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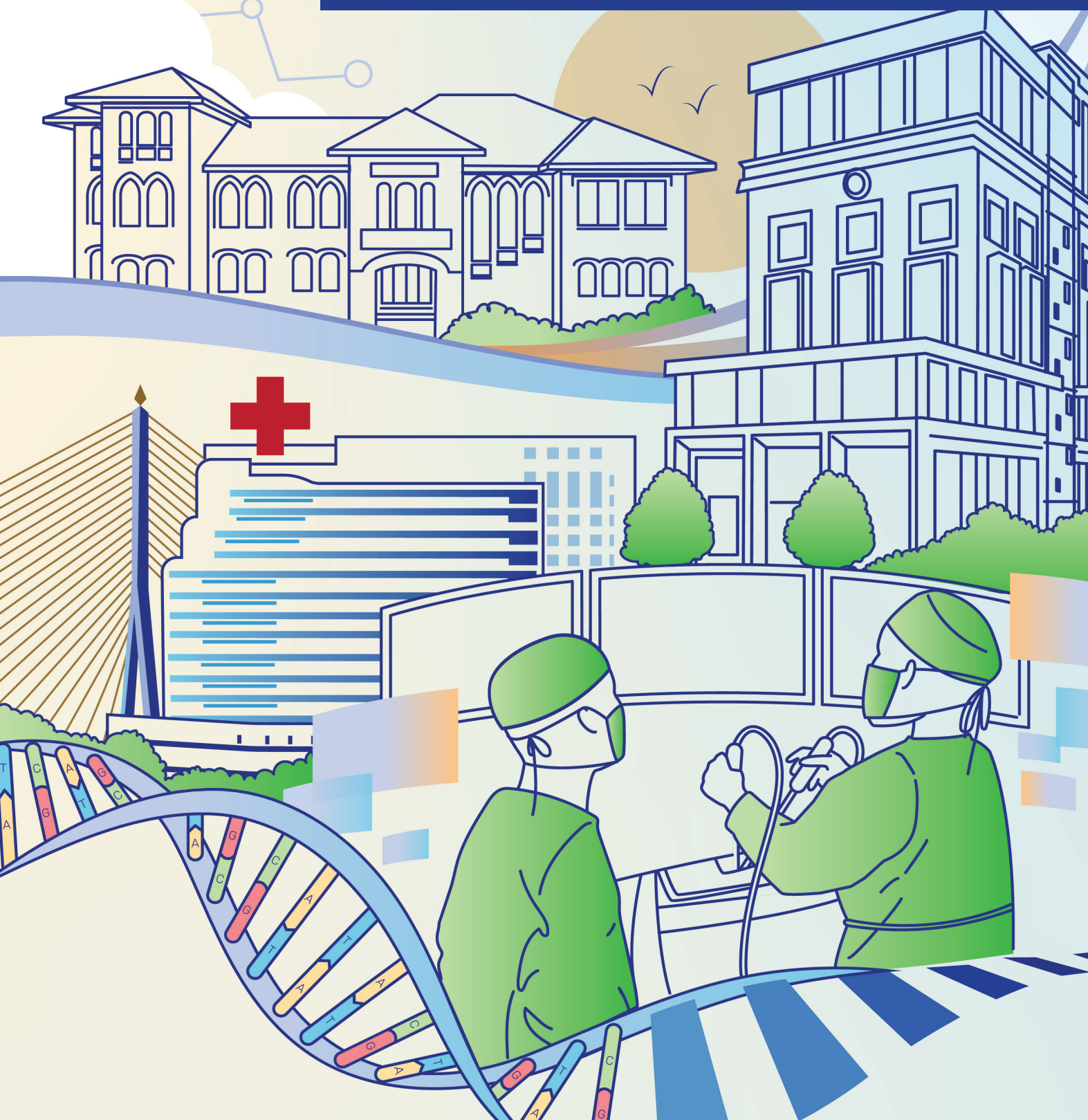

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ORIGINAL ARTICLES

REVIEW ARTICLES

Original Article

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The Effects of Two Interventions between Elastic Therapeutic Taping with Exercise and Sham Taping with Exercise on Pain Intensity, Knee Disability Reduction, Leg Strength, and Functional Ability Improvement for Gonarthrosis Patients at the Moderate Level

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ABSTRACT

OBJECTIVE: To investigate the effects of elastic therapeutic taping with exercise on the pain, disability, muscle strength, and functionality of knee in patients with moderate knee osteoarthritis (OA) compared with the sham taping technique with exercise.

METHODS: Eighty patients with moderate knee OA (Kellgren-Lawrence grade II-III) were randomized and separated into 2 groups, including an elastic therapeutic taping group and a sham taping group. Both groups received the same homework exercise. The assessments were performed at baseline, and 2 weeks and 12 weeks after the elastic therapeutic taping application. Pain level, the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) scale, muscle strength, Time Up and Go and Sit-to-Stand were used for the evaluation.

RESULTS: Patients that received elastic therapeutic taping and the sham taping technique with exercise demonstrated improvement in pain level, the WOMAC scale, muscle strength, Time Up and Go and Sit-to-Stand after 12 weeks of the applications, but the results showed a statistically significant difference in the outcome measurement of pain level, the WOMAC scale, and Time Up and Go between the 2 groups ($p < 0.01$, $p = 0.03$ and $p = 0.03$ respectively).

CONCLUSION: Elastic therapeutic taping with exercise can be an effective intervention for pain relief, reduced knee disability, and Time Up and Go in patients with moderate knee OA when compared with the sham taping technique with the exercise group.

KEYWORDS: elastic therapeutic taping, knee osteoarthritis, pain, Time Up and Go, WOMAC scale

INTRODUCTION

Knee osteoarthritis (OA) is a common joint disease found in the elderly. With an increasing prevalence, knee OA remains one of the major public health concerns[1-2]. According to systematic reviews and meta-analyses, the risk factors associated with the onset of knee OA are obesity, previous knee trauma, and the female gender and older age[3]. Knee pain, stiffness, and loss of functional ability reduce the quality of life and increase the risks of morbidity and mortality in knee OA patients[2].

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The core treatments of knee OA include nonpharmacologic, pharmacologic, and surgical management targeted at relieving pain, slowing disease progression, and improving functional ability in daily activities. For the non-surgical treatments, the Osteoarthritis Research Society International (OARSI) guidelines[4] addressed education, activities modification, weight management, transcutaneous electrical nerve stimulation, ultrasound diathermy, exercise, and muscle strengthening as the main rehabilitation protocols.

Elastic therapeutic taping is emerging as add-on treatment for knee OA[5] due to its safety, cost effectiveness, and immediate effect on pain alleviation. Elastic taping is preferred over rigid taping due to its causing less skin irritation[6]. The physiological effects of elastic taping include the facilitation of blood flow and lymphatic drainage by lifting the skin and increasing fascia space, encouraging pain relief, promoting normal biomechanics and neurofacilitation[7]. The tape adheres to the skin for three to five days on average or until it peels off.

Conservative management, including strengthening exercise, is recommended in moderate knee OA[4,8]. Better muscle strength results in the improvement of pain and physical function[8]. The exercises recommended by the OARSI[4] are squats and step-ups, evidencing better outcomes in quality of life and functional capacity over the non-exercise group[9]. However, the current data regarding elastic therapeutic taping with reference to knee OA are more difference studies[5]. Therefore, the purpose of this study is to investigate the efficacy of elastic therapeutic taping combined with exercise regarding pain, disability, and strength and function in moderate knee OA compared with the sham taping technique with the exercise group. It is hoped that the study results can guide the clinical usage of elastic taping, which can be a form of therapy for knee OA.

METHODS

This study was a randomized controlled trial with a double-blinded design.

The objective of the study was to investigate the efficacy of elastic therapeutic taping with exercise in moderate knee OA patients in relation to pain, disability, and strength and functional movement in daily activities. All of the patients gave informed written consent to participate in the study. Ethics committee approval for the study was obtained from the Bangkok Metropolitan Administration Human Research Ethics Committee (Project ID: 015h/63).

The participants were enrolled in the study from the outpatient rehabilitation clinic at Ratchaphiphat Hospital. The inclusion criteria were age greater than 50 years with moderate knee OA (Kellgren-Lawrence grade II-III)[10-11] diagnosed by an orthopedic surgeon or physiatrist, a pain score of 3-7 out of 10[12], body mass index (BMI) below 30 kg/m^2, and being able to do homework exercise as prescribed. The exclusion criteria were being allergic to elastic taping, having a rash or wound or infection in the taping region, sciatica sign[13], having taken opioid or steroid medication during the past 6 months, or knee injection during the past year, having a history of lower extremity fracture or surgery in the past year or scheduled in the next 12 weeks, gout, diabetic neuropathy, and rheumatoid arthritis. The drop-out criteria were pain having increased more than 3 levels on the visual analog scale (VAS) from baseline during the research and other treatment results in the VAS increasing more than 3 levels from baseline. The participants were requested to stop other treatments or medications, except for using paracetamol when they experienced pain.

All of the participants were divided into 2 groups by computer randomization; the experimental group was assigned to applied elastic therapeutic taping using the technique of Van Den Dries[14] (the tension around patella, figure 1) but was not applied to tension in the control group, which had the same color and design followed by the same exercise. The physiotherapists (PT) that applied the tape in both groups were blinded and were given an explanation of both new techniques (the same PT in each group with no crossing). On the first day, the participants were assigned to always keep the tape on and to re-visit for re-taping if it peeled off until the 12th week.

Figure 1 Taping technique by Van Den Dries[14]

Each exercise, including squats, step-ups, and quadricep muscle exercise[9] (figure 2), was prescribed by the 3rd PT in both groups for homework exercise until the 12th week (12 repetitions per set, 2 sets a day, and 3 days a week[15]). The outcome was collected by the blinded PT and included the VAS[16] at the 0, 2nd, and 12th week. The outcome was collected the modified the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC scale)[2], leg strength[12], Time Up and Go (TUG)[17-18], and the Sit to Stand (STS) test[19-21] at the 0 week.

The VAS[16] was used for assessing pain. The pain scale ranged from 0 to 10 where 0 represented no pain and 10 represented maximum pain. Knee disability was assessed by the modified Thai WOMAC scale[2] measuring pain, joint stiffness, and functional limitation. Leg maximum isometric strength was tested with leg dynamometers. TUG[17-18] and STS[19-21] were assessed functional ability and the mean time of the two tests was used in study.

The statistical package for the social science for windows was used in the analysis of the study results. The sample size used in this study was calculated and referenced from the study of Lu et al. in 2018[22]. The research design includes type I error set to 0.025, power of rest at 0.84, delta at 0.43,

Squat 1 Squat 2 Step-up 1 Step-up 2

Quadriceps muscles exercise

Figure 2 Homework exercise (The photos are granted permission to publish.)

and standard deviation[1]. The ninety-six subjects were calculated from an eighty minimal sample size and a dropout rate of twenty percent. The demographic data were identified as mean with standard deviation and compared by t-test. The treatment outcomes (VAS, WOMAC, leg strength, TUG, and STS) were analyzed by t-test. The statistical significance of the study was set at $p < 0.05$. The related factors were analyzed by logistic regression.

RESULTS

As indicated, ninety-six participants were recruited and eighty participants completed the study. Eighty moderate knee OA participants with demographic characteristics were described in Table 1. There were no statistically significant differences between the two groups. Comparing the two groups, the pain score showed a statistically significant reduction after taping by week 0, 2, and the 12th week ($p < 0.01$, $p = 0.018$ and $p < 0.001$ respectively). The pain was significantly reduced in the experimental group ($p < 0.001$, $p < 0.001$ and $p < 0.001$) and in the control group ($p < 0.001$, $p < 0.001$ and $p = 0.05$). The experimental group had a difference in the VAS score (1.49, 2.13 and 0.71), greater than the control group (0.57, 1.14 and 0.23) by the week 0, 2 and 12 as presented in Table 2.

Table 1 Demographic characteristics

Demographic data	Elastic taping group (n = 40)	Sham taping group (n = 40)	P-value
Gender: n (percent)			0.24
Male	5 (12.50)	2 (5)	
Female	35 (87.50)	38 (95)	
Age (years)	61.10 ± 11.64	62.60 ± 5.97	0.46
Body weight (kg)	67.91 ± 10.65	67.04 ± 12.66	0.74
Height (m)	1.56 ± 0.07	1.56 ± 0.06	1.00
BMI (kg/m^2)	27.96 ± 4.10	27.45 ± 3.88	0.57
Educational profile: n (percent)			0.68
Uneducation	4 (10)	6 (15)	
Elementary school	17 (42.50)	17 (42.50)	
Middle school	8 (20)	4 (10)	
High school	6 (15)	5 (12.50)	
Bachelor Degree	5 (12.50)	7 (17.50)	
Master/Doctoral degree	0	1 (2.50)	
Previous treatment of knee osteoarthritis: n (percent)			0.37
No previous treatment	24 (60)	20 (50)	
Previous treatment	16 (40)	20 (50)	

Abbreviations: kg, kilogram; m, meter; n, number

Table 2 Pain evaluations before and after treatment at week 0, 2nd, and 12th

VAS	Elastic taping group (n = 40)				Sham taping group (n = 40)				Difference 95% (CI)	P-value
	Before taping	After taping	VAS**	P-value	Before taping	After taping	VAS**	P-value		
0 week	5.94 ± 1.30	4.45 ± 1.40	1.49	< 0.001	5.88 ± 1.50	5.31 ± 1.40	0.57	< 0.001	0.86 (0.24, 1.47)	< 0.01
2nd week	5.94 ± 0.20	3.81 ± 0.20	2.13	< 0.001	5.88 ± 0.20	4.74 ± 0.00	1.14	< 0.001	0.93 (0.17, 1.70)	0.018
12th week	3.81 ± 0.20	3.10 ± 0.30	0.71	< 0.001	4.74 ± 0.30	4.51 ± 0.30	0.23	0.05	1.42 (0.62, 2.21)	< 0.001

Abbreviations: CI, confidence interval; n, number; VAS, visual analog scale
Statistical significance, p-value < 0.05

Comparing the efficacy, before at 0 week and after taping at week 12, the WOMAC scale showed a statistically significant reduction (p = 0.01 in the elastic taping group and p = 0.014 in the control group). The leg strength also showed a statistically significant increase (p < 0.01) in both groups. The TUG and STS tests showed a significantly decrease (p < 0.001) in both groups. Comparing the WOMAC scales and TUG showed a statistically significant reduction (p = 0.03 and p = 0.03 sequentially) as presented in Table 3. From the results, a history of no previous treatment of knee OA was found to be a pain related factor at the 12th week (p = 0.032) as described in Table 4.

Table 3 Comparing WOMAC scale, leg strength, TUG, and STS at week 0 and 12th

	Elastic taping group (n = 40)			Placebo taping group (n = 40)			Difference 95% (CI)	P-value
	Before taping at week 0	After taping at week 12th	P-value	Before taping at week 0	After taping at week 12th	P-value		
WOMAC	87.07 ± 6.60	76.77 ± 6.30	0.010	103.55 ± 4.60	94.55 ± 5.10	0.014	17.78 (1.60, 33.95)	0.03
Leg strength	9.32 ± 2.20	10.64 ± 2.80	< 0.01	8.88 ± 2.10	10.69 ± 2.00	< 0.001	0.05 (-1.03, 1.14)	0.93
TUG	19.58 ± 9.40	17.06 ± 7.90	< 0.001	16.41 ± 4.90	14.10 ± 3.70	< 0.001	-2.96 (-5.70, -0.22)	0.03
STS	16.60 ± 6.74	13.76 ± 2.92	< 0.001	16.14 ± 4.75	12.67 ± 3.59	< 0.001	-1.09 (-3.47, 1.28)	0.36

Abbreviations: CI, confidence interval; n, number; STS, Sit to Stand; TUG, Time Up and Go; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index
Statistical significance, p-value < 0.05

Table 4 Factors affecting the treatment efficacy of moderate knee osteoarthritis at week 12th

VAS at week 12th	Coefficient	Standard error	T-test	P-value	Difference 95% (CI)	
Age (years)	0.0106057	0.0250297	0.42	0.673	-0.0393145	0.0605259
BMI (kg/m^2)	-0.0608154	0.0584244	-1.04	0.301	-0.1773392	0.0557084
Female gender	1.015899	0.8090033	1.26	0.213	-0.5976071	2.629405
Education profile						
Elementary school	-0.3643198	0.6974061	-0.52	0.603	-1.755252	1.026613
Middle school	-0.2311001	0.8642506	-0.27	0.790	-1.954794	1.492593
High school	-0.2086383	0.8547513	-0.24	0.808	-1.913432	1.496064
Bachelor Degree	-0.0856019	0.8257467	-0.10	0.918	-1.732502	1.561298
Master/Doctoral degree	2.500807	2.04882	-1.22	0.226	-1.585436	6.587049
Previous treatment of knee OA						
No previous treatment	0.9953422	0.4538784	2.19	0.032	0.0901103	1.900574
Previous treatment	3.662506	2.510733	1.46	0.149	-1.344992	8.670005

Abbreviations: CI, confidence interval; kg, kilogram; m, meter; OA, osteoarthritis

DISCUSSION

The eighty participants in this study were mostly moderate knee OA female patients in both groups. Corresponding to previous studies, knee OA is mostly diagnosed in women aged over 50 years, with pronounced symptoms at age over 60 years[23], and obesity was one of the causative factors[3]. The logistic regression analysis demonstrated a relationship between a history of no previous knee OA treatment and pain level at the 12th week (p = 0.032). Consistent with the study of Neogi in 2013[24] and Teixeira et al. in 2020[25], osteoarthritis is a disease that cannot be resolved and that results in chronic pain. Mood and general health condition affect pain intensity in knee OA. The pain score significantly improved at the 0, 2nd, and 12th weeks in both groups as shown in Table 2. Sham taping might have some psychological benefits through the placebo effect as individuals may feel more confident and thus perform better because the tape provides a protective barrier of sorts or psychological acupressure for treating pain. However, our study did not investigate the psychological factors that effect pain level in knee OA participants. Elastic taping activates the mechanoreceptor and stimulates the large-diameter A-alpha and A-beta nerve fibers, resulting in pain inhibition according to gate control theory[26]. Moreover, the tape improves circulation, enhances the healing process, and allows a full range of motion that is not demonstrated in rigid tape[14,27]. The elastic taping technique depends on the objective and area of treatment. Size, length, direction, and the tension of the tape must be considered[28]. In this study, we applied Van Den Dries's technique, which is similar to the study of Hinman et al.[29]. According to medial gliding, and the medial and anteroposterior tilt of the patella, the tape brings the patella into proper alignment (unloading of the patellofemoral joint), resulting in pain reduction. The study of Huang et al.[30] reported the improvement of knee joint alignment and loads during standing and walking in knee OA led to pain reduction. Further, the study of Wageck et al.[31] reported ineffective pain reduction using different taping techniques. The corrected taping techniques were related to knee OA treatment results. Pain reduction can provide effectiveness of muscle action that can improve knee disability (WOMAC), physical abilities (TUG, STS), and leg muscle strength, consistent with the results shown in Table 3. In this study, the WOMAC, TUG, STS, and leg strength were improved in the control group. The WOMAC scale, which has some parts of pain assessment, and leg strength in sham taping, might be some psychological effects while the TUG and STS might have some psychological effects and homework exercise program. There was a significant difference in the WOMAC and TUG, but no significant differences in leg strength or STS between the experimental and control group. Because leg strength was measured in the sitting position, it might have affected tape efficiency rather than muscle strength. The STS was used for balance assessment. Other outcomes were also improved after taping in both groups. Several studies have reported that strengthening exercise can reduce knee pain and improve function in knee OA. Fukaya et al.[32] for example reported that weakness in knee extensor muscles in knee OA patients contributes to walking limitations; and the study of Alnahdi et al.[33] showed that quadricep, hamstring, and hip muscle deficiency is associated with knee OA and has an effect on physical function[34-36]. However, our study did not investigate the minimal clinically important difference (MCID)[37-38] or substantial clinical benefit[39] of the WOMAC scale.

The limitations of this study were that it did not measure pain level at rest or during activities which could demonstrate the efficacy of elastic taping. Balance training was not included in this study so the STS, measuring both leg strength and balance, showed no difference between the groups. Finally, the effect of the home program might not be clear as only quadricep strength was measured.

CONCLUSION

Elastic taping therapy with exercise could be used as an effective intervention for pain relief, reduced knee disability, and Time Up and Go in patients with moderate knee OA when compared with the sham taping technique with the exercise group[40].

CONFLICT OF INTEREST

The authors report no conflict of interest for this article.

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DATA AVAILABILITY STATEMENT

All of the data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Original Article

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Appropriate Use of Anticoagulants among Nonvalvular Atrial Fibrillation Patients at a University Hospital in Thailand

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ABSTRACT

OBJECTIVE: Warfarin is primarily used for stroke prevention in atrial fibrillation (AF) patients in Thailand. Novel oral anticoagulants (NOACs) are used less commonly due to their high cost. This study aimed to evaluate the appropriate use of anticoagulants and clinical outcomes among nonvalvular AF (NVAF) patients.

METHODS: This retrospective study collected data from the electronic medical records of patients who were diagnosed with NVAF between January 2014 and December 2019 at the Faculty of Medicine, Vajira Hospital. Baseline characteristics, prescribed indication, types and doses of anticoagulant, and ischemic and hemorrhagic outcomes were recorded and analyzed.

RESULTS: We analyzed 783 patients with NVAF in this study. Of these, 539 (68.90%) were treated with oral anticoagulants (OAC), including 344 patients (43.90%) with warfarin therapy and 195 (24.90%) with NOACs. Meanwhile, 492 (73.10%) patients with CHA_2DS_2VASC score ≥ 2 received OAC therapy that was suitable for their indication. Of the 344 patients who received warfarin, 112 patients (32.60%) had an optimal time in therapeutic range (TTR) level of ≥ 65%. Of the 195 NOAC patients, only 98 (50.30%) received appropriate doses of NOACs. There was no statistically significant difference in the overall incidence rates of ischemic stroke/systemic embolism, bleeding, cardiovascular death, and all-cause death between the warfarin and NOACS groups. Appropriate TTR levels in the warfarin group was associated with significantly lower incidence rates of cardiovascular death (hazard ratio: 0.14; 95% CI: 0.02–0.79; p = 0.02) and all-cause death (hazard ratio: 0.36; 95% CI: 0.12–0.87; p = 0.01), than inappropriate TTR levels.

CONCLUSION: Most NVAF patients received oral anticoagulants with the appropriate indication. Warfarin is the most prescribed oral anticoagulant for patients with NVAF. About half of the patients received inappropriate doses of oral anticoagulants that potentially adversely affected the study outcomes of cardiovascular and all-cause deaths.

KEYWORDS: nonvalvular atrial fibrillation, novel oral anticoagulant, warfarin

INTRODUCTION

Atrial fibrillation (AF) is a common arrhythmia worldwide. In the general Thai population, the prevalence of AF is relatively low at 0.36%[1], while it is 1.90% in adults older than 65 years[2]. AF patients are at five times greater risk of developing stroke and systemic embolism (SE) than the normal population without AF[3].

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The aim of AF treatment with oral anticoagulants (OAC) is to prevent complications, such as ischemic stroke and SE[4-5]. Over the past ten years, the use of novel anticoagulants (NOACs) in patients with nonvalvular AF (NVAF) has increased globally. In Asia, only 60.70% of AF patients with a high risk of stroke received OAC treatment[6]. In Thailand, historical data show that 75.30% of AF patients received oral anticoagulants. Of these, 90.10% received warfarin and only 9.10% received NOACs[7].

Warfarin has several disadvantages including the need for close monitoring of the international normalized ratio (INR) level, which creates an extra burden for physicians and patients. NOACs, on the other hand, require no monitoring. However, they are more expensive than warfarin and are not covered by the country's public healthcare scheme. Therefore, they are not affordable for many patients. The aim of this study was to investigate the appropriateness of anticoagulant use in NVAF patients and compare the incidence of stroke, SE, and bleeding between anticoagulated and nonanticoagulated patients.

METHODS

This study was a single center, retrospective longitudinal descriptive study that collected data from the Vajira electronic database (Ephis) from January 2014 to December 2019. The trial was designed and led by three investigators. The study was approved by the ethics committee of the Faculty of Medicine, Vajira Hospital, Navamindradhiraj University (COA number 165/61). Eligible patients were those diagnosed with NVAF or atrial flutter who had been followed up at the Vajira outpatient clinic for at least three months and were more than 18 years old. All eligible patients were included in this study. We excluded patients with valvular AF, including moderate to severe rheumatic mitral stenosis and prosthetic valve disease. Baseline characteristics collected included age, sex, body weight, height, systolic blood pressure, diastolic blood pressure, heart rate, date of diagnosis, type of AF, first clinical presentation, underlying medical illnesses including coronary artery disease (CAD), heart failure, previous stroke or transient ischemic attack (TIA), peripheral arterial disease, thyroid disease, liver disease, chronic kidney disease, sick sinus syndrome and heart block, cancer, history of bleeding, OAC use (type and dose), antiplatelet use, and other medications. The investigators also gathered baseline laboratory investigations including serum creatinine, hemoglobin level, and platelet count. Patients with liver cirrhosis were noted along with the Child–Turcotte–Pugh classification. The CHA_2DS_2-VASc score (consisting of heart failure, hypertension, age, diabetes mellitus, peripheral arterial disease or CAD, and female sex) was then calculated for all patients. The investigators were able to determine the appropriateness of anticoagulant use by physicians at Vajira Hospital during the study period as a primary outcome based on 1) indications for OAC use in NVAF patients and 2) the standard dosage of OACs prescribed. According to standard guidelines, OAC is indicated in NVAF patients with a CHA_2DS_2-VASc score ≥ 2 in males and greater than and ≥ 3 in females. Antiplatelets or anticoagulants are not recommended for patients with a CHA_2DS_2-VASc score of zero (including women without other stroke risk factors)[8]. Based on such indications, the investigator was able to categorize all patients studied into two groups: those whose indication was appropriate for OAC use and those whose indication was inappropriate. Regarding the prescribed dosage of OACs, both the warfarin and NOACs groups were studied. In the warfarin group, the appropriate drug dosage was determined by time in therapeutic range (TTR) at the optimal INR level of 2–3[8] based on the most recent three or more consecutive INR levels. A TTR of greater than 65% was appropriate for the warfarin dose[9-10]. The TTR was calculated using the Rosendaal et al. method[11]. In the NOACs group, the dosing was considered appropriate if adhering to adjusted dose criteria as outlined in the current standard guideline recommendations[4-5,8] which based on the patients' creatinine clearance (CrCl) calculated by the Cockcroft–Gault Equation,

ml/min, and based on the Child–Turcotte–Pugh score in liver cirrhosis patients. Based on the dosage, the investigator was able to categorize all patients on OAC therapy into appropriate and inappropriate dosage groups. In addition to the primary outcome, this study's other primary outcomes were the incidence rates of ischemic stroke or SE, cardiovascular death, all-cause death and bleeding events. We compared anticoagulated patients with nonanticoagulated patients and appropriate OAC dose with inappropriate OAC dose. Patients in the study were followed up from the date of diagnosis of AF or OAC start date until the index date that was defined as the date of the first event or the end of the study period, December 11, 2019, whichever came first. AF was categorized into 1) paroxysmal, 2) persistent, 3) long-standing persistent, and 4) permanent[12]. The definition of bleeding used was in accordance with the global use of strategies to open occluded arteries (GUSTO) bleeding definition[13]. Sample size calculations were based on estimating the single proportion from a reported prevalence of NVAF[9] and based on two independent proportions, to find the correlation of stroke incidence between anticoagulated and nonanticoagulated patients. With a statistical power of 80%, two-sided p-value of 0.05, and a 4.54% difference of incidence of ischemic stroke between NVAF patients in the anticoagulant and nonanticoagulant groups[14], the appropriate sample size was 768 patients. SPSS version 23 and STATA version 13 were used for statistical analysis.

RESULTS

From January 2014 to December 2019, 783 patients were included in the study. The consort diagram is shown in Figure 1 for more details. The median follow-up period was 47 months.

The mean participant age was 74.08 (± 11.49) years; 416 patients (53.10%) were women. Regarding AF type, 557 (71.10%) patients had paroxysmal AF, 193 (24.60%) had permanent AF. 16 (20.00%) had persistent AF and 13 (1.70%) had long-standing persistent AF. Atrial flutter was present in 5.40% of patients. The median CHA_2DS_2-VASc score was 4.0 (IQR 3–5). Overall, there were statistical differences in baseline characteristics between OAC and non-OAC patients, in weight, clinical presentation, history of hypertension, previous stroke/TIA, valvular heart disease, baseline LVEF, CHA_2DS_2-VASc score and HAS-BLED score (table 1). The distribution of the CHA_2DS_2-VASc score and HAS-BLED score by choice of anticoagulation are shown in Figure 2 and 3.

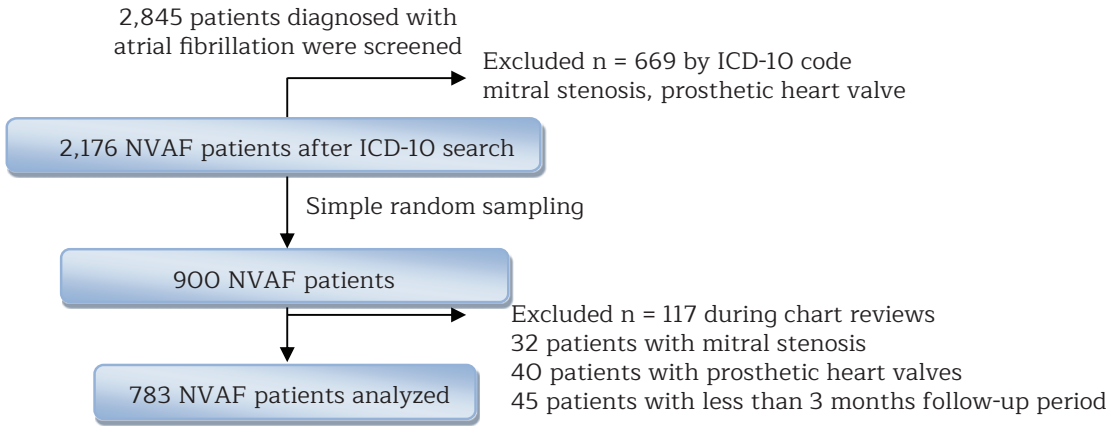
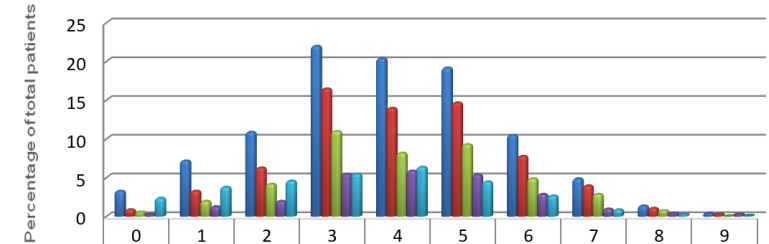


Figure 1 Consort diagram of study patients

Table 1 Baseline characteristics of patients with nonvalvular atrial fibrillation

Variables	Total (n = 783)	OAC (n = 539)	No OAC (n = 244)	P-value
Age (years)	74.08 ± 11.49	74.45 ± 0.47	73.26 ± 0.82	0.18
Female sex	53.10%	54.54%	50.00%	0.23
Weight (kg)	62.82 ± 14.20	63.64 ± 14.80	60.95 ± 12.60	0.01
Heart rate	77 ± 17	77 ± 17	77 ± 17	0.63
Type of AF				
Paroxysmal	557 (71.10%)	72.20%	68.90%	0.12
Persistent	16 (20.00%)	2.60%	0.80%	
Long standing persistent	13 (1.70%)	2.00%	0.80%	
Permanent	193 (24.60%)	22.80%	28.70%	
Previous diseases				
Hypertension	67.90%	72.20%	58.60%	0.00
Diabetes	31.90%	33.60%	28.30%	0.16
Hyperlipidemia	37.30%	39.30%	32.80%	0.08
Previous stroke or TIA	27.70%	33.20%	15.60%	0.00
Thromboembolic event	1.70%	2.00%	0.80%	0.22
CKD	17.50%	18.40%	15.60%	0.34
Peripheral arterial disease	1.40%	1.70%	0.80%	0.35
Coronary artery disease	25.80%	26.90%	23.40%	0.29
LVEF < 40%	26.90%	29.60%	19.70%	0.03
Valvular heart disease	11.00%	10.20%	5.30%	0.03
Permanent pacemaker implantation	9.60%	8.70%	11.90%	0.17
Sick sinus syndrome	10.00%	8.20%	14.30%	0.01
Thyroid disease	11.90%	11.70%	11.70%	0.81
Liver disease	2.30%	2.40%	2.00%	0.75
CHA_2DS_2 VASC score	4 (3,5)	4 (3,5)	3 (2,5)	0.00
HAS-BLED score	2 (2,3)	3 (2,4)	2 (1,5)	0.00
LVEF	50.97 ± 26.10	49.22 ± 26.33	55.88 ± 24.88	0.01
Left atrial dimension (cm)	3.85 ± 1.90	3.94 ± 1.90	3.60 ± 1.90	0.12
Creatinine clearance (ml/min)	51.34 ± 30.79	49.64 ± -27.05	49.36 ± 29.44	0.90

Abbreviations: AF, atrial fibrillation; CKD, chronic kidney disease; cm, centimeter; kg, kilogram; LVEF, left ventricular ejection fraction; min, minute; ml: milliliter; n, number; OAC, oral anticoagulant; TIA, transient ischemic attack
Data with normal distribution are mean (± 2SD), with skew distribution are median (IQR), categorical data n(%)



	0	1	2	3	4	5	6	7	8	9
Total	3.3	7.2	10.9	22	20.4	19.2	10.5	4.9	1.4	0.4
OAC	0.9	3.3	6.3	16.5	14	14.7	7.8	4	1.1	0.3
Warfarin	0.6	2	4.2	11	8.2	9.3	4.9	2.9	0.8	0
NOACs	0.3	1.3	2	5.5	5.9	5.4	2.9	1	0.4	0.3
No OAC	2.4	3.8	4.6	5.5	6.4	4.5	2.7	0.9	0.3	0.1

Figure 2 Distribution of CHA2DS2-VASc score by choice of anticoagulation

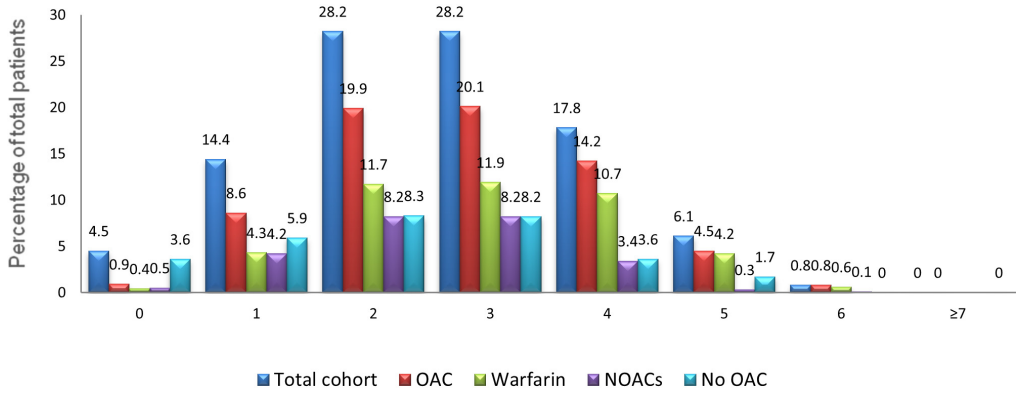


Figure 3 Distribution of HAS-BLED score by choice of anticoagulation

Regarding anticoagulant and antiplatelet therapy received, of the total 783 patients, most (539 patients, 68.92%) were treated with OAC therapy, and of these, 344 (63.80%) received warfarin therapy while 195 (36.20%) received NOAC therapy. Of the 195 patients who received NOACs, dabigatran was the most prescribed NOAC with 86 patients (44.10% of those on NOAC therapy) while rivaroxaban was prescribed for 77 patients (39.50% of those on NOACs therapy). Apixaban was prescribed for 32 patients (16.40% of those on NOAC therapy). Edoxaban was not available at the hospital at the time of the study. Antiplatelets were used in 211 of the 783 patients (26.90% of the total patients). There were 99 patients (12.60% of 783 patients) who received a combination of antiplatelet and OAC. Overall, 132 patients (16.90% of 783 patients) did not receive any antiplatelet or anticoagulant therapy (table S1).

Regarding the appropriateness of the OAC therapy use according to indication, of the 783 patients, there were 701 NVAF patients with a CHA2DS2-VASC score ≥ 2 (including women with two additional risk factors). Of these, 492 patients (70.20%) received OAC therapy, while 209 patients (29.80%) did not receive it despite having a CHA_2DS_2-VASC score ≥ 2 although 98 of them received antiplatelet therapy (from other indications) instead of OAC therapy. There were 48 patients with a CHA_2DS_2-VASC score of 0 (including women without additional stroke risk factors). Of these, 16 patients (33.30% of 48 patients) received OAC therapy that was not in accordance with the indication for OAC use (figure 2 and table S2).

Regarding the appropriate dose of warfarin, the mean TTR of target INR 2–3 in the warfarin group was 45.33 (± 30.71). Only one third of patients on warfarin treatment (112, 32.60% of 344 patients) had an optimized TTR level of more than 65%, and 57.30% of the 344 patients had a TTR less than 50% (figure S1).

Regarding the appropriate dose of NOACs, among the 195 patients who were on NOAC therapy, 98 patients (50.30%) received appropriate doses of NOACs, while 97 patients (49.70%) did not. Of these, 80 patients (82.40%) received less than the appropriate dose, while 14 patients (14.40%) received higher than appropriate dose. Three patients (3.20%) received NOACs despite not meeting the criteria for use (figure S2 and table S3).

The overall incidence rate of ischemic stroke or SE in the total study population during the follow-up period was 1.47/100 person-years. The incidence rates of stroke/SE in the warfarin, NOACs, and no anticoagulant groups were 1.83, 1.28, and 1.20 per 100 person-years, respectively. No significant difference in the incidence rate of ischemic stroke or SE was observed between different treatment groups, except for the warfarin group and NOACS group at 1 year with a hazard ratio (HR) of 7.49 (95% CI: 1.33–42.13,

p = 0.0172) (table S4, S5). In the warfarin group, 11 of 13 patients with ischemic stroke or SE that occurred at 1 year had a TTR lower than 65%. No statistically significant difference of incidence rate of ischemic stroke or SE was observed in patients receiving the appropriate dose, compared with inappropriate dose of NOACs therapy and within the warfarin group (table 2).

Bleeding occurred in 72 (18.80%) of 382 patients. The overall incidence rate of bleeding in the study patients during the follow-up period was 1.76/100 person-years. The incidence rates of bleeding in the warfarin, NOACs, and no anticoagulant groups were 2.81, 1.79, and 0.56 per 100 person-years, respectively. During the entire study period, bleeding occurred in the warfarin group more often than in the NOACs group but this was not statistically different (HR 1.54, 95% CI: 0.81–2.94, p = 0.18). In addition, at the 1-year and 5-year follow-up, the patients on warfarin had a higher incidence of bleeding than patients on NOACs with HR 6.42; 95% CI:1.58–56.29; p = 0.002 and HR 1.89; 95% CI: 0.96–4.06.29; p = 0.05 respectively (table S5). Among the patients who received warfarin, bleeding events occurred less often in those with an appropriate TTR but with no statistical difference (HR 0.77, 95% CI 0.43–1.38, p = 0.39). Among the patients who received NOAC therapy, bleeding events occurred in those with appropriate dose less often than in those with an inappropriate dose of NOACs therapy but with no statistical difference (HR 0.48, 95% CI: 0.15–1.61, p = 0.26) (table 2).

The overall incidence rate of cardiovascular death in the study patients during the follow-up period was 0.66/100 person-years. The incidence rates of cardiovascular death in the warfarin, NOACs, and no anticoagulant groups were 0.72, 0.31, and 0.70 per 100 person-years, respectively. There was no difference of incidence rate of cardiovascular death between the warfarin, NOACs and No OAC group. However, in patients in the warfarin group, there were fewer cardiovascular deaths in patients with a TTR ≥ 65% than in those with an inappropriate TTR. This was statistically significant (HR 0.14, 95% CI: 0.02–0.79, p = 0.02). For NOACs patients, no statistically significant differences in the incidence rate of cardiovascular death was observed between patients on an appropriate dose and those on an inappropriate dose of NOACs.

Table 2 The incidence of efficacy and safety outcomes in NVAF patients

	Stroke or SE	Bleeding	Cardiovascular death	All-cause death
Warfarin (n = 344)	No. of events/ Incidence rate*	No. of events/ Incidence rate*	No. of events/ Incidence rate*	No. of events/ Incidence rate*
Appropriate TTR ≥ 65	9/1.33	16/2.43	1/0.15	6/0.94
Inappropriate TTR < 65	26/2.13	38/3.13	13/1.06	31/2.64
Hazard ratio of IR (appropriate/inappropriate TTR)	0.62 (0.29-1.32), 0.22	0.77 (0.43-1.38), 0.39	0.14 (0.02-0.79), 0.02	0.36 (0.12-0.87), 0.01
NOAC (n = 195)				
Appropriate dose	3/1.03	4/1.20	1/0.30	6/0.80
Inappropriate dose	6/1.79	7/2.49	1/0.34	12/2.29
Hazard ratio of IR (appropriate/inappropriate dose)	0.57 (0.15-2.25), 0.45	0.48 (0.15-1.61), 0.26	0.87 (0.54-13.77), 0.93	0.44 (0.13-1.25), 0.10
No OAC (n = 244)	19/1.20	9/0.56	11/0.70	29/2.14

Abbreviations: IR, incidence rate; n, number; NOAC, novel oral anticoagulant; NVAF, nonvalvular atrial fibrillation; SE, systemic embolism; TTR, time in therapeutic range
*Incidence rate in 100-person year

The overall incidence rate of all-cause death in total patients was 1.97/100 person-years. The incidence rates of all-cause death in the warfarin, NOACs, and nonanticoagulated groups were 2.00, 1.69, and 2.14 per 100 person-years, respectively. In the warfarin group, there were fewer all-cause deaths in patients with an appropriate TTR, < 65%, than in those with an inappropriate TTR. This was a statistically significant difference (HR 0.23, 95% CI: 0.08–0.68, p = 0.003). For NOAC patients, no statistically significant difference in incidence rates of all-cause death was observed between patients on an appropriate dose and those on an inappropriate dose of NOACs (table 2).

According to the univariate analysis performed to determine factors for predicting the ischemic and hemorrhagic outcomes, previous ischemic stroke, peripheral arterial disease, $CHA_2DS_2VASc \geq 2$, HAS-BLED ≥ 3 and labile INR were the predictive factors for ischemic stroke outcome. After the multivariate analysis, diabetes and a history of stroke/TIA were the statistically significant independent predictive factors for ischemic stroke or SE outcome. For the bleeding outcome, an age of more than 65, previous ischemic stroke, $CHA_2DS_2VASc \geq 2$, HAS-BLED ≥ 3, CrCl < 30 and labile INR were the predictive factors. However, after the multivariate analysis, there was no significant correlation between the above factors and the bleeding outcome. A post-hoc analysis comparing the efficacy and safety outcome between the NOACs and warfarin group, stratified by various predictive factors, showed no statistically significant differences in the incidence rate of ischemic stroke/SE or bleeding outcome between the two groups (table 3).

Table 3 Factors that influenced the risk of stroke/SE and bleeding in patients with nonvalvular atrial fibrillation

	Stroke/SE					Any Bleeding				
	Univariate		Multivariate		Hazard ratio NOAC vs Warfarin, P- value	Univariate		Multivariate		Hazard ratio NOAC vs Warfarin, P-value
	OR (95% CI)	P-value	OR (95% CI)	P-value		OR (95% CI)	P-value	OR (95% CI)	P-value	
Age > 65	1.48 (0.73-2.98)	0.33			0.71 (0.33-1.54), 0.81	2.87 (1.29-6.38)	0.007	1.42 (0.50-4.03)	0.51	0.65 (0.30-1.26), 0.19
Female Sex	1.09 (0.62-1.89)	0.79			0.83 (0.25-2.27), 0.74	1.11 (0.68-1.81)	0.71	0.81 (0.43-1.53)		
Diabetes	1.36 (0.79-2.34)	0.31			0.39 (0.09-1.58), 0.22	0.93 (0.55-1.58)	0.90	0.92 (0.46-1.84)		
Hypertension	1.60 (0.86-2.97)	0.15			0.99 (0.41-2.19), 1.01	1.01 (0.60-1.69)	1.00	0.47 (0.20-1.07)		
Previous stroke	3.32 (1.95-5.67)	0.00	1.89 (1.19-3.02)	0.007	0.51 (0.13-1.49), 0.20	2.00 (1.22-3.29)	0.008	1.16 (0.79-1.69)	0.45	0.84 (0.29-2.49), 0.53
CAD	1.37 (0.77-2.42)	0.28			1.07 (0.28-4.12), 0.59	1.30 (0.77-2.20)	0.33	1.12 (0.53-2.38)		0.73 (0.24-2.22), 0.73
PAD	4.7 (1.21-18.22)	0.05	2.06 (0.18-23.83)	0.56	1.97 (0.03-154.43), 0.67	3.82 (0.99-14.73)	0.07	4.1 (0.59-28.5)		
Liver disease	1.52 (0.34-6.79)	0.64			0	1.24 (0.28-5.51)	0.68	0.47 (0.05-4.89)		
CHA_2DS_2 VASc ≥ 2	10.47 (1.44-76.39)	0.002	1.62 (0.31-8.54)	0.57	0.74 (0.31-1.56), 0.42	2.98 (1.06-8.34)	0.03	1.98 (0.37-10.72)	0.43	0.57 (0.29-1.12), 0.26
HAS-BLED score ≥ 3	2.20 (1.24-3.90)	0.007	1.38 (0.35-5.36)	0.65	0.68 (0.20-1.76), 0.40	2.74 (1.57-4.66)	0.000	1.97 (0.64-6.04)	0.24	0.94 (0.45-1.93), 0.18
CrC < 30	1.59 (0.89-2.86)	0.14			0.30 (0.04-2.05), 0.32	1.93 (1.51-3.25)	0.02	1.87 (0.89-3.95)	0.09	0.70 (0.21-2.37), 0.91
Labile INR	1.98 (1.15-3.39)	0.016	1.57 (0.14-17.41)	0.72	-	2.42 (1.48-3.97)	0.001	0.45 (0.10-1.95)	0.29	-
TTR < 65%	1.89 (0.80-4.51)	0.17			-	1.14 (0.6-2.15)	0.75	1.78 (0.39-8.02)	0.45	-
Antiplatelet use	1.28 (0.73-2.26)	0.45			1.56 (0.35-5.6), 0.46	0.82 (0.47-1.45)	0.58	0.63 (0.26-1.54)		

Abbreviation: AF, atrial fibrillation; CAD, coronary artery disease; CrC, creatinine clearance; INR, international normalized ratio; NOAC, novel oral anticoagulant; OR, odd ratio; PAD, peripheral arterial disease; SE, systemic embolism; TIA, transient ischemic attack; TTR, therapeutic range

DISCUSSION

The results of this study showed that the majority of NVAF patients received OAC therapy with most receiving OAC with the appropriate indication. Regarding choice of anticoagulants used, warfarin was more commonly prescribed at Vajira Hospital (63.90%) than NOACs (26.10%). The Thailand registry reported the use of warfarin in 90.90% of the country's registered patients and NOACs use in 9.10% of patients[8]. This implies more NOAC than warfarin use in NVAF patients in recent years. Moreover, the results from this study showed that most patients on warfarin therapy did not achieve the target TTR level of > 65%. In contrast to warfarin, the prescription of NOACs was low at our center due to its high price with prescription limited to subspecialists. We found that only half of NOACs patients received appropriate doses. Physicians tended to prescribe below the recommended dose of NOACs more than they prescribed higher than the recommended dose. Regarding the efficacy and safety outcome results, there was no statistical difference in the incidence of ischemic stroke or SE among different OACs and between appropriate and inappropriate doses of OAC. This may result from the low target TTR in this study population, inappropriate doses of NOACs in some patients and inadequate power in this study to differentiate the efficacy outcomes. However, among warfarin group, patients with inappropriate TTR of < 65% were associated with a significantly increased incidence of both cardiovascular and non-cardiovascular deaths, compared to those with a TTR ≥ 65%. Our study has a consistent result with a previous Thailand registry reported poor TTR control is associated with adverse clinical outcome, including ischemic events, major bleeding, intracranial hemorrhage and death[15]. The underlying reasons for the higher incidence rate of cardiovascular and all-cause death in inappropriate TTR patients could be from warfarin level fluctuations leading to bleeding and subsequently to discontinuation of the drug, which then leads to the adverse events. Regard to NOACs dosing and clinical outcome, out findings

This study has several limitations. Due to its retrospective design, the subjects were not fully randomized. Because of the study's limited duration, its sample size is relatively small compared with prior studies. Some data were missing due to the retrospective nature of the study and the electronic medical records. Furthermore, due to inadequate power regarding the ischemic and bleeding outcomes, we are unable to determine differences in the efficacy and safety outcomes between different patient groups. A larger prospective cohort or randomized study with a longer follow-up period are suggested for further study.

CONCLUSION

Most NVAF patients received OACs with appropriate indications. Warfarin was used for patients with NVAF more than NOACs were. About half of the patients received an inappropriate dose of OACs (both warfarin and NOACs). A suboptimal TTR, < 65%, was associated with significantly higher cardiovascular and all-cause mortality than an optimal TTR.

CONFLICT OF INTEREST

The authors have no financial interest in any of the products mentioned in this article.

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None

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to restrictions.

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Original Article

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Non-neoplastic Kidney Diseases in Adult Tumor Nephrectomy and Nephroureterectomy Specimens in a Southeast Asian Tertiary Medical Center

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ABSTRACT

OBJECTIVE: Non-neoplastic kidney diseases are concurrently present in up to 15% of patients with renal and ureteral tumors, which have been most studied in the United States. This study was conducted to determine the prevalence and spectrum of renal parenchymal diseases in similar patients from a Southeast Asian academic institution.

METHODS: We searched the database of the Department of Anatomical Pathology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University (2012–2022) and found 194 adult nephrectomy and nephroureterectomy specimens with renal, renal pelvis, and ureteral tumors. Additional stains included periodic acid-Schiff, methenamine silver, and Masson trichrome. Direct immunofluorescence microscopy was performed on the paraffin tissue sections for immunoglobulin (Ig) G, IgA, IgM, and kappa and lambda light chains. Clinical information, including age, gender, and co-morbidities, was obtained from the electronic medical records.

RESULTS: Analysis of the 194 cases demonstrated the average age was 61 years (range: 17-89 years), with 126 males (65%) and 68 females (35%). After re-examination of the non-neoplastic renal parenchyma, 14 cases (7%) had diffused and/or nodular mesangial sclerosis. Diabetic nephropathy (12 cases) and idiopathic nodular glomerulosclerosis (2 cases) were diagnosed and associated with either stage 1 or 2 genitourinary cancers. Another case was diagnosed with atheroembolic renal disease. In all cases, the concurrent renal diseases were not identified during the initial evaluation.

CONCLUSION: Examination of the non-neoplastic renal parenchyma is important to identify non-neoplastic kidney diseases, such as diabetic nephropathy, so early treatment may result in improved clinical outcomes for kidney and urothelial cancer patients.

KEYWORDS: chronic kidney disease, diabetic nephropathy, nephrectomy, nephroureterectomy, non-neoplastic parenchyma, renal tumor

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INTRODUCTION

In 2020, there were an estimated 431,288 new cases of kidney cancer globally[1]. In Thailand, kidney cancer is the 20th most common malignant tumor, accounting for 2,170 (1.1 %) of new cancer diagnoses and 1,230 (1%) of cancer deaths according to GLOBOCAN 2020[2], radical nephrectomy, partial nephrectomy, and nephroureterectomy are the standard treatments for renal, renal pelvis, and ureteral cancers[3-10] but these procedures also remove large numbers of functional nephrons and increase the risk of chronic kidney disease (CKD)[4-5]. Long-term follow-up studies of patients undergoing nephrectomy and nephroureterectomy reveal a significant decline in renal function[11-12]. In addition, non-neoplastic kidney diseases are concurrently present in up to 15% of tumor nephrectomy and nephroureterectomy specimens, and can further accelerate CKD progression and decrease life expectancy[6-10].

The cancer synoptic reports developed by the College of American Pathologists (CAP) are widely used. These synoptic reports remind the pathologist to evaluate a variety of important pathologic parameters for every specimen. Prior to 2010, the evaluation of the non-tumor renal parenchyma was optional for both tumor nephrectomy and nephroureterectomy specimens[9]. Early-stage renal malignancies are increasingly detected, which have 5-year survival rates that approach 100% in the United States[13]. Therefore, the identification of a concurrent non-neoplastic kidney disease can result in early intervention and improve patient outcomes.

To our knowledge, the incidence of non-neoplastic kidney diseases in kidney cancer patients has not been well studied in Asia. This study was conducted to determine the spectrum and incidence of non-neoplastic renal diseases (NNRD) in kidney and urothelial cancer specimens in a Southeast Asian medical center.

METHODS

We searched the Department of Pathology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University database for adult tumor nephrectomy and nephroureterectomy specimens from January 2012 to August 2022. Basic clinical data, such as age, sex, and history of diabetes/hypertension, were obtained from electronic medical records. Exclusion criteria included renal allografts, specimens that were consistent with end-stage renal disease, and partial nephrectomies given that this procedure is rarely performed at this institution and they are no available slides or paraffin blocks for review. This research was approved by the institutional review board of the Faculty of Medicine Vajira Hospital (COA168/2565).

The hematoxylin and eosin-stained slides were reviewed by a pathologist. The slides were initially assessed for the presence or absence of non-neoplastic renal parenchyma. The pathologic evaluation was performed without prior knowledge of the patients' clinical histories or laboratory data. If glomerular alterations (e.g. diffuse or nodular mesangial sclerosis, segmental sclerosis, mesangial hypercellularity, endocapillary hypercellularity, or capillary wall thickening) were present, this triggered further evaluation by periodic acid–Schiff, Jones methenamine silver, Masson trichrome and Congo red stains with immunofluorescence (IF) microscopy of immunoglobulin (Ig) G, IgA, IgM, and kappa and lambda light chains on paraffin tissue sections. Global glomerulosclerosis, interstitial fibrosis, tubular atrophy, and arteriosclerosis were considered non-specific findings and we did not include arterionephrosclerosis as a specific diagnosis for this study.

RESULTS

One hundred and ninety-four cases were identified and the patient demographics, pathologic diagnoses, and clinical information are summarized in Table 1. We identified significant diffuse and/or nodular mesangial sclerosis in 14 (7%) cases and another one with atheroembolic disease.

The remaining 179 specimens did not demonstrate definite diagnostic parenchymal alterations. Review of the electronic medical record confirmed a clinical diagnosis of diabetes in 12 of 14 with diffuse and focally nodular mesangial sclerosis, and none of these 12 had a prior kidney biopsy or diagnosis of diabetic nephropathy (DN) (figure 1). Of these 12 DN cases, there were seven associated with stage 1 and two cases associated with stage 2 renal cell carcinoma (RCC). Two additional DN cases were present with stage 1 and stage 2 transitional cell carcinoma/urothelial carcinoma. The last case of DN was found with an angiomyolipoma. In the absence of a clinical history of diabetes, the remaining two cases with prominent mesangial sclerosis were considered to represent idiopathic nodular glomerulosclerosis, as both patients were hypertensive and heavy cigarette smokers, which are known associations with this entity. Of these, one of each was present in stage 1 and 2 RCC. The additional case of atheroembolic disease had a clinical diagnosis of hyperlipidemia and was associated with stage 3 RCC. In all 15 cases, the concurrent renal diseases were not identified during the initial evaluation.

Table 1 Demographics of the study population

Patient variable	Number (%) N = 194
Age	61 (17-89 years)
Gender	
Male	126 (65)
Female	68 (35)
Underlying Disease	
Hypertension (HTN)	16 (8)
Diabetes mellitus (DM)	11 (6)
Hyperlipemia	7 (4)
DM with HTN	3 (1)
DM with HTN and hyperlipidemia	4 (2)
None provided/unknown	153 (79)
Procedure	
Nephrectomy	155 (80)
Nephroureterectomy	39 (20)
Pathological Diagnosis	
Renal cell carcinoma, clear cell	80 (41)
Renal cell carcinoma, papillary	25 (13)
Renal cell carcinoma, chromophobe	9 (5)
Renal cell carcinoma, sarcomatoid	2 (1)
Renal cell carcinoma, unspecified	7 (4)
Oncocytoma	2 (1)
Angiomyolipoma	16 (8)
Transitional cell carcinoma/Urothelial carcinoma	31 (16)
Squamous cell carcinoma	4 (2)
Other*	18 (9)
AJCC Cancer Staging	Number (%) N = 174
Stage 1	103 (59)
Stage 2	38 (22)
Stage 3	13 (8)
Stage 4	20 (11)

Abbreviations: AJCC, The American Joint Committee on Cancer; DM, diabetes mellitus; HTN, hypertension; N, number
*Includes: Solitary fibrous tumor, neuroendocrine carcinoma, liposarcoma, malignant epithelial tumor, pleomorphic undifferentiated sarcoma, metastatic carcinoma

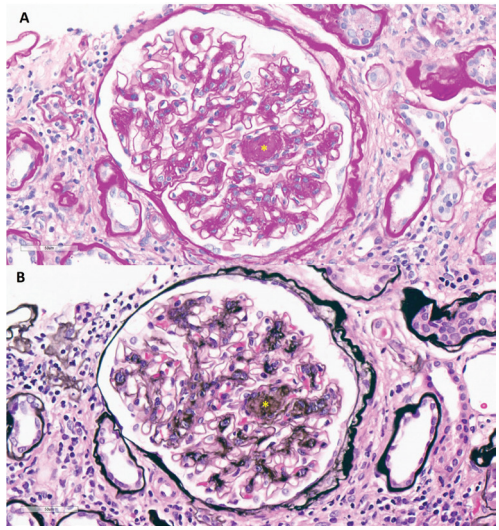

Figure 1 Diabetic glomerulopathy
Histopathological findings reveal mesangial expansion mainly due to increased mesangial matrix, with nodular formation (*) (Kimmelstiel-Wilson nodule). The nodule is round with a hypocellular matrix core surrounded by patent capillary loops. (A. x400, periodic acid-Schiff stain, B. x400, Jones methenamine silver stain)

Of the 15 patients with NNRDs, none were diagnosed with CKD or end-stage kidney disease before their surgeries. Additionally, at the 6-month follow-up, all patients had elevated blood urea nitrogen and creatinine levels and a decreased estimated glomerular filtration rate (eGFR) (table 2).

Direct IF microscopy performed on the paraffin tissue sections in these 15 cases for IgG, IgA, IgM, and kappa and lambda light chains showed no staining. Congo red studies in this subset also showed no evidence of amyloidosis.

The presence of non-neoplastic parenchymal renal alterations was associated with increased body mass index and underlying disease ($p < 0.001$, table 3).

Table 2 Summary of demographics, histology, and clinical features for the fifteen cases diagnosed with NNRDs

No.	Gender	Age	Pathological Diagnosis	Stage	NNRDs Diagnosis	BUN (mg/dL)		Cr (mg/dL)		eGFR (mL/min/ 1.73 m^2)	
						Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
1	Male	70	Renal cell carcinoma, papillary	I	DN	25	54	0.8	2.1	69	43
2	Male	55	Renal cell carcinoma, clear cell	II	ING	18	20	1.1	1.3	98	89
3	Male	60	Transitional cell carcinoma/ Urothelial carcinoma	II	DN	18	27	1.2	2.2	75	61
4	Male	59	Renal cell carcinoma, papillary	I	DN	21	30	1.3	1.9	82	54
5	Male	73	Renal cell carcinoma, unspecified	I	DN	28	32	1.1	1.8	64	39
6	Male	68	Renal cell carcinoma, clear cell	I	DN	25	31	1.3	1.7	71	51
7	Male	42	Renal cell carcinoma, clear cell	II	DN	19	26	1.5	2.2	76	64
8	Female	89	Renal cell carcinoma, clear cell	I	DN	18	20	1.3	1.7	65	55
9	Male	64	Renal cell carcinoma, papillary	III	AED	20	24	0.9	1.1	72	65
10	Female	78	Transitional cell carcinoma/ Urothelial carcinoma	I	DN	23	31	1	1.6	63	42
11	Male	66	Renal cell carcinoma, papillary	I	DN	24	41	0.9	2	92	54
12	Male	57	Renal cell carcinoma, clear cell	I	DN	26	38	1.1	1.9	80	64
13	Male	39	Angiomyolipoma	-	DN	15	20	0.8	1.4	115	90
14	Female	69	Renal cell carcinoma, clear cell	II	DN	14	25	0.9	1.5	83	69
15	Male	62	Renal cell carcinoma, papillary	I	ING	17	20	0.8	1.2	100	98

Abbreviations: AED, atheroembolic disease; BUN, blood urea nitrogen; Cr, creatinine; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; ING, idiopathic nodular glomerulosclerosis; m, meter; mg/dL, milligrams per decilitre; min, minute; NNRDs, non-neoplastic renal diseases; post-op, post-operation; pre-op, pre-operation

Table 3 Overall association among Sex, BMI, underlying disease, and non-neoplastic diagnosis

Parameter	Non-neoplastic Diagnosis, n (%)				P-value
	DN	ING	AED	No definite-diagnostic parenchymal alterations	
Sex					
Male	9 (5)	2 (1)	1 (< 1)	114	0.844
Female	3 (2)	-	-	65	
BMI*					
Underweight	-	-	-	16 (8)	< 0.001
Normal weight	1 (~ 1)	-	1 (< 1)	111 (57)	
Overweight	5 (3)	1 (< 1)	-	46 (24)	
Obesity	6 (3)	1 (< 1)	-	6 (3)	
Underlying disease					
Hypertension (HTN)	-	2 (1)	0	14 (7)	< 0.001
Diabetes mellitus (DM)	8 (4)	-	0	3 (2)	
Hyperlipemia	-	-	1 (< 1)	6 (3)	
DM with HTN	2 (1)	-	-	1 (< 1)	
DM with HTN and Hyperlipemia	2 (1)	-	-	2 (1)	
None provided/unknown	-	-	-	153 (79)	

Abbreviations: AED, atheroembolic disease; BMI, body mass index; DM, diabetes mellitus; DN, diabetic nephropathy; HTN, hypertension; ING, idiopathic nodular glomerulosclerosis; n, number
* Body mass index (BMI) Categories (kg/m^2): underweight ≤ 18.5, normal weight 18.5–24.9, overweight 25–29.9, obesity ≥ 30; Fisher exact test; P-value is indicating association between those factors. P < 0.05 considered as having significant association.

DISCUSSION

This is the first study from a Southeast tertiary care center to demonstrate that NNRDs occur at a rate of 8% in tumor nephrectomy/nephroureterectomy and interestingly the 7% rate of DN is similar to other larger studies[6,12]. NNRD can be found in 9 to 38% of kidney and ureteral cancer patients (table 4)[6,9,12,14-22]. Up to 90% of these diagnoses were not found at the initial pathologic evaluation, because pathologists focused on the renal neoplasm, and none of the patients in our cohort were initially diagnosed.

Table 4 Literature review

Study, Country	Year	Number of cases	Number of cases with non-neoplastic renal parenchyma disease (%)	Procedure
Bijol V et al,[14] USA	2006	110	42 (38)	partial and radical nephrectomy
Henriksen KJ et al,[6] USA	2007	246	24 (10)	partial and radical nephrectomy
Salvatore SP et al,[12] USA	2013	381	46 (12)	partial and radical nephrectomy
Bazzi WM et al,[15] USA	2015	800	72 (9)	partial nephrectomy
Wee JW et al,[16] Korea	2016	51	14 (27)	radical nephrectomy and nephroureterectomy
Tewari R et al,[17] India	2018	36	9 (25)	partial and radical nephrectomy
Shaw NM et al,[18] USA	2019	225	38 (17)	partial and radical nephrectomy and nephroureterectomy
Tjota MY et al,[9] USA	2020	63	7 (11)	total nephroureterectomy
Tripathy A et al,[19] India	2020	100	10 (10)	partial and radical nephrectomy
Dernell C et al,[20] USA	2021	59	15 (25)	radical nephrectomy
Kläger JP et al,[21] Austria	2021	206	39 (19)	partial and radical nephrectomy
Jia Y et al,[22] Canada	2022	156	14 (9)	partial and radical nephrectomy
Present study, Thailand	2022	194	15 (8)	radical nephrectomy and total nephroureterectomy

Almost 60% of the RCC and transitional cell carcinoma/ urothelial carcinoma in our cohort were stage 1 cancers, which have a five-year survival rate that is greater than 90%[23]. For the vast majority of patients with low-stage cancers, the oncologic outcomes should be excellent, but the NNRD has the potential to decrease their life expectancy through the detrimental effects of CKD and early intervention and management provides additional opportunities to improve outcomes. Thirteen of 15 patients with NNRD in our study had either stage 1 or 2 cancers, so early management of their NNRD could slow their CKD progression. One patient had an angiomyolipoma, which highlights the importance of evaluating the non-neoplastic parenchyma when benign neoplasms are present and synoptic reports may not be used. Preservation of renal function will be particularly important as 5-year actuarial cancer-specific survival for low-stage carcinoma has been estimated at ≥ 90%[9,23-24].

In our cohort, most patients who were identified to have diabetic nephropathy had mildly decreased eGFR pre-operatively. The diabetic patients in our study did not have a prior biopsy or clinical diagnosis of diabetic nephropathy, so the surgical pathologist often has the first opportunity to establish the diagnosis of diabetic nephropathy. Moreover, elderly patients (age ≥ 70 years) revealed pre-operative eGFR closer to 60 mL/min/1.73 m^2. The patients with a nephroureterectomy developed novel CKD or experienced progression of preexisting CKD or ESRD[25-28].

Synoptic reporting of cancer specimens is now common, and CAP developed one that is widely used. Prior to 2010, the evaluation of the non-neoplastic renal parenchyma in tumor nephrectomy and nephroureterectomy specimens was optional in the CAP protocol[29]. More than 25% of European genitourinary pathologists surveyed by the European Network of Uropathology in 2012 did not look at the non-tumor kidney parenchyma in tumor nephrectomy and nephroureterectomy specimens[30]. We suspect that this percentage is higher, especially beyond academic medical centers. There are many possible causes, but minimal exposure to nephropathology during residency training may be a significant contributor[6-7].

Investigating NNRD in kidneys removed for tumor event is a crucial method for determining the condition of the renal parenchyma in patients who will continue to have a single kidney. It is necessary to carefully examine appropriate sections of the nonneoplastic tissue, sectioned as far away from the tumor mass as feasible, utilizing standard special staining techniques used to evaluate renal pathologic changes including periodic acid-Schiff, methenamine silver, and Masson trichrome stains. It is necessary to obtain tissue samples from the renal cortex during the gross examination for potential immunofluorescence and electron microscopy examinations. Other stains, including Congo red for amyloid, should be conducted in specific situations such as patient who had history of a monoclonal protein, hereditary disorders. We have discovered that a systematic approach that includes a meticulous sequential examination of each kidney compartment (glomeruli, tubulointerstitium, and vasculature) yields the best results.

Strengths of this study: 1) Comprehensive data collection: The study collected data over a substantial period from a specific medical center, allowing for a focused analysis of NNRD in kidney and urothelial cancer specimens. 2) Clear methodology: The methodology section outlines the search criteria, inclusion/exclusion criteria, and the process of evaluation, providing clarity on how the study was conducted. 3) Clinical relevance: The study addresses a significant gap in research regarding the incidence and impact of NNRDs in kidney cancer patients, particularly in Southeast Asia, thereby contributing to the understanding of renal complications in this population. 4) Identification of NNRDs: The study identified various non-neoplastic renal diseases, including diabetic nephropathy, idiopathic nodular glomerulosclerosis, and atheroembolic disease, highlighting the importance of thorough pathological evaluation. 5) Emphasis on early intervention: The discussion section underscores the importance of early identification and management of NNRDs to improve patient outcomes, particularly in patients with low-stage cancers.

Weaknesses of this study: 1) Limited sample size: The study sample size of 194 cases may limit the generalizability of the findings, especially considering the diverse spectrum of renal diseases. 2) Single-Center Study: The study was conducted in a single medical center, which may not fully represent the broader population's demographics and disease prevalence. 3) Lack of longitudinal data: The study primarily focuses on the incidence of NNRDs at the time of surgery without longitudinal follow-up to assess the long-term impact on renal function and patient outcomes. 4) Potential bias in pathological evaluation: The retrospective nature of the study and the reliance on pathological evaluation.

Overall, while this study contributes valuable insights into NNRDs in kidney cancer patients, its limitations underscore the need for larger, multicenter studies with longitudinal follow-up to validate the findings and assess the long-term implications on patient outcomes.

CONCLUSION

In summary, our study found non-neoplastic kidney diseases involving nearly 8% of tumor nephrectomy and nephroureterectomy specimens from a Southeast tertiary care center. As oncologic outcomes continue to improve for kidney and urologic cancers, preservation of renal function and identification of non-neoplastic kidney diseases will provide opportunities for earlier interventions that may result in improved clinical outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

All data analyzed in this study are included in this published article.

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Original Article

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The Effect of a High Monosodium Glutamate Diet in Inducing Changes in Microbiota Diversity and Kidney Pathology in Hamsters Infected with *Opisthorchis viverrini*

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ABSTRACT

OBJECTIVE: To investigate the effect of a combination of a high dose of monosodium glutamate (MSG) and chronic *Opisthorchis viverrini* (*O. viverrini*) infection on kidney pathology and microbiota changes compared to either factor alone.

METHODS: Forty male golden hamsters were divided into four groups (10 hamsters per group): non-infected hamsters fed with standard diet (NC), *O. viverrini* infected hamsters fed with standard diet (OV), non-infected hamsters fed with high doses of MSG in drinking water (MS), and *O. viverrini* infected hamsters fed with high doses of MSG in drinking water (OM). After 8 months, fecal samples were collected, DNA extracted and subjected to 16S-rRNA sequencing analysis to determine microbial diversity. Kidneys were also collected for histopathological study.

RESULTS: Kidney histopathology showed tubular damages and tubular fibrosis were significantly prominent in the OM group, which showed higher pathology changes than in the OV group or MS groups. Next generation sequencing indicated that the levels of Firmicutes to Bacteroides ratio decreased in the OV group (0.28), MS group (0.43) and OM group (0.43) respectively when compared to control group (0.52). In genus levels, *Methanobrevibacter, Ruminococcus_1, Escherichia-Shigella, Bacteroides, Akkermansia* and *Oligella* were abundance in the OM group.

CONCLUSION: The changing of gut microbiota distribution and kidney pathology changes were more severe in the cases of *O. viverrini* infection together with MSG consumption. This study provides a first step towards focusing on diet and parasitic infections.

KEYWORDS: chronic infection, gut microbiota, monosodium glutamate, *Opisthorchis viverrini*

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INTRODUCTION

A major public health problem in many developing countries is parasitic infection. *Opisthorchis viverrini* (*O. viverrini*) infection is known to cause hepatobiliary disease and cholangiocarcinoma. Up to date, at least 6.71 million people are infected with *O. viverrini* in Thailand[1] and the highest prevalence is found in the northeastern region (18.6% and may be up to 85.6% of population in some areas). Moreover, kidney disease was observed in Syrian golden hamsters infected with *O. viverrini* experiment by showing a complete obsolesce of the glomeruli characterized by deposition of amyloid proteins, tubular atrophy, interstitial inflammation, and tubular fibrosis[2]. In human studies, many biomarkers of opisthorchiasis were represented including miR-192 in the urine in *O. viverrini* infected, periductal fibrosis and also cholangiocarcinoma (CCA) groups[3]. In chronic opisthorchiasis study found that urinary 8-oxodG is a biomarker of the progression of advanced periductal fibrosis and CCA[4]. Moreover, urinary excretion of microproteinuria were found in patients during *O. viverrini* infection[5] but the associations of *O. viverrini* infection and kidney disease is unclear.

Monosodium glutamate (MSG) is a sodium salt of glutamic acid and it is naturally present in the bodies of humans and animals; therefore, it would be present in a diet that is rich in protein-containing foods such as meat, vegetables and dairy products. MSG was used as a flavor enhancer, that increases the taste of food that usually added to Asian foods such as Japanese miso soup and processed meat[6]. Although the Food and Drug Administration has considered MSG as a food ingredient that is "generally recognized as safe," many people exhibit symptoms of allergies and other disorders[7-9]. Thus, many researchers are investigating whether MSG could be harmful[9-10]. According to the WHO suggested daily MSG consumption should not be more than 120 mg/kg/day[11]. The average daily intake of MSG in Japan and Korea in the 1990s was 1.20–1.70 g/day[12]. In addition, the average daily MSG intake in Khon Kaen, Thailand is 4.00 ± 2.20 g/day and can be as high as 14.00 g/d[13]. Daily MSG consumption has been associated with decreased pancreatic β-cell mass and increased bleeding and islet fibrosis[14]. Chronic oral intake of 4.00 mg/g body weight MSG increased kidney function and structural abnormalities, including glomeruli, tubular swelling, capillary congestion and microhemorrhages in the stromal areas of the kidney tubules[15], and there appears to be a risk of kidney stones[16].

In recent decades, several studies reported that the gut microbiota, a community of microorganisms including bacteria, yeasts, archaea and viruses plays the most important role in maintaining human health. In addition, the community of gut microbiota in the human body can be used to monitor disease and health[16]. The two major types of phyla are Firmicutes (such as *Roseburia* spp., *Lactobacillus* spp. and *Faecalibacteriums* spp.) and Bacteroides (such as *Bacteroides* spp. and *Akkermansia* spp.) found in the human gut microbiota, and they play crucial roles in health maintenance, including digestion of complex carbohydrates and fiber, preventing of inflammation, the synthesis of essential vitamins (vitamin B12 and vitamin K) and regulation of metabolism[17-19]. The expression between Firmicutes/Bacteroides ratio was used as a marker of several pathological conditions[19-20]. However, the relative distribution of the gut microbiome can be vary depending on age, gender, behavior and environmental factors. The most important factor affecting the community and types of gut microbiota is diet[21]. For example, a decrease in Bacteroides levels and an increase Firmicutes levels were observed in hamster fed a high fat diet[20,22]. The reduction in Bacteroides and Firmicutes was observed in MSG-fed hamsters. In addition, hamsters with chronic opisthorchiasis showed an increase in *Methanobrevibacter*, *Desulfovibrio*, *Akkermansia* and *Roseburia*, which is associated with metabolic syndrome[20,23]. Moreover, MSG consumption also affected levels of *Faecalibacterium*, *Megamonas*, *Blautia* and

Collinsella compared to healthy controls[24]. Taken together, we hypothesize that a combination of a high dose of MSG and chronic opisthorchiasis induces more severe of kidney pathology and microbiota changes than either factor alone.

In this study, we aim to investigate the effects of *O. viverrini* infection in combination with MSG intake using advanced sequencing technologies focusing on microbiota community balance and histopathological changes in the hamster model. This result could be a first step towards a focus on nutrition and parasitic infections that could lead to new prevention strategies for opisthorchiasis and opisthorchiasis-associated metabolic diseases.

METHODS

The animal experiment was conducted in the Animal Unit, Faculty of Medicine, Khon Kaen University, and was approved by the Animal Ethics Committee of Khon Kaen University, based on the Ethics for the Animal Experiment of the National Research Council of Thailand (IACUC-KKU-22/63). Forty male golden hamsters (*Mesocricetus auratus*) aged 6-8 weeks were randomly divided into 4 groups (ten hamsters per group): non-infected hamsters fed standard chow (NC), *O. viverrini*-infected hamsters fed with standard diet (OV), non-infected hamsters fed with high levels of monosodium glutamate (MSG concentration 4 mg/g-body weight) in drinking water (MS), and *O. viverrini*-infected hamsters fed with high levels of MSG in drinking water (OM) for 8 months. For *O. viverrini* infection, animals were infected with 50 viable *O. viverrini* metacercariae by oral inoculation as previously described[25]. The animals were kept under controlled environmental conditions and had access to free food and water consumption throughout the period. All hamsters were starved for 2 days prior to euthanasia. Fecal samples were collected individually from the colon and followed by transferred to a sterile tube and stored at -80°C until DNA extraction. Kidney tissues were collected and immediately placed in 10% buffered formalin for histopathological study.

For histopathological study, the kidney tissue was stained with hematoxylin and eosin[23]. The area of fibrosis was visualized by staining with picrosirius red kit. The sections were examined under a light microscope. Ten random tissue areas were selected for examination at a magnification of 2000. The percentage of positive fibrosis areas was analyzed using ImageJ software (National Institutes of Health, Bethesda, MD, USA) and expressed as mean ± SD[26].

Fecal DNA was extracted from individual hamsters using the TIANamp Stool DNA Kit (Tiangen Biotech, Beijing). DNA samples in each group were then pooled and the measured concentrations using a NanoDrop 2000 spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA) and the extracted DNA samples were stored at -20°C. The assessment of the presence of gut microbiota profiles was performed according to the procedures previously reported by our research group[22].

The percentages of positive fibrosis areas were expressed as mean ± SD. To compare the significance of the differences between groups, one-way Analysis of Variance (ANOVA) with post-hoc correction (Fisher's Least Significant Difference) was performed using IBM SPSS Statistics version 26 (IBM Corporation, NY, USA).

RESULTS

The effects of *O. viverrini* infection and high consumption of monosodium glutamate on kidney pathologies were determined by H&E staining (figure 1A). In the control group, hamsters represented normal tubular cells and glomeruli, whereas tubular dilatation was obviously observed in the OM and OV groups. In addition, slightly tubular dilatation was visualized in the MS group. Kidney fibrosis was presented by picrosirius red staining (figure 1B). Accumulation of fibrosis was noted in the glomerulus and in the proximal and distal tubules in OM group. The percentage of fibrosis areas in the OM group was significantly highest positive on picrosirius red staining (3.54 ± 1.17), compared with the MS group (1.10 ± 0.38) ($p < 0.001$), the OV group (1.25 ± 0.19) ($p < 0.001$) and NC group (0.62 ± 0.24) ($p < 0.001$), as shown in Figure 1C.

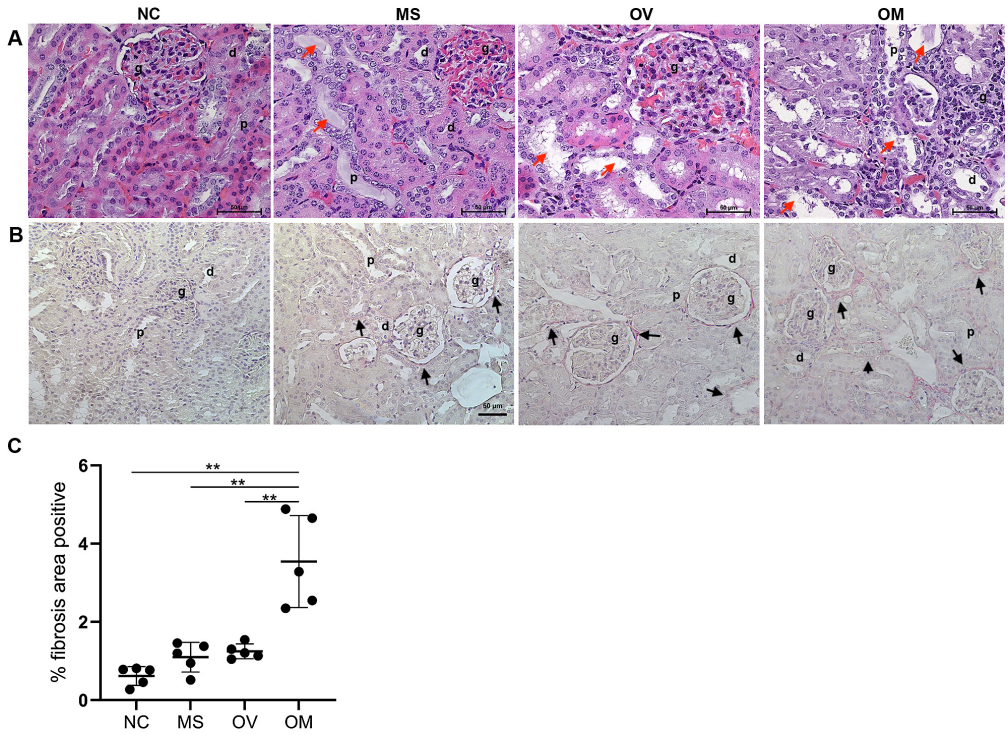

Figure 1 Histopathology and fibrosis expression in kidney tissues. A) histopathology of H&E staining kidney tissues, B) picrosirius red staining, C) percentage of fibrosis area positive (n = 5 per group). Scale bars 50 µm and magnification 400x.

Abbreviations: d, distal tubule; g, glomerulus; MS, hamsters fed with high monosodium glutamate; NC, non-infected control; OM, *Opisthorchis viverrini*-infected hamsters fed with high monosodium glutamate; OV, *Opisthorchis viverrini*-infected; p, proximal tubule

Black arrows mean fibrosis while red arrows mean tubular dilatation.

** $p < 0.001$

The effects of *O. viverrini* infection and high monosodium glutamate consumption on microbiota diversity. The alteration of microbial composition at the phylum level (figure 2A): Bacteroides and Firmicutes were most abundant in all experimental groups. The highest abundance of Euryarchaeota was recorded in the MS group, OV and OM compared to the normal control. The ratio of Firmicutes and Bacteroidetes was reduced in the OV group (0.28), the MS group (0.43) and the OM group (0.43) compared to the NC group (0.52). We further investigated the different changes at the genus level, as shown in Figure 2B and Table 1. The MS group showed high abundance of *Methanobrevibacter, Roseburia*, *Ruminococcus_1* and *Lachnospiraceae NK4A136*_group compared to the control group. The abundance of *Methanobrevibacter*, *Roseburia, Ruminococcaceae_UCG*-013, *Akkermansia*, and *Candidatus_Saccharimonas* was increased in the OV group. In addition, the levels of *Methanobrevibacter*, *Ruminococcus_1*, *Escherichia-Shigella*, *Bacteroides*, *Akkermansia* and *Oligella* were increased in the OM group compared to the control group.

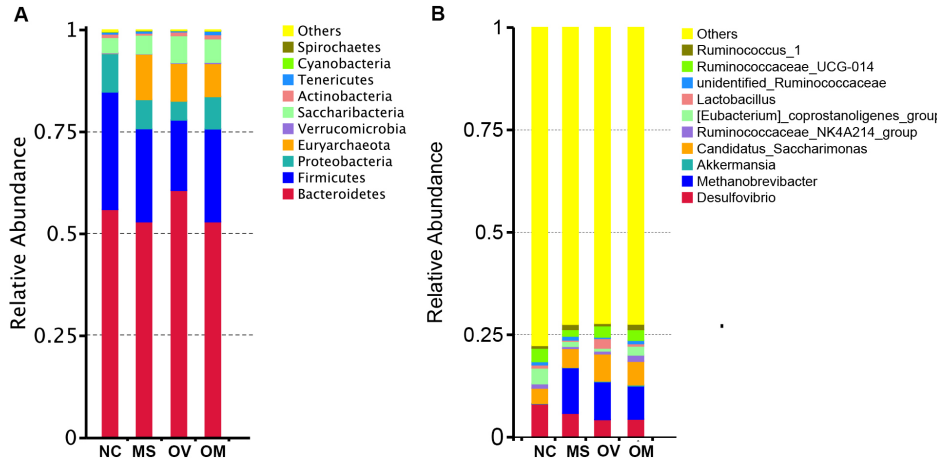

Figure 2 The effect of *Opisthorchis viverrini* infection and high monosodium glutamate consumption on microbiota diversity. A) At the level of phylum and B) At the level of genus.
Abbreviations: MS, hamsters fed with high monosodium glutamate; NC, non-infected control; OM, *Opisthorchis viverrini*-infected hamsters fed with high monosodium glutamate; OV, *Opisthorchis viverrini*-infected

Table 1 The relative abundance of microbial expression at genus level

Taxon	Groups			
	NC	MS	OV	OM
Ruminococcaceae_UCG-014	0.03287	0.01617	0.02754	0.02627
Oligella	0.00007	0.00007	0.00007	0.00014
Acinetobacter	0.00000	0.00000	0.00000	0.00004
Lachnospiraceae_NK4A136_group	0.00617	0.01326	0.00276	0.00365
Ruminiclostridium	0.00446	0.00392	0.00077	0.00185
Prevotellaceae_UCG-001	0.00408	0.00148	0.00130	0.00232
Enterorhabdus	0.00059	0.00037	0.00068	0.00077
Anaerotruncus	0.00465	0.00483	0.00160	0.00267
Ruminiclostridium_5	0.00463	0.00446	0.00262	0.00241
[Eubacterium]_coprostanoligenes_group	0.03859	0.01255	0.00702	0.02193
Candidatus_Saccharimonas	0.03736	0.04606	0.06624	0.05745
Paenalcaligenes	0.00000	0.00000	0.00000	0.00012
Lactobacillus	0.00750	0.00285	0.02374	0.00583
dgA-11_gut_group	0.00210	0.00020	0.00009	0.00023
Desulfovibrio	0.08123	0.05845	0.04303	0.04415
Akkermansia	0.00082	0.00075	0.00173	0.00267
Burkholderia-Paraburkholderia	0.00164	0.00116	0.00098	0.00059
Ruminococcaceae_NK4A214_group	0.01070	0.00522	0.00709	0.01535
Bacteroides	0.00349	0.00182	0.00061	0.00954
Ruminiclostridium_9	0.01405	0.01150	0.00337	0.00756
Tyzzerella	0.00734	0.00560	0.00146	0.00230
Escherichia-Shigella	0.00059	0.00052	0.00025	0.02848
Oscillibacter	0.00508	0.00389	0.00093	0.00257

Table 1 The relative abundance of microbial expression at genus level (continued)

Taxon	Groups			
	NC	MS	OV	OM
Prevotellaceae_UCG-003	0.01499	0.00175	0.00062	0.00517
Ruminococcus_1	0.00647	0.01266	0.00592	0.01332
Ruminococcaceae_UCG-013	0.00831	0.00809	0.01399	0.00829
Peptococcus	0.00242	0.00234	0.00111	0.00166
Anaerostipes	0.00000	0.00000	0.00000	0.00014
Allobaculum	0.01235	0.01119	0.01351	0.01718
Christensenellaceae_R-7_group	0.00276	0.00169	0.00267	0.00280
Ruminococcaceae_UCG-009	0.00774	0.00597	0.00442	0.00497
Unidentified_Ruminococcaceae	0.00793	0.00959	0.00330	0.00815
Roseburia	0.00070	0.01091	0.00128	0.00041
Helicobacter	0.00312	0.00216	0.00053	0.00299
Methanobrevibacter	0.00046	0.11141	0.09244	0.08107

Abbreviations: MS, hamsters fed with high doses of monosodium glutamate; NC, non-infected control; OM, *Opisthorchis viverrini*-infected hamsters fed with high doses of monosodium glutamate; OV, *Opisthorchis viverrini*-infected

DISCUSSION

This study confirmed that persistent infection with *O. viverrini* and consumption of MSG increased the severity of liver and kidney pathology and altered microbiota diversity in the hamster model using advanced sequencing technologies.

Prolong *O. viverrini* infection affects the liver and biliary ducts, leading to inflammation, fibrosis and cholangiocarcinoma. Several studies have reported the effects of chronic *O. viverrini* infection on pathological changes in the kidneys[2,20,23,27]. Infection with *O. viverrini* can trigger inflammatory responses in the hepatobiliary system and the inflammatory mediators may enter the blood circulation and contribute to kidney disfunction. In addition, *O. viverrini* -infected hamsters, histopathological changes of the kidneys were detected after 8 weeks of infection. Moreover, tubular atrophy, interstitial inflammation and tubular fibrosis were observed after 12 weeks of infection[2]. Moreover, *O. viverrini* antigens were observed in glomerular endothelial cells, mesangial cells, tubular cells and peritubular capillaries[27]. In addition, daily MSG consumption was associated with decreased pancreatic β-cell mass and increased hemorrhages and fibrosis[14]. Chronic oral intake of 4 mg/g body weight MSG resulted in decreased renal function and caused kidney pathology, including glomeruli, tubular swelling, capillary congestion and microhemorrhages in stromal areas of renal tubules[15], and there appears to be a risk of kidney stones in animal model[16]. No current information is available on the combination of hamsters infected with *O. viverrini* and fed with MSG. Our data showed that tubular dilatation and increased fibrosis of the glomerulus and the proximal and distal tubules were found in the OM group. This finding may suggest that prolonged consumption of MSG in *O. viverrini* infected hamsters leads to increased severity in kidney pathology.

It has been observed that infection with *O. viverrini* affects the microbiome of the host[28]. The alteration of bacteria can lead to an imbalance of bacteria that is associated with disease progression[29]. The severity of fibrosis has been found to be related to the dysbiosis of the microbiota caused by the infection[30]. *O. viverrini* infection led to changes in the microbiota components of the gastrointestinal tract, including biliary and had an impact on kidney tissue[31-32]. In addition, a previous study suggested that the increasing number of *Methalobrevibacter*

was related to kidney damage and kidney disease, and the change in the gut microbiome diversity was related to more pathogenic microorganisms with uremic toxin and renal fibrosis[20]. Our study found that the alteration of *Methanobrevibacter*, *Roseburi*, *Ruminococcaceae_UCG*-013, *Akkermansia*, *Candidatus_Saccharimonas* was identified in the feces of hamsters infected with *O. viverrini*. Fecal microbial communities showed numerous other differences at the genus level. In one study, it was also reported in previous studies that *O. viverrini* causes a change in Firmicutes by an increase in *Ruminococcaceae*, *Lacnospiracea* and *Lactobacillus*[30]. In addition, the production of *Methanobrevibacter*, *Akkermansia*, and *Burkholderia–Paraburkholderia* was relative higher in animals infected with *O. viverrini* than in the control group after 4 months[23]. The MSG diet increased the alteration of *Methanobrevibacter*, *Roseburia* and *Ruminococcus_1* after 4 months and also affected the gut microbiota diversity including the levels of *Faecalibacterium*, *Megamonas*, *Blautia* and *Collinsella*, which tended to be increased compared to non-treated controls[24]. The presence of microbial communities was consider as one of many different factors driving changes. Infection of *O. viverrini* in the bile ducts and liver causes tissue damage and obstruction leading to infection by microorganisms from the intestine, resulting to cholangitis and CCA[30]. The increasing of pathogenic bacteria communities may affect the host immune responses, metabolism and susceptibility to other infection. The detection of microbial presence-associated with *O. viverrini* infection may help to predict disease progression and guide treatment decisions.

The combination of *O. viverrini* infection and MSG intake resulted in the alteration of the major phyla of the gut microbiome and the ratio of Firmicutes to Bacteroides. This study showed that a combination of *O. viverrini* infection and MSG intake are the factors that cause the diversity of the bacterial community and the increase of the bacteria associated with metabolic syndrome, including *Methanobrevibacter*, which is associated with obesity[33], and *Akkermansia*[22]. In addition, *Methanobrevibacter* can produce methane (0.35 L/day) and be excreated in feces. Previous studies have found that methane is associated with inflammation, colon cancer[34-35], type I diabetis[36], coronary artery and heart disease[37]. Although there is no evidence of *Methanobrevibacter*-related kidney disease, previous study suggest that the imbalance of the gut microbiome leads to an increase in uremic toxin (trimethylamine *N*-oxide metabolite) and oxidative stress, inflammation and kidney disease[38]. We suggest that *Methanobrevibacter* proliferation might be involved in the inflammatory response to diet and parasite-induced kidney pathologies. However, in this experiment, the relative abundance of gut microbiota profiles was analyzed from pooled samples and we did not evaluate the gut microbiota before exposing it to the experiment. Therefore, a statistical analysis should be performed in the further work for comparison, as the abundant of some genera varies. This could affect on the abundance of some bacteria in our result, which is one of the limitations in our study.

CONCLUSION

Prolonged combination of *O. viverrini* infection and daily high dose of MSG consumption leads to pathological changes such as fibrosis and tubular dilatation and kidney damages. This study shows that *O. viverrini* infection and MSG affect both pathological changes and the diversity of the gut microbiome. However, our study has limitations in the data related to the use of pooled samples to observe microbiota changes. A more comprehensive understanding of the taxon presented would require an individual sample approach. However, this observation provides a first step towards understanding the severity of feeding behavior and parasitic infections.

CONFLICT OF INTEREST

There are no potential conflicts of interest.

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DATA AVAILABILITY STATEMENT

All data generated or analyzed in this study are included in this article. Future questions may be directed to the corresponding author.

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Review Article

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Ultrasound Percutaneous Tenotomy: An Intervention for Managing Lateral Epicondylitis: A Narrative Review

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ABSTRACT

A growing emphasis is being focused on percutaneous ultrasonic tenotomy for expedited recovery from lateral epicondylitis (LE) and enhanced functionality. The TX1 tissue removal system, also known as the Tenex device from Tenex device (Tenex Health Inc., Lake Forest, CA, USA), notably excels in the management of chronic LE. Utilizing ultrasonic energy, this device offers three tips, namely, TX1, TX2, and TXBone-introducing novel avenues, for determining the previously inaccessible tendon pathology. The procedure disrupts degenerated segments, which creates fenestrations that induce local hemorrhage and the release of vasoactive substances. The overarching goal of Tenex is to boost vascularity through the initiation of tendon repair via the deposition of new collagen and elimination of necrotic tissues. This review assesses Tenex's effectiveness though gathering information, aiming to understand how it helps doctors and other healthcare professionals in their work.

KEYWORDS: lateral epicondylitis, percutaneous ultrasonic tenotomy, Tenex device, treatment results

INTRODUCTION

Lateral epicondylitis (LE) refers to a prevalent musculoskeletal condition identified by its effect on the lateral epicondyle of the elbow; it features an annual incidence rate of 2.4–4.5 per 1,000 individuals[1]. A standard therapeutic approach for the treatment of lateral elbow tendinosis has yet to be established. Traditionally, conservative management constitutes the primary strategy for initial intervention, encompassing measures, such as activity modification, physiotherapeutic interventions, administration of anti-inflammatory agents, and implementation of counterforce bracing, acupuncture, and corticosteroid administration[2-4]. Surgical intervention may be warranted in cases with persistent symptoms despite these conservative measures.

Research focus is being increasingly centered on the use of percutaneous ultrasonic tenotomy (PUT) as a surgical procedure to alleviate symptoms of LE and improve functionality within a reduced recovery timeframe. Notably, PUT using the TX1 tissue removal system, also known as the Tenex device (Tenex Health Inc., Lake Forest, CA, USA), has been proven effective in the management of chronic refractory LE. The Tenex device (Tenex Health Inc., Lake Forest, CA, USA). uses ultrasonic energy to debride

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and aspirate pathological tendon tissue. This device is equipped with three distinct tips (TX1, TX2, and TXBone). The introduction of the longer TX2 tip and the more powerful TXBone tip has opened up new possibilities for the treatment of tendon pathology, which was previously inaccessible via a percutaneous approach[5]. The procedure involves the disruption of degenerated segments through the creation of fenestrations, which elicit local hemorrhage and subsequently induces the release of vasoactive substances, such as calcitonin gene-related peptide and substance P[6]. The overarching objective of this procedure is the augmentation of vascularity, thereby prompting the initiation of tendon repair through the deposition of new collagen and concomitantly eliminating degenerated and necrotic tendon tissue.

This review assessed the efficacy of Tenex and obtained the latest empirical findings on PUT in the context of LE. This narrative review aimed to aid healthcare professionals in conducting comprehensive evaluations and rendering informed treatment choices rooted in optimal clinical practices.

PATHOGENESIS OF LATERAL EPICONDYLITIS

The definitive etiological factors of LE remain controversial. This condition is frequently associated with repetitive microtrauma linked to daily activities, such as gripping overload and wrist motion in various positions, particularly the extension position[7-8]. The extensor muscle group, particularly the extensor carpi radialis brevis muscle, is often impacted[9]. Initially characterized as an inflammatory process, especially in its early stages, LE is currently assumed to result from prolonged exposure to repetitive microtraumatic stressors, leading to the rupture of collagen fibril and triggering the innate immune response[10-11]. Nonetheless, histopathological examination of this condition through biopsies has yielded unexpected results, including the lack of inflammatory cells in individuals with chronic LE[12-13]. To date, based on cumulative pieces of empirical evidence, an increased presence of fibroblasts, heightened vascular hyperplasia, and disorganized collagen within the affected tendon tissue are speculated to be causes of a symptomatic degenerative process[14].

INDICATIONS AND CONTRAINDICATIONS FOR PERCUTANEOUS TENOTOMY

The procedure is indicated for patients suffering from chronic lateral elbow tendinopathy with persistent symptoms for more than 3 months, regardless of attempted conservative therapies, such as anti-inflammatory treatments, physical therapy, and activity modification[15]. Notably, the presence of an active infection is a contraindication for this procedure.

MECHANISM OF ACTION OF TENEX

The mechanism of action of Tenex in the treatment of LE is based on the selective removal of damaged tissue and the promotion of tissue healing. With ultrasound (US) serving as a guide to target and break down the degenerated or scarred tissue in the tendon, the procedure stimulates the body's natural healing response. As a result, production of healthy collagen and other tissue components occurs, which promotes the regeneration and repair of the affected tendon.

PROCEDURAL TECHNIQUE OF TENEX

The TX2 MicroTip ultrasonic device (Tenex Health Inc., Lake Forest, CA, USA) was used in this study (figure 1). With the aid of US-guided identification, aberrant regions within the lateral part of the elbow, which are indicative of the pathological site, were located along the proximal-to-distal direction from the elbow to the forearm using a sterile technique. A surgical blade was used to create a small surgical wound to facilitate the passage of the Tenex needle system, which is an instrument with an 18-gauge caliber, through skin layers, subcutaneous adipose tissue, and the superficial fascia enveloping the tendon (figure 2).

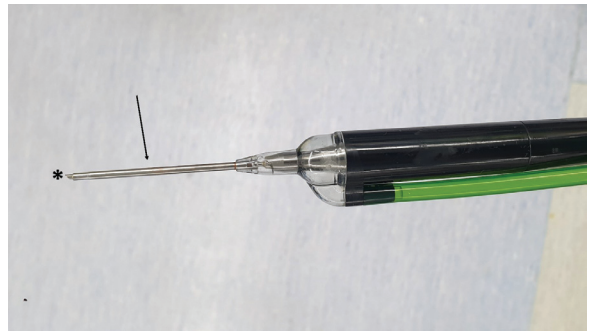

Figure 1 Operational end of the TX2 MicroTip ultrasonic device (Tenex Health Inc., Lake Forest, CA, USA). The working tip, constructed from 18-gauge hollow stainless steel (indicated by the black arrow), oscillates at elevated frequencies, facilitating the emulsification of tissues in close proximity. The tip has a cannula (denoted by asterisk), with the tip and cannula affixed to a handpiece resembling a pencil. This handpiece establishes a connection with the TX2 console, serving as the energy source that propels the tip and incorporates a motor for the management of the inflow/outflow of irrigation fluid and debris. Continuous irrigation is maintained through fluid circulation into the working site, which occurs between the canula and shaft of the working tip, with the efflux of fluid from the working site facilitated through the hollow working tip.

Figure 2 Left: Alignment of patient for percutaneous tenotomy and debridement procedure on the common extensor tendon (lateral elbow) using the TX2 device (Tenex Health Inc., Lake Forest, CA, USA). Right: Image captured after surgical intervention, featuring the incision secured with a strap.

The Tenex needle must be precisely guided to remain within the aberrant tendon region under US guidance (figure 3). A pedal mechanism was then engaged to initiate the Tenex module, which induced rapid oscillations in the 18-gauge inner needle at frequencies between 18 and 24 MHz. These oscillations created ultrasonic energy, which effectively emulsified the pathological tissue. Simultaneously, a saline irrigation procedure was performed to enhance the therapeutic process. Systematic movement of the device was made possible by a controlled, back-and-forth motion, akin to the technique employed in dry needling. Guided by real-time US visualization, the Tenex needle can be repositioned to address any additional aberrant areas within the tendon (figure 4). Typically, the needle's high-frequency oscillations result in the progressive softening of the initially rigid tendon tissue in the region afflicted by tendinosis after a few passes, which reduces the required pressure during needle manipulation. In instances involving the detection of microcalcifications, the oscillating needle, in conjunction with saline flush, effectively facilitates their removal. The overall duration of the cutting procedure ranges from 40 to 60s, depending on the extent and severity of tendon degeneration[16-17].

Figure 3 Left: US probe strategically placed on the lateral epicondyle to pinpoint the origin of the common extensor tendon. Right: Introduction of TX2 device (Tenex Health Inc., Lake Forest, CA, USA) following the meticulous creation of strap incision.

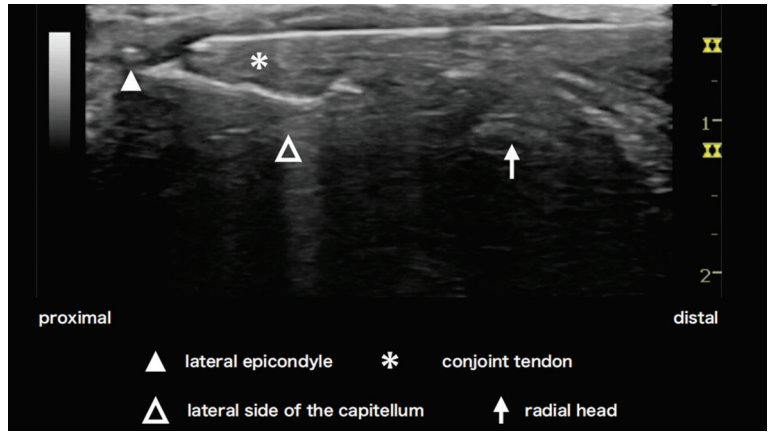

Figure 4 The outer sheath is distinctly visualized, with the metallic tip protruding from the sheath and positioned within the common extensor tendon (*).

REVIEW OF EVIDENCE OF PUT

Several studies have explored Tenex's effectiveness and compared it with those of other procedures. In this section, we delved into the latest evidence regarding PUT (table 1).

PUT ALONE

Koh et al.[18] (2013) investigated a case series of an innovative and minimally invasive approach for the treatment of persistent lateral elbow tendinopathy. This method utilizes an ultrasonic microsection procedure using a specialized device called TX1 under local anesthesia. The process is secure and well received, with no adverse incidents ever documented. The patients treated with this method experienced notable improvements in both pain levels, as indicated by their visual analog scale (VAS) scores, and functional outcomes measured through disabilities of the arm, shoulder, and hand (DASH) scores after one month. These improvements lasted until the 12-month follow-up period. Sonographic evaluations at the 6 month revealed positive changes in tendon thickness and vascularity. A total of 19 out of 20 patients expressed their satisfaction with this procedure.

Table 1 Evidence related to PUT

Authors (year)	Patient (n)	Study Design	Comparisons	Study duration	Conclusions
Ferrero et al.[21] (2011)	32	Retrospective cohort study	Steroid injection (SI)	12 months	The SI group initially exhibited a significant reduction in pain levels during the 2-week assessment ($p < 0.001$), favoring this approach. However, the PUT group did not demonstrate significant improvement after 2 weeks. In longer-term evaluation (3 months to 12 months), the PUT group revealed more substantial pain relief in comparison with the steroid group ($p < 0.001$).
Koh et al.[18] (2013)	20	Case series	No comparison	12 months	Significant and rapid improvements were observed in the VAS, DASH-compulsory, and DASH-work scores following the procedure, with sustained benefits observed at 3, 6, and 12 months.
Barnes et al.[19] (2015)	19	Case series	No comparison	12 months	Procedural complications were absent. Significant improvements were noted in the average VAS scores ($p < 0.0001$). Similar positive trends were noted in Quick-DASH ($p < 0.0001$) and MEPS ($p < 0.001$).
Seng et al.[1] (2016)	20	Case series	No comparison	36 months	The study achieved 100% clinical follow-up with US assessment, maintaining patient satisfaction. Initial improvements in pain and function scores were sustained, and further significant decrease in the DASH-compulsory scores was observed. Tendon abnormalities presented notable improvements, with progressive reduction in scar tissue over time.
Battista et al.[15] (2018)	7	Case series	No comparison	24 months	ASES scores showed significant improvements ($p < 0.001$), which were evident at 6 weeks and maintained until 24 months. Statistically significant improvements in ASES and VAS scores were noted, demonstrating sustained benefits.
Boden et al.[17] (2019)	62	Retrospective Cohort Design	PRP injections	PRP and Tenex groups (17 and 10 months, respectively) varied significantly ($p = 0.002$)	The PRP and Tenex groups exhibited clinical and statistical improvements in the VAS pain, Quick-DASH, and EuroQol-5D scores. No statistically significant difference was observed between the two treatment modalities.
Altahawi et al.[23] (2021)	200	Retrospective Study	Surgical Tenotomy	12 months	Average VAS scores improved significantly ($p < 0.001$). This positive trend extended to Quick-DASH ($p < 0.001$) and MEPS ($p < 0.001$), indicating a sustained and significant improvement across various assessment measures.
Ang et al.[20] (2021)	20	Case series	No comparison	90 months	Satisfaction remained at 100%, with sustained improvement in VAS and DASH-compulsory scores ($p < 0.001$). No symptom recurrence occurred, eliminating the need for secondary interventions. Hypervascularity remained resolved in 79% of patients at 90 months, indicating the durability of positive outcomes.

Abbreviations: ASES, American shoulder elbow surgeons shoulder score; DASH, disabilities of the arm, shoulder, and hand; MEPS, Mayo elbow performance score; n, number; PRP, platelet-rich plasma; PUT, percutaneous ultrasonic tenotomy; SI, steroid injection; VAS, visual analog score

Seng et al.[1] (2016) reported a case series that investigated the long-term efficacy of PUT for this condition in all 20 participants. The study revealed the showed sustained improvements in all participants after 3 years. They reported minimal pain (0 ± 0.9) and excellent functionality (DASH-work score of 0 ± 0). Furthermore, tendon vascularity was resolved in 94% of the patients, and all of then experienced a decrease in tendon thickness. Hypoechoic scar tissue, which indicates tissue healing, decreased in all participants, with 90% experiencing positive results within 6 months. In conclusion, this minimally invasive technique provides long-lasting pain relief and functional improvement and is a favorable alternative to surgical intervention for recalcitrant tennis elbow.

Barnes et al[19] (2015) conducted a case series in which the TX1 procedure was examined as a therapeutic approach for chronic, refractory lateral, or medial elbow symptoms persisting for over 6 months. A total of 19 patients (mean age: 55.3 years) participated in this study. At the 12 months of follow-up after the procedure, 78.9% of the participants reported reduced pain, with scores reaching more than 75%.

In a 2021 case series authored by Ang et al.[20], the long-term clinical and sonographic outcomes of PUT applied to the extensor tendon were investigated. In previous study, 19 patients were assessed, with 16 undergoing US examination, with a follow-up period between 86 and 102 months. No adverse events were observed, and patient satisfaction consistently remained high, with 6 patients expressing satisfaction and 13 claiming very high levels of satisfaction. Notable, none of the patients experienced recurrence of symptoms or signs lateral elbow tendinitis associated with, obviating the need for any subsequent interventions. The baseline and early term improvements were sustained over time, with statistical significance ($p < 0.001$ for all). Specifically, at the 90-month mark, a significant enhancement was observed in the pain and functional scores compared with the preprocedure scores and all follow-up assessments up to the 3-month interval. Notably, no discrepancies were observed in the pain and functional scores at the 90-month evaluation compared with the scores on other points. Functional scores were notably enhanced at the 90-month juncture compared with the preprocedure scores although no distinctions were identified when comparing DASH-work scores at the 90-month milestone with scores at any other follow-up time points. At the 90-month evaluation, 79% of the patients exhibited a continued resolution of hypervascularity, and all of then presented decreased tendon swelling, coupled with persistent resolution or reduction of the hypoechoic lesion.

PUT VERSUS STEROID INJECTION (SI)

IA 2011 clinical trial conducted by Ferrero et al.[21] examined a cohort of 46 patients with LE. The study included 16 patients subjected to PUT treatment and another 16 who received SI under US guidance. The initial findings indicate a preference for the SI group, which exhibited a notable decline in pain levels compared with the baseline during the 2-week assessment ($p < 0.001$). Conversely, the PUT group showed no notable enhancement in pain at the 2-week mark. However, in longer-term follow-up evaluations spanning from 12 weeks to 48 weeks, the PUT group exhibited more substantial pain relief than the SI group ($p < 0.001$).

PUT VERSUS PLATELET-RICH PLASMA (PRP) INJECTION

A retrospective cohort study led by Boden et al.[17] (2019) conducted a comparative evaluation to assess the effectiveness of Tenex and (PRP) injection as interventions for chronic epicondylitis. The study involved 62 subjects, with 30 undergoing PUT and 32 receiving a single PRP injection. Both therapeutic treatments resulted in substantial and statistically notable alleviation of pain and improved functional outcomes and overall quality of life. No statistically significant differences were recorded ($p < 0.05$) at 10 and 17 months of follow-up.

A separate prospective study in 2013, with randomized controlled trials documented by Stenhouse et al.[22], reported the PUT (n = 13) and

combined PUT and PRP injection (n = 15) treatments of participants afflicted with this condition. The incorporation of PRP injection with needle tenotomy increased the effectiveness on pain relief and functional outcomes during the 2- and 6-month follow-up assessments. However, none of the intergroups achieved statistical significance ($p > 0.05$).

PUT VERSUS SURGICAL THERAPY

In retrospective investigation conducted by Altahawi et al.[23] (2021), comparative analysis of tenotomy was performed using the Tenex device and surgical tenotomy. The study included 23 patients treated with the TX-1 device and 10 patients undergoing surgical tenotomy. The results reveal similar outcomes between the two treatment groups, with noteworthy improvements in pain and functional capacity at 3–6 and 12 months posttreatment intervals ($p < 0.05$). A 2-week follow-up assessment suggested a disparity in symptom progression, with the surgical cohort experiencing aggravation of symptoms and the TX-1 device-treated group showing symptom improvement. However, these distinctions did not reach statistical significance.

The investigations scrutinized in this review collectively suggest the potential efficacy of PUT as a therapeutic modality for LE. However, given the limited number of studies and participants, interpretation of these findings must be fulfilled with caution, thereby affording only a modest level of confidence in drawing definitive conclusions. Consequently, additional research is imperative to substantiate and fortify these preliminary observations. Specifically, high-quality prospective randomized controlled clinical trials in this domain are limited. The present evidence underscores the exigency for rigorous studies characterized by robust methodologies. Ideally, such trials require a meticulous design and must employ randomized, double-blind paradigms and meticulous procedures aimed at mitigating bias. Furthermore, comparative evaluation of diverse surgical interventions must be considered, with particular emphasis on various surgical modalities. Extant literature is also devoid of randomized controlled trials that systematically assessed the spectrum of surgical treatments for LE. Methodologically sound investigation should encompass prolonged follow-up periods, that is, an interval exceeding 6 months, to determine the durability of reported therapeutic gains. Key component parameters should include pain assessment through VAS or analogous metrics, alongside evaluations of functional and impairment outcomes using instruments such as the DASH score or similar indices. Supplementary investigations should also thoroughly monitor secondary occurrences of adverse events. In summary, a call for methodologically diligent and comprehensive research endeavors is underscored to obtain robust evidence that can guide clinical decision making in the management of LE.

CONCLUSION

PUT represents a minimally invasive therapeutic approach suitable for patients with LE unresponsive to conservative interventions. However, more robust investigations are required for the precise assessment of the comparative efficacy of this treatment modality.

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Review Article

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Outcomes Comparison in the Management of Displaced Femoral Neck Fractures among Elderly Patients: Total Hip Arthroplasty versus Bipolar Hemiarthroplasty

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ABSTRACT

Treating femoral neck fractures in the elderly demands careful strategies for optimal results. This review explores into the roles of total hip arthroplasty (THA) and bipolar hemiarthroplasty (BHA) in addressing these fractures, considering their distinct advantages. THA, catering to active elderly patients, delivers excellent pain relief, enhanced mobility, and sustained functionality. In contrast, BHA presents a more conservative option suitable for less mobile patients. Factors like surgery time and dislocation risks play a crucial role in selecting between the two options, while postoperative complications, including infections and joint issues, significantly impact recovery. Adequate post-surgical care and advancements in techniques are pivotal for overcoming these challenges. Continuous research and enhancements in diagnostic methods and post-surgical care are critical for refining strategies, ultimately improving the recovery and quality of life for elderly patients.

KEYWORDS: bipolar hemiarthroplasty, femoral neck fractures, total hip arthroplasty

INTRODUCTION

Femoral neck fractures are common among the elderly, with projections indicating that the worldwide annual incidence of hip fractures will reach 6.26 million by 2050[1]. Surgical intervention remains the primary treatment choice. Surgical options range from hip arthroplasty, typically used for displaced femoral neck fractures in elderly patients, to various fixation techniques such as multiple screw fixation, sliding hip screw, and intramedullary nail, usually used in younger patients[2]. Total hip arthroplasty (THA) involves replacing the entire hip joint, while bipolar hemiarthroplasty (BHA) replaces only the femoral head—these advanced procedures contribute significantly to the treatment landscape by aiming to improve mobility and reduce pain. This article reviews the roles of THA and BHA in the treatment of femoral neck fractures in elderly patients, to improve their quality of life by reducing pain and enhancing mobility.

DIAGNOSIS AND TREATMENT OPTIONS

Femoral neck fractures in the elderly are usually classified into high-energy and low-energy types. Patients typically present with a history of falls, hip pain, and mobility issues. Diagnosis primarily relies on X-ray imaging, although 2-10% of cases might not reveal distinct fracture lines, especially with

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non-displaced fractures[3]. In such instances, magnetic resonance imaging is indispensable, with a diagnostic sensitivity of 100% and specificity between 93% and 100%[4].

Treatments for femoral neck fractures are surgical and non-surgical depending upon fracture severity, type, and mobility. Extracapsular fractures require surgical fixation, with considerations including bone quality, fracture pattern complexity, and fracture configuration[5]. The management of intracapsular fractures may involve open reduction and internal fixation (ORIF), closed reduction and internal fixation (CRIF), or arthroplasty. Comparative studies evaluating fixation versus arthroplasty outcomes have consistently favored the latter[6-7]. Studies, such as those by Chammout et al.[8], comparing parameters such as the Harris Hip Score and complication rates, have established arthroplasty's long-term superiority. Rogmark et al.[9], demonstrated that arthroplasty patients aged over 70 had reduced rates of falls, reduced pain, and enhanced mobility within two years of surgery.

CLASSIFICATION OF FEMORAL NECK FRACTURES

Femoral neck fractures are typically classified using the Pauwels classification, which delineates the angle of the fracture in the horizontal plane[10], and the Garden Classification, based on X-ray images[11]. The Garden Classification is widely favored for its detailed differentiation between complete, incomplete fractures and level of displacement (figure 1), and plays a pivotal role in choosing between ORIF, CRIF, and arthroplasty.

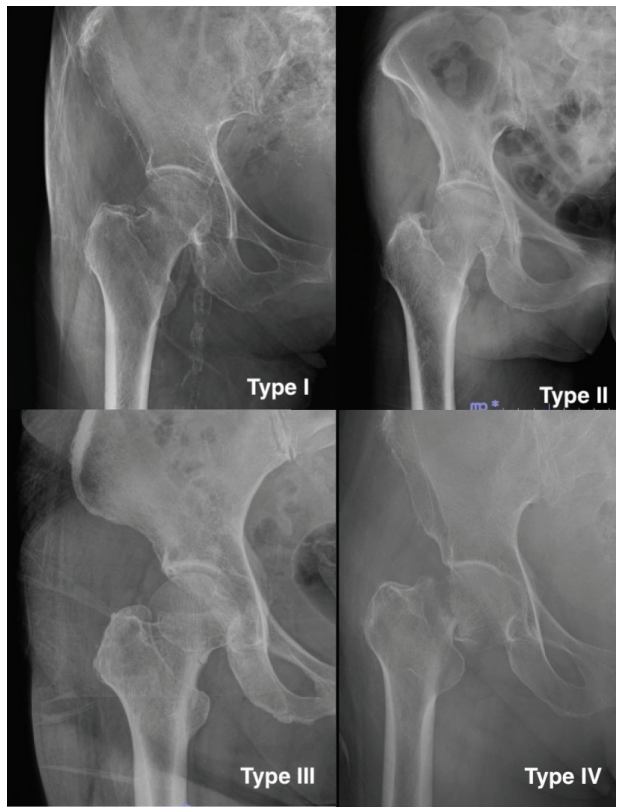

Figure 1 The images of femoral fractures categorized under the Garden classification.

Each surgical approach has distinct indications. The American Academy of Orthopedic Surgeons (AAOS) and the United Kingdom's National Institute for Health and Care Excellence (NICE) recommend THA for elderly patients who retain mobility, even in the presence of significant hip pain or osteoarthritis[12]. Conversely, BHA is suitable for elderly patients with limited activities of daily living, especially those with multiple comorbidities[13]. For patients with medical concerns that preclude prolonged surgery or blood loss, closed reduction with cannulated screw fixation is the optimal choice[14]. Hip arthroplasty has the best outcomes for Garden types 3–4 fractures, whereas patients with Garden types 1–2 with minimal displacement benefit from CRIF using cannulated screws[15].

TOTAL HIP ARTHROPLASTY VS. BIPOLAR HEMIARTHROPLASTY

Surgical interventions for displaced femoral neck fractures include THA and BHA (figure 2). Numerous studies have compared these procedures' outcomes[16-19]; however, conclusive evidence on the superior method remains elusive due to inherent patient-specific factors. According to the NICE guidelines, there is no substantial disparity in benefits and importance between THA and BHA, even in long-term follow-up regarding the necessity for revision surgery[16].

However, a prevailing trend in research favors THA over BHA, especially in elderly patients with displaced femoral neck fractures. THA consistently demonstrates superior results using metrics such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), encompassing pain scores, stiffness scores, and functional outcomes[17]. Research by Migliorini et al.[18], and Muslim et al.[19], corroborates THA's superiority in metrics, including gait, range of motion, and re-operation rates.

THA takes longer operation time[20], leading to increased risks from potential excessive bleeding in patients with underlying health conditions. Additionally, THA requires a longer anesthesia time, and post-surgery recovery may also be prolonged[21-22]. Therefore, THA is recommended for active patients with a longer life expectancy, normal cognitive function, and significant hip pain or osteoarthritis. However, BHA may be a better option for physiologically older patients with limited mobility, multiple comorbidities, and reduced daily activities. THA involves higher expenses due to extended hospital stays and increased medical and physiotherapy costs[21-22].

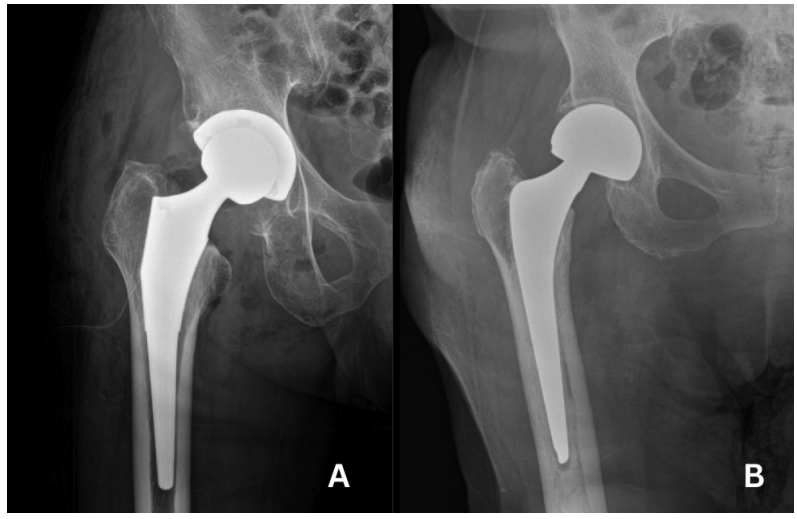

Figure 2 The postoperative images of right total hip arthroplasty (A) and hemi-hip arthroplasty (B)

PROGNOSIS AND COMPLICATIONS

Hip fractures cause significant patient morbidity and mortality, with nearly half of patients failing to regain normal functionality[23]. Surgery has its challenges; postoperative complications afflict up to 20% of hip fracture cases, particularly among the elderly, significantly impacting mortality rates within the first year after surgery. Several factors, including preoperative cognitive state, medical comorbidities, and mobility levels, contribute to these complications[24].

Postoperative complications include myocardial infarction or heart failure (35%–42%), anemia (24%–44%), and urinary retention or infection (12%–61%). Delirium affects 13.5%–33% of cases, deep venous thrombosis occurs in 27%, acute kidney injury in 11%, and skin pressure damage in 7%–9%. Pneumonia occurs in 7%, and pulmonary embolism in 1.4%–7.5% of cases[10].

Hip arthroplasty has specific complications that may require revision surgery. Both THA and BHA have a revision rate of more than 5.2%[25]. Dislocation is a hip arthroplasty complication, influenced by factors such as the surgeon's experience, treatment procedures, and the use of inappropriate equipment[26]. Dislocation incidents often lead to revision surgery. Patients undergoing THA face a dislocation rate of 2–20%[27], while BHA has a lower short-term (3-year) and long-term (5-year) rate[28].

Hip prosthesis loosening, which is influenced by factors such as gender and physical activity levels, decreases with age and correlates with daily activity levels. Patients with a body mass index (BMI) below 25 kg/m^2 maintain better joint implant integrity, with the loosening risk increasing by 3% for higher BMI individuals[29]. Loosening is also linked to cardiovascular events, including myocardial infarction, heart failure, and cerebral infarctions, which are observed in up to 30% of cases[30].

Post-surgical infections are primarily associated with pre-existing patient conditions. Infections occurring within 3 months include urinary tract infections (UTIs) and pneumonia. Studies indicate that postoperative pneumonia occurs in 9% of cases, UTIs in 4%, wound infections in 1.1%, and deep infections in 1%[31].

CONCLUSION

Managing femoral neck fractures in the elderly is a complex task. Choosing the right procedure involves considering age, activity level, and overall health. Despite its longer surgery time and higher complication risk, THA suits active patients, while BHA is safer for older, less mobile patients. Post-surgery complications like infections and joint problems underscore the need for careful care. Further research and improved surgical techniques are crucial for enhancing outcomes in elderly patients recovering from femoral neck fractures.

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