flip angle of the RF pulse >75 degrees, 0.77 W/Kg and 0.94 W/Kg, accordingly (p < 0.001) similar to the MRI 1.5T.

Conclusion: The average SAR of patients evaluated using the MRI 3T was lower than those of patients evaluated using the MRI 1.5T in every body part examined. SAR was lower when the TR was increased and flip angle was decreased.

Keywords: Specific Absorption Rate (SAR), 3 Tesla MRI machine, 1.5 Tesla MRI machine

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Introduction

The magnetic resonance imaging (MRI) machine is an important diagnostic tool generating imaging using an electromagnetic field and the spinning of the nucleus of the hydrogen atom which is the fundamental composition in the human body such as in the water molecule (H_2O). The magnet embedded within the MRI scanner can act on these positively charged hydrogen ions (H^+ ions) and cause them to 'spin' in an identical manner. Varying the strength and direction of this magnetic field can change the direction of the 'spin' of the protons, enabling us to build layers of detail. When a patient enters the MRI machine, it would transmit a radiofrequency (RF) wave at a specific radio frequency transforming into heat within the patients' tissue. When the magnet is switched off, the protons will gradually return to their original state in a process known as precession. Fundamentally, the different tissue types within the body return at different rates allowing us to visualize and differentiate between the different tissues of the body to distinctly detect abnormalities for diagnosis.

As the electromagnetic radiation that is used is the non-ionizing radiation, the energy of the radio waves is not sufficiently high to cause the disintegration of the charges in the atoms or molecules [1]. However, related studies have indicated that electromagnetic waves alter the body's biology and affects vision, hearing, the endocrine system, the nervous system, the cardiovascular system, the immune system and the reproductive system. These biological alterations occur due to the induction of heat from the electromagnetic waves that the body receives, [2-11] which are used to create MR images, most significantly from the induction of the magnetic fields [12-21]. The rise in the body temperature of the patients by the electromagnetic waves, depends on several factors related to the regulation of body temperature and control of the environment [3-8]. The temperature changes and other body changes from the reception of electromagnetic waves depend upon the amount of energy that the body absorbs, called the specific absorption rate (SAR) [2-4]. This is the value that depicts the amount of heat per mass of the tissue or the body part that is receiving the energy from electromagnetic waves. This value is measured in watts/kg (W/kg)[2-4] and constitutes a factor affecting the calculation of SAR while the MRI is obtained including, but not limited to, the flip angle of the RF pulse, the repetition time (TR), the type of the RF coil, the anatomical region exposed and the patient's body weight[19-22].

The Food and Drug Administration (FDA) [23] has recommended that the SAR should not exceed the value indicated below to decrease the risks involved from using radio waves on the patient. The average SAR of the body should not exceed 4 W/kg in 15 minutes, the average SAR of the head should not exceed 3 W/kg in 10 minutes, the average SAR of the head and body should not exceed 8 W/kg in 5 minutes and the average SAR of the arms should not exceed 12 W/kg in 5 minutes. Therefore, MRI machines have been programmed, to be alerted to and immediately terminate when the patient is being examined using the MRI machine and the SAR exceeds the set limits [23]. The study aimed to compare the SAR recorded among patients undergoing MRI using MRI 3T and MRI 1.5T machines. The result of this study would help to adjust the parameters used for the MRI machine to evaluate patients to further increase safety and efficacy of the MRI.

Methods

This study employed a retrospective descriptive study design approved by the Ethics Committee, Institutional Review Board, Royal Thai Army Medical Department (S013h/61). The inclusion criteria comprised data sets including the parameters SAR, age, weight, SAR, repetition time, type of RF pulse and anatomical region exposed recorded from the MRI studies and information only obtained from patients who were 16 years of age or above. The exclusion criteria included any incomplete data sets that did not have all required information on the parameters. The appropriate sample size calculated for each MRI machine was at least 8,182 series of images. Simple random sampling was employed using computer generated simple random samples from data sets from both MRI machines obtained from January to December 2018.

Collecting data from patients evaluated using the MRI 3T model Philips Achieva 3.0T TX (1,159 patients, 8,225 series) and 1.5 T model Philips Achieva 1.5T XR (1,423 patients, 8,605 series) using the DoseMonitor Program by PACSHealth, LLC included age, body weight and specific absorption rate (SAR), repetition time (TR), type

of RF pulse and anatomical region exposed. Data acquisition was achieved by sending Digital Imaging and Communications in Medicine (DICOM) of the MRI to the Dose Monitor Program. The program obtained the data from the DICOM header and exported the data in the form of an Excel file.

The SAR values, as estimated by the MR system console, were noted from the DICOM, allowing the data to be categorized in two groups of body weight based on the Thai body shape and body database (SizeThailand)[24]. The range of the body weight used was the normal weight range of the average weight of Thai men and women ± 5 kg. The age group was divided and subdivided in underweight patients (<58 kg), normal weight (58-68 kg) and overweight (>68 kg), SAR and TR. The patients with T1 weight image in spin echo pulse sequence (SE) would have TR <800 msec and those with T2 weight image SE would have TR >2,500 msec[25]. Data also included the flip angle of the RF pulse divided in a group with flip angle <75 degrees and a group with flip angle >75 degrees.

The statistics used included mean and standard deviation. For qualitative analysis, the data included the type of coil and the anatomical region exposed; which were divided into the head and neck, spine, abdomen and extremities; as percentile. To compare differences between the SAR among patients evaluated using the MRI 3T versus those that were evaluated using the MRI 1.5T; the unpaired t-test was used to compare the means of two unmatched groups, and one-way analysis of variance (ANOVA) was used to determine any statistically significant differences between three independent groups, where the level of significance was 0.05.

Results

The demographic information of the patients who had undergone MRI using the MRI 3T machine revealed mean age of 44.82 ± 19.66 years and mean body weight of 65.45 ± 14.59 kg. In total, 8,225 series of images were divided into 2,551 series of head and neck images, 2,142 series of spine images and 3,532 series of extremities images as shown in **Table 1.**

Table1. Demographics of participants imaged with 3 Tesla MRI and 1.5 Tesla MRI of each organ

.

Variables	Magnetic Field Strength		
	3 T N=8,225 Series	1.5 T N=8,605 series	*p*-value
Gender *(%)*	Male=4,761 (57.88) Female=3,464 (42.12)	Male =4,557 (52.96) Female=4,048 (47.04)	<0.001
Age Years, Mean (SD)	44.82 (19.66)	54.63 (17.39)	<0.001
Weight kg. Mean (SD)	65.45 (14.59)	63.27 (12.07)	<0.001
Anatomical region exposed:			
Head & Neck	2,551	2,443	<0.001
Spine	2,142	2,225	<0.001
Extremities	3,532	3,937	<0.001

Note: n = number of series of images

The general demographic information of the patients that had undergone MRI in the 1.5T machine revealed mean age of 54.63 ± 17.39 years and mean body weight of 63.27 ± 12.07 kg. In total 8,605 series of images were divided into 2,443 series of head and neck images, 2,225 series of spine images and 3,937 series of extremities images.

The average SAR of all the patients that had been evaluated using the 3T MRI machine was significantly lower that the SAR of those that had been evaluated using the 1.5T MRI machine (p <0.001) SAR = 0.92 ± 0.57 W/Kg and 2.45 ± 1.01 W/Kg, accordingly. When categorized and analyzed according to the anatomical regions exposed, patients that had been evaluated using the 3T and the 1.5T machines showed the least SAR in the head and neck studies and the SAR from the 3T machine was significantly lower than the 1.5T machine, p-value <0.001) SAR = 0.21±0.20 W/kg and 1.87 ± 1.05 W/kg, accordingly. The anatomic region exposed having the highest SAR among the patients that were evaluated by the 3T machine was the spine = 1.39± 0.37 W/kg whereas the anatomic region exposed that had the highest SAR among the patients that were evaluated by the 1.5T machine was the extremities = 2.80± 0.84 W/kg as shown in **Table 2.**

SAR for patients who were imaged using the spin echo technique found that T2 weight image (long TR >2500 msec) had significantly higher SAR than T1 weight image (short TR <800 msec) in both MRI 3T and the MRI 1.5T machines (p <0.001), 0.98 and 0.87 and 0.98 W/kg for 3T, 2.20 and 2.83 W/kg for 1.5T. When considering the SAR value by weight groups, the underweight group (<58 kg) had the lowest SAR = 0.89W/kg (MRI 3T), 2.40 W/kg (MRI 1.5T) and the overweight group (>68 kg) had the highest SAR = 0.97 W/kg (MRI 3T), 2.52 W/kg (MRI 1.5T). When comparing the SAR the patient received from the MRI 3T machine, the SAR in the underweight (0.89 W/kg), normal weight (0.90 W/Kg) and overweight (0.97 W/Kg) groups significantly differed (p < 0.001). When comparing the SAR that patients received from the 1.5T MRI machine, the SAR of the underweight (2.40 W/Kg), normal weight (2.44 W/Kg) and overweight (2.52 W/Kg) groups significantly differed (p < 0.001) as shown in **Table 3**.

When analyzing the SAR categorized by the flip angle of the RF pulse among patients examined by the 3T MRI machine, the group with the flip angle of the RF pulse <75 degrees received significantly less SAR than the group with the flip angle of the RF pulse >75 degrees, which were 0.77 W/kg and 0.94 W/kg, accordingly (p=0.001). Similarly, among patients examined using the 1.5T MRI machine, the group with the flip angle of the RF pulse <75 degrees received significantly less SAR than the group with the flip angle of the RF pulse >75 degrees, i.e., 2.18 W/kg and 2.48 W/kg, accordingly (p = 0.001).

Table 2. Specific absorption rates among patients evaluated using the 3T and 1.5 MRI machines

Variables	Specific absorption rate (SAR)/ Type of coil		
	3 Tesla (mean±SD)	1.5 Tesla (mean±SD)	p-value
Anatomical region exposed:			
Head & Neck	0.21 ± 0.2*0*	1.87±1.05	<0.001
Spine	1.39 ± 0.37	2.41±0.90	<0.001
Extremities	1.09 ± 0.30	2.80±0.84	<0.001
Total	0.92 ± 0.57	2.45±1.01	<0.001

Table 3. Specific absorption rate (SAR) of each parameter used for patients who were evaluated using the 3T and 1.5 MRI machines

Variables	3 Tesla (n= 8,225)		1.5 Tesla (n=8,605)	
	SAR	*p*-value	SAR	*p*-value
Type of Image				
T1 weighted Image (TR < 700 msec)	0.93(n=3,319)		2.83(n=3,344)	
T2 weighted Image (TR >2,500 msec)	0.87(n=4,906)	<0.001	2.20(n=5,261)	<0.001
Weight Group				
Under weighted (<58 kg.)	0.89(n=2,620)		2.40(n=2,652)	
Normal weighted (58-68 kg.)	0.97(n=2,561)		2.44(n=3,331)	
Over weighted (>68 kg.)	0.90(n=3,044)	<0.001	2.52(n=2,622)	<0.001
Flip angle of RF Pulse				
< 75 degree	0.77(n=1,113)		2.18(n=715)	
> 75 degree	0.94(n=7,112)	<0.001	2.52(n=7,890)	<0.001

Note: n = number of series of images

Discussion

The average SAR value for all patients evaluated using the 3T MRI machine was lower than that of patients evaluated using the 1.5T MRI machine. This coincides with the study by Krishnamurthy[26] reporting that fetal brain images with higher resolution and better SNR with MRI 3.0T exhibited simultaneously reduced SAR compared with MRI 1.5T. In addition, the SAR received by the patients did not exceed the SAR limits set by FDA[23] which recommends that SAR for the whole body study should be lower than 4 W/kg within 15 minutes, for the head and neck should be lower than 3W/kg within 10 minutes and for the extremities should be lower than 12 W/kg within 5 minutes; to decrease the possible effects on the patient's tissues from the radio waves used in the MRI.

The SAR in studies where the spin echo technique was used showed that T2 weighted image (long TR > 2,500 music) had lower SAR than T1 weighted image (short TR < 800 msec) similar to the study by Allision et al.[27] and Chavhan et al.[28] showing that SAR decreased when TR increased. When considering the SAR according to weight group, for the underweight patients (<58 kg), the SAR was the lowest, 0.89 W/kg (3T), 2.40 W/kg (1.5T) and for the overweight patients (>68 kg) SAR was the highest = 0.97 W/kg (3T), 2.52 W/kg (1.5T). This coincides with the study by Gach et al. [29] revealing obese patients had a higher risk of absorbing heat from MRI than non-obese patients because obese patients required more field of view to scan.

When analyzing SAR according to the flip angle of the RF pulse, patients who were examined with the flip angle of the RF angle <75 degrees received less SAR than those examined with the flip angle of the RF pulse >75 degrees. This coincides with the study by Allison et al. [27] and Chavhan et al.[28] showing the SAR decreased when the flip angle decreased. The results of this study could help radiologists and MR technologists to experience greater confidence regarding the information that the SAR received by the patients not exceeding the SAR limits set by the FDA. In addition, the SAR decreased with decreased flip angle and increased TR.

Conclusion

The study revealed the average SAR of all patients, evaluated using the 3T MRI machine, was lower than those investigated using the 1.5T MRI machine for every anatomical region examined. For both of the MRI 3T and the MRI 1.5T groups, patients undergoing head and neck

studies would have the lowest SAR. Overweight patients would receive higher SAR. SAR could be reduced when TR increased and the flip angle decreased.

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Potential conflicts of interest

The authors declare they have no conflict of interest.

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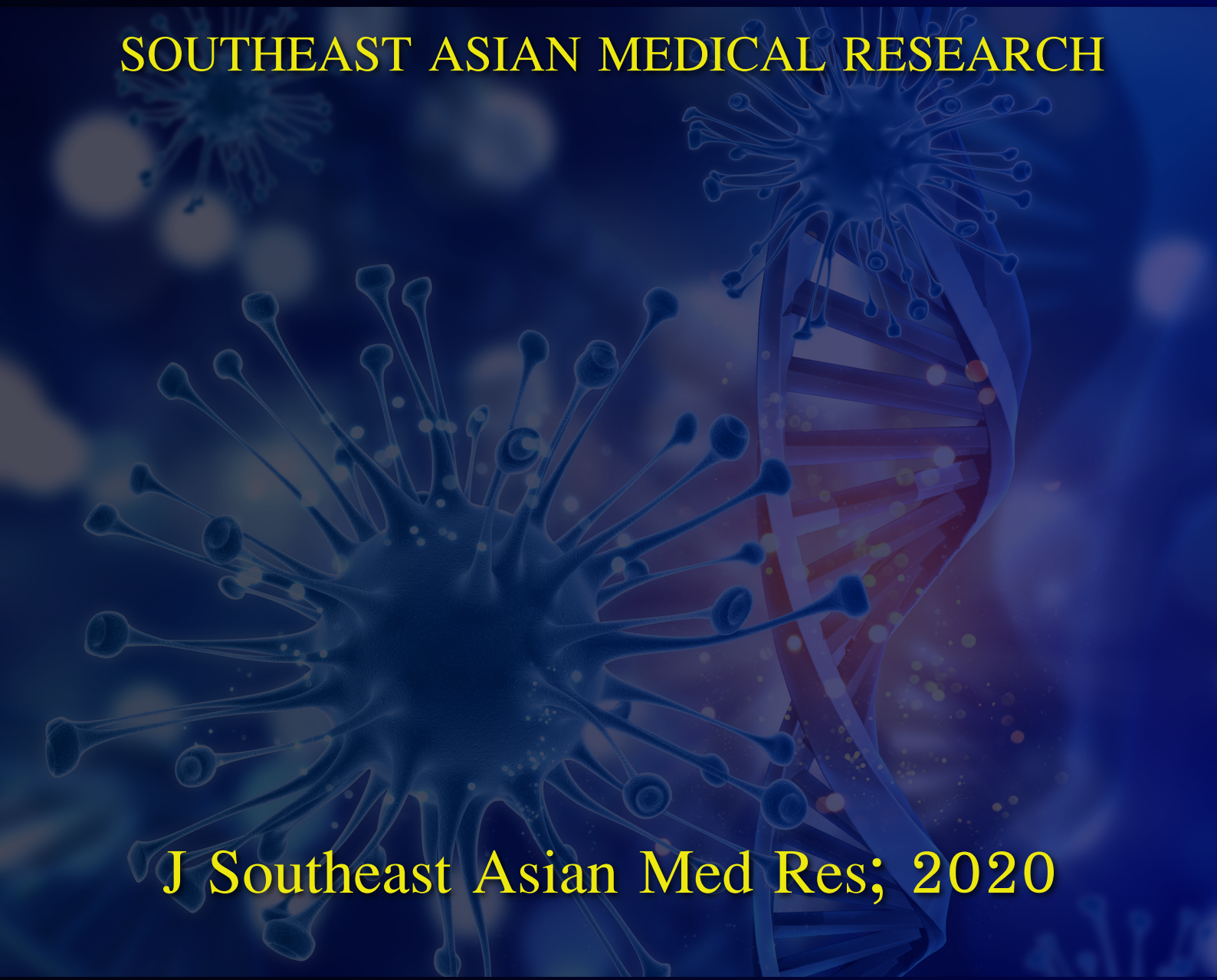

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