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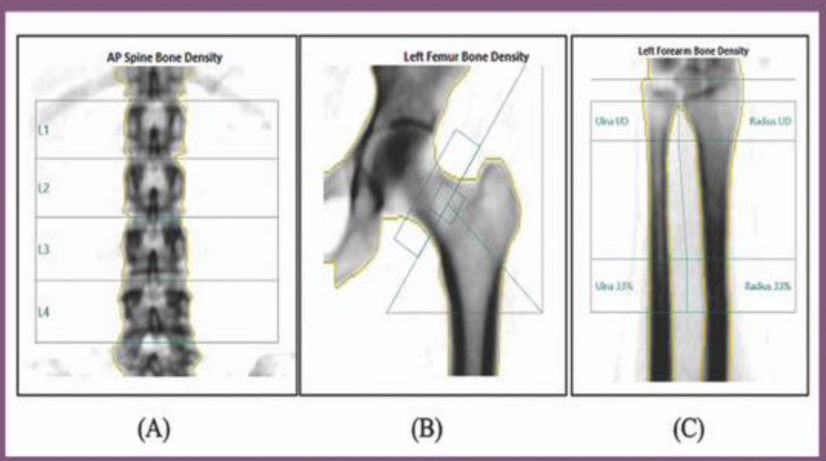

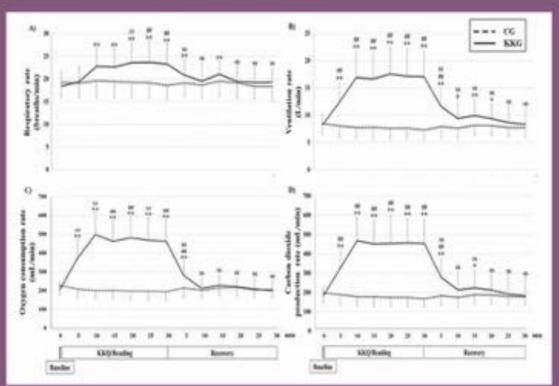

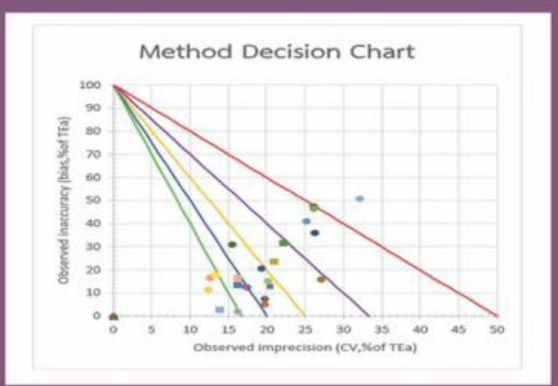

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Production and editorial assistance:
Arpassanan Wiyanad
Sirirut Multakorn
Gresilia Tambing

All correspondence concerning manuscripts, editorial issues and subscription should be addressed to:
Editorial Officer: ArchAHS.TH@gmail.com
Faculty of Associated Medical Sciences,
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ORIGINAL ARTICLE

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The immediate effects of whole-body vibration on flexibility and ankle systolic blood pressure in middle-aged individuals with type 2 diabetes mellitus

May Thandar Khin, Ponlapat Yonglitthipagon*, Peeraphat Sripanya, Woramate Chodnok, Kritnapat Wannakarn, Saowanee Nakmaroeng, Wantana Siritaratiwat, Punnee Peungsuwan, Wanida Donpunha

School of Physical Therapy, Faculty of Associated Medical Sciences, Khon Kaen University, Khon Kaen, Thailand.

KEYWORDS
Vibration exercise;
Ankle brachial index;
Ankle blood pressure;
Diabetes mellitus;
Squat exercise.

ABSTRACT

Poor body flexibility in middle-aged individuals with type 2 diabetes mellitus (T2DM) could increase the risk of falls and injuries. Insulin resistance induces vascular alterations in the lower extremities, leading to increased ankle systolic blood pressure (SBP), which correlates with an increased risk of cardiovascular disease. The aim of this study was to investigate the acute effects of whole-body vibration (WBV) on flexibility and ankle SBP in middle-aged T2DM patients. This randomized single-blinded crossover design was used to study 14 participants (average age: 49.71 ± 5.28 years, average body mass index: 26.98 ± 3.24 kg/m^2, average duration of diabetes: 2.32 ± 1.74 years) who were randomly assigned to two intervention sequences, starting with non-whole-body vibration (NWBV) or WBV, with seven participants in each sequence. On days 1 and 8, the intervention varied between NWBV and WBV. The outcomes, including flexibility, ankle blood pressure, brachial blood pressure, and the ankle brachial index, were measured at baseline and 15 min, and 45 min after completing the interventions. A repeated measures two-way ANOVA was used for the data analysis. After a 7-day washout period, neither group exhibited a carryover effect. At the post-intervention period, the WBV intervention resulted in a significant increase in flexibility (+3.52 cm after 15 min and +4.20 cm after 45 min; *p*-value < 0.05) and a significant decrease in ankle SBP (–7.91 mmHg after 15 min; *p*-value < 0.05) and the ABI (–0.09 after 15 min and –0.07 after 45 min; *p*-value < 0.05). In contrast, the NWBV intervention led to a significant increase in ankle SBP (+10.50 mmHg after 45 min; *p*-value < 0.05). These findings show that middle-aged patients with T2DM might benefit from a single session of 12-min WBV training in terms of improving flexibility, ankle SBP, and the ABI. Therefore, it may be an exercise option for middle-aged T2DM patients.

***Corresponding author:** Ponlapat Yonglitthipagon, PT, PhD. School of Physical Therapy, Faculty of Associated Medical Sciences, Khon Kaen University, Khon Kaen, Thailand. Email address: ponlapat@kku.ac.th
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Introduction

In 2019, Thailand had an estimated 4.8 million adults with type 2 diabetes mellitus (T2DM), and this number is projected to increase to 5.3 million by 2039[1]. T2DM typically emerges in middle-aged individuals over the age of 45[2]. It reduces flexibility, especially in overweight or obese individuals, due to decreased mobility and glycation of joint structures, particularly in the lower extremities, significantly impacting overall quality of life[3]. Additionally, insulin resistance-induced vascular changes in the lower extremities, evidenced by increased ankle systolic blood pressure (SBP), are linked to cardiovascular disease risk[4]. Implementing interventions for middle-aged individuals with T2DM at an early stage of the disease is essential to control blood sugar and prevent irreversible vascular and joint limitations[5].

Aerobic, resistance, and flexibility exercises are effective physical therapy approaches for people with T2DM. However, individuals with T2DM who cannot follow prescribed exercise routines since they are strenuous, time-consuming, and difficult to follow may encounter difficulties in maintaining optimal blood sugar levels[6]. Whole-body vibration (WBV) is an innovative fitness practice that involves standing on a platform with electric motors that provide regulated vibrations. This activity has acquired popularity as an alternative or complementary treatment for several health issues, including diabetes[7].

Research has found that a single WBV session led to immediate flexibility improvements in middle-aged individuals with metabolic syndrome and Parkinson's disease, which was attributedto circulatory, thermoregulatory, and neural factors[8,9]. However, these studies did not explore the effect of WBV on flexibility beyond the immediate post-WBV period. Another research found that a single WBV session significantly lowered ankle SBP at 30 minutes, but not at 15 minutes, in healthy participants as a result of activating endothelial function, leading to increased nitric oxide production[10]. In addition, Figueroa and colleagues found that after 12 weeks of WBV, ankle SBP decreased in post-menopausal women with hypertension[11]. However, these studies did not investigate the impact of WBV on ankle SBP at 15 and 45 minutes following the WBV session. Hence, there is a notable gap in evidence regarding the immediate impact of WBV on flexibility and ankle SBP at 15 and 45 minutes after completing the intervention in middle-aged individuals with T2DM. Consequently, the objective of this study was to investigate the immediate effects of WBV on flexibility and ankle SBP in middle-aged patients with T2DM.

Materials and methods

Study design and participants

This study used a randomized, single-blinded crossover design. The participants were recruited through posters displayed at the village hall in Mueang Khon Kaen District in Khon Kaen, Thailand, between March and July 2023. Figure 1 presents a flowchart of the study enrollment. The sample size calculation was conducted employing the crossover study design formula[12] and considered a 2.1 cm change in flexibility following WBV, as observed in a prior study[8]. A significant level of alpha of 0.05 and a statistical power of 0.8 were chosen for the two-tailed test, and the total sample size resulted in 11 participants. Given a 10% rate of loss to follow-up, the adjusted total sample size would require 14 participants[13]. Therefore, there were 14 middle-aged individuals with T2DM, of which 7 participants were allocated to non-whole-body vibration (NWBV) and 7 participants to WBV in a randomized crossover design using stratified block randomization (block sizes of 4 and 6), with sex as the stratification variable.

The inclusion criteria were as follows: (1) diagnosis with T2DM between 1 and 10 years earlier; (2) age between 40 and 59 years; (3) body mass index (BMI) of 18.5–29.9 kg/m^2; (4) ability to walk without any assistive devices; and (5)

ability to understand and follow the instructions in the research protocol. The exclusion criteria were as follows: (1) brachial blood pressure (BP) ≥ 140/90 mmHg; (2) lower extremity pain (visual analog scale > 3) at rest or in a high squat position; (3) regular physical exercise (moderate intensity of ≥ 30 min/session ≥ 3 sessions/week); (4) musculoskeletal, cardiovascular, or neurological problems; (5) retinopathy and nephropathy; (6) diabetic foot ulcer; (7) tumors or metastases; (8) gall bladder and kidney stones; and (9) pregnant women.

This study was carried out at the School of Physical Therapy, Faculty of Associated Medical Sciences, Khon Kaen University, Thailand. The protocol of this study was registered in the Thai Clinical Trial Registry (ID 20230125003) and approved by the Ethics Committee of the Center for Ethics in Human Research, Khon Kaen University (HE652122) and written informed consent was obtained from all participants for this study.

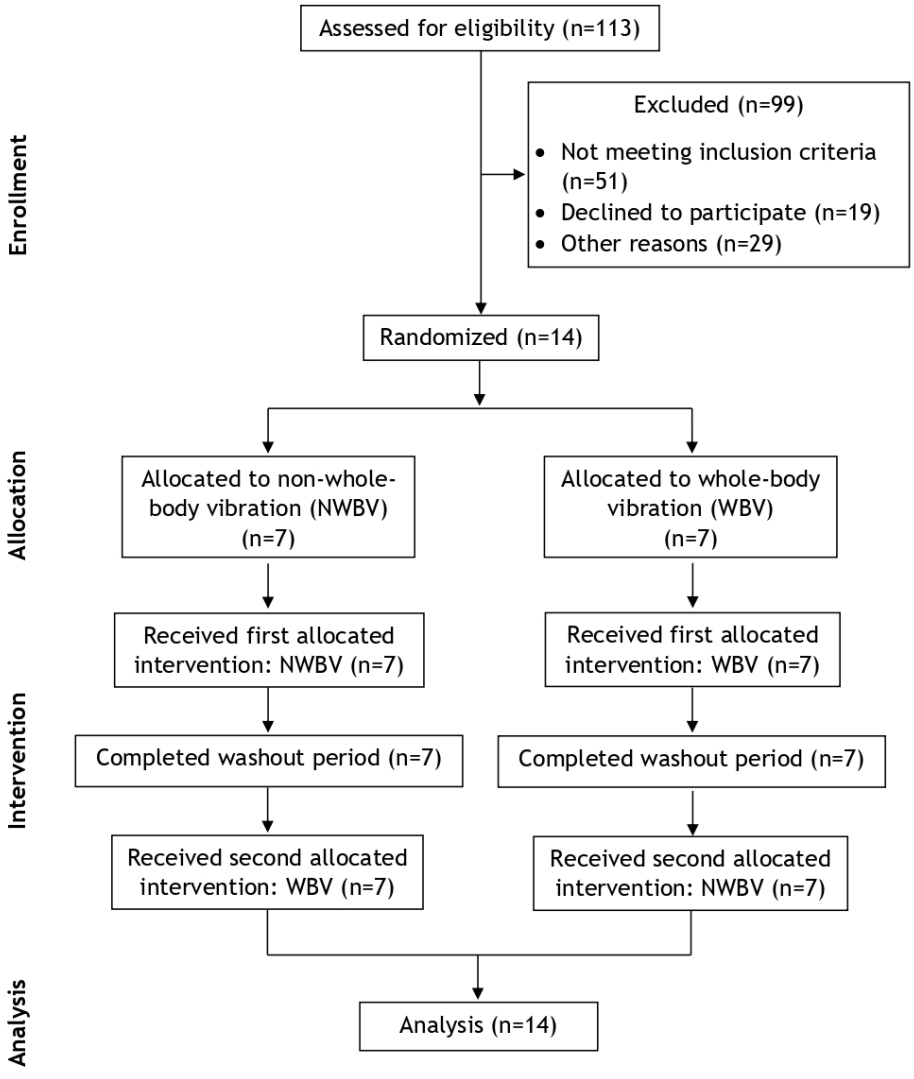

Figure 1 Flowchart of study participants.

Interventions

At the beginning of the study, all participants received a 3-minute educational session, and information was provided in a take-home brochure that included a QR code for a video-based education program on T2DM. This session occurred during a 15-minute resting period in the supine position before the initial measurements. The participants were randomized to first receive either NWBV or WBV intervention and after a seven-day washout period[14], they were crossed over to receive the other intervention. The WBV protocol, including frequency, amplitude, and duration was adjusted for participant safety based on previous studies[10,11,15] and our own trials. The participants were asked to maintain a static squat position (knees bent at 120°) on a vibrating plate for 1 minute at 25 Hz frequency and 2 mm amplitude. Six sets were performed, with a one-minute rest between sets in a comfortable standing position. Both the WBV and NWBV interventions thus lasted for 12 minutes. This high squat position was employed to reduce vibration transmission to the participant's head, minimizing risks such as vertigo and visual impairment[16]. The participants also wore socks to prevent skin irritation. The WBV was administered using a Galileo® S 35 device (Novotec Medical GmbH, Pforzheim, Germany). The NWBV intervention followed the same protocol without the WBV machine being turned on. Before the study began, all participants had the opportunity to become familiar with the equipment and research procedures.

Figure 2 Standing with high squat position on the whole-body vibration machine.

Outcome measures

The participants were instructed to avoid alcohol and caffeine, not to engage in strenuous physical activity for 24 hours, and refrain from heavy meals for a minimum of 4 hours before the experimental sessions to reduce the possibility of external factors affecting the measurements. A physical therapist with at least five years of clinical experience, who was blinded to the study procedure, sequentially measured brachial and ankle BP and flexibility to minimize confounding factors. The measurements were taken individually before the intervention and at 15 minutes and 45 minutes after the intervention on both days. Each measurement session lasted for 15 minutes, and the participants were required to rest for 15

minutes before each measurement, according to the American Heart Association guideline[17]. The room temperature was kept at 25ºC, and external stimuli were minimized.

Ankle and brachial BP were measured using a digital sphygmomanometer in the supine position (ICC > 0.9)[18,19]. The automatic device's cuff was placed above the ankles[20] and on the upper arms[17] in a random sequence. The BP readings were taken three times on each side, with a 2-minute gap between each measurement. The average of the higher side measurements was used for the statistical analysis.

The sit and reach test was used to assess hamstring and lower back flexibility (ICC = 0.92)[21]. The participants were seated on the floor without shoes and with their legs extended straight in front of them. They were instructed to slowly lean forward, aiming to reach as far as possible toward a measuring ruler positioned on a box, which ranged from -30 to +30, without bending their knees. Flexibility was measured twice for each participant, and the average of these two measurements was used for the statistical analysis[21].

The ankle brachial inde x was determined through utilization of a formula derived from a prior study[22].

Statistical analysis

The data were analyzed using SPSS version 28.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were employed to analyze the participants' demographic data. The normality of the data was analyzed using the Shapiro–Wilk test. The parametric test was selected for the data analysis because all the variables were normally distributed. All data are expressed as means and standard deviations. The baseline and post-intervention data within the groups and interventions were compared using a repeated measures two-way ANOVA (*p*-value corrected using the Bonferroni procedure). A *p*-value < 0.05 was considered significant.

Results

Table 1 shows the participants' demographic characteristics. Throughout the study duration, neither group exhibited any adverse events, such as nausea, dizziness, hypoglycemia, itching, or skin lesions. Furthermore, no carryover effect was observed, since the baseline values in both groups did not show statistical significance.

Table 1 Demographic characteristics of the participants (n = 14)

Characteristic	Values [Min-Max]
Age (years)	49.71 ± 5.28 [41–59]
Male/female, n (%)	2 (14.29) / 12 (85.71)
BMI (kg/m^2)	26.98 ± 3.24 [19.98–29.94]
Duration of diabetes (years)	2.32 ± 1.74 [1–6]

Note: All values are presented as mean and SD.

Abbreviation: BMI, body mass index; kg/m^2, kilogram per square meter.

In terms of flexibility, significant time*group interaction and time effects were observed (*p*-value < 0.05). Furthermore, significant increases were observed between baseline and both 15 and 45 minutes and between 15 minutes and 45 minutes after the WBV intervention (*p*-value < 0.05), while the NWBV intervention showed no difference (Table 2).

Ankle SBP showed a significant time*group interaction and time effects (p-value < 0.05). The NWBV intervention showed a significant increase in ankle SBP at 45 minutes after the intervention compared to the baseline. In contrast, the WBV intervention showed a significant decrease from baseline to 15 minutes and a significant increase between 15 minutes and 45 minutes after the intervention (p-value < 0.05). Furthermore, at 15 and 45 minutes after the intervention, the WBV intervention showed a statistically significant lower ankle SBP than the NWBV intervention (p-value < 0.05), as shown in table 2.

Regarding the ABI, time*group interaction, time, and group effects were significant (p-value < 0.05). Compared to the baseline, only the WBV intervention demonstrated significant decreases at 15 and 45 minutes after the intervention (p-value < 0.05). Interestingly, at 15 and 45 minutes after the intervention, the WBV intervention had a statistically significant lower ABI than the NWBV intervention (p-value < 0.05), as shown in table 2. In contrast, no significant changes from the baseline were observed in ankle diastolic blood pressure (DBP), brachial SBP, and brachial DBP at any time points following between the interventions, as shown in table 2.

Table 2 Analysis of the variables between the WBV and NWBV interventions (n = 14)

Variables	Group	Baseline (95% CI)	15 minutes after interventions (95% CI)	45 minutes after interventions (95% CI)	Time*group interaction effect	Time effect	Group effect
Flexibility (cm)	NWBV	1.52 ± 5.95 (-1.92 to 4.96)	1.87 ± 6.04 (-1.61 to 5.36)	2.05 ± 5.91 (-1.37 to 5.46)	$F(1.45, 37.79) = 46.85$ $p < 0.001$ $\eta^2 = 0.64$	$F(1.45, 37.79) = 75.12$ $p < 0.001$ $\eta^2 = 0.74$	$F(1, 26) = 1.26$ $p = 0.272$ $\eta^2 = 0.05$
	WBV	1.72 ± 5.91 (-1.69 to 5.14)	5.24 ± 5.71* (1.94 to 8.54)	5.92 ± 5.80*, † (2.57 to 9.27)			
Ankle SBP (mmHg)	NWBV	146.38 ± 9.70 (140.78 to 151.98)	151.52 ± 13.52 (143.72 to 159.33)	156.88 ± 18.37* (146.28 to 167.49)	$F(2, 52) = 10.42$ $p < 0.001$ $\eta^2 = 0.29$	$F(2, 52) = 6.03$ $p = 0.004$ $\eta^2 = 0.19$	$F(1, 26) = 4.03$ $p = 0.055$ $\eta^2 = 0.13$
	WBV	145.60 ± 10.51 (139.53 to 151.66)	137.69 ± 12.17 *, # (130.66 to 144.72)	143.26 ± 14.13†, # (135.11 to 151.42)			
Ankle DBP (mmHg)	NWBV	75.71 ± 6.82 (71.78 to 79.65)	78.60 ± 7.48 (74.28 to 82.92)	78.93 ± 6.69 (75.07 to 82.79)	$F(1.56, 40.35) = 0.78$ $p = 0.435$ $\eta^2 = 0.03$	$F(1.56, 40.35) = 3.29$ $p = 0.059$ $\eta^2 = 0.11$	$F(1, 26) = 1.18$ $p = 0.288$ $\eta^2 = 0.04$
	WBV	74.36 ± 7.39 (70.09 to 78.63)	75.17 ± 7.45 (70.87 to 79.47)	75.62 ± 7.13 (71.50 to 79.73)			
Brachial SBP (mmHg)	NWBV	124.60 ± 7.35 (120.35 to 128.84)	126.81 ± 10.78 (120.58 to 133.04)	128.95 ± 12.08 (121.98 to 135.93)	$F(1.58, 41.19) = 0.02$ $p = 0.957$ $\eta^2 = 0.00$	$F(1.58, 41.19) = 5.89$ $p = 0.009$ $\eta^2 = 0.19$	$F(1, 26) = 0.25$ $p = 0.624$ $\eta^2 = 0.01$
	WBV	122.62 ± 6.57 (118.83 to 126.41)	125.12 ± 9.40 (119.69 to 130.55)	127.55 ± 11.96 (121.98 to 135.93)			
Brachial DBP (mmHg)	NWBV	79.88 ± 5.87 (76.49 to 83.27)	83.12 ± 7.23 (78.94 to 87.30)	81.91 ± 6.72 (78.03 to 85.78)	$F(2, 52) = 0.69$ $p = 0.507$ $\eta^2 = 0.03$	$F(2, 52) = 2.54$ $p = 0.088$ $\eta^2 = 0.09$	$F(1, 26) = 2.09$ $p = 0.160$ $\eta^2 = 0.08$
	WBV	77.40 ± 7.20 (73.25 to 81.56)	78.43 ± 6.72 (74.55 to 82.31)	79.21 ± 6.96 (75.20 to 83.23)			
ABI	NWBV	1.18 ± 0.06 (1.14 to 1.21)	1.20 ± 0.07 (1.16 to 1.24)	1.22 ± 0.09 (1.17 to 1.27)	$F(2, 52) = 10.92$ $p < 0.001$ $\eta^2 = 0.30$	$F(2, 52) = 3.66$ $p = 0.03$ $\eta^2 = 0.12$	$F(1, 26) = 9.65$ $p = 0.005$ $\eta^2 = 0.27$
	WBV	1.19 ± 0.06 (1.15 to 1.22)	1.10 ± 0.05*, # (1.07 to 1.13)	1.12 ± 0.05*, # (1.09 to 1.15)			

Note: All values are presented as means and SDs. *indicates a statistically significant difference within the group compared with the baseline (p-value < 0.05); †indicates a statistically significant difference within the group when comparing 15 minutes to 45 minutes (p-value < 0.05); #indicates a statistically significant difference between the groups (p-value < 0.05).

Abbreviation: 95% CI, 95% confidence interval; F, F-test; η^2, partial eta square; WBV, whole-body vibration; NWBV, non-whole-body vibration; Ankle SBP, ankle systolic blood pressure; Ankle DBP, ankle diastolic blood pressure; Brachial SBP, brachial systolic blood pressure; Brachial DBP, brachial diastolic blood pressure; ABI, ankle brachial index.

Discussion

This study aimed to examine the acute effects of WBV on flexibility and ankle SBP in middle-aged individuals with T2DM. The results showed that the WBV intervention significantly increased flexibility and decreased ankle SBP and the ABI. The higher number of female participants might be attributed to increased insulin resistance and decreased estrogen levels following menopause in the 49–51-year-old age group[23]. The participants, with a mean BMI of 26.98 kg/m^2, were overweight and at increased risk of diabetes[24]. Additionally, our study did not show significant carryover effects for any variables, indicating that the washout duration was adequate.

Flexibility improved from "fair" to "good"[25] at different time points: 15 minutes (+3.52 cm) and 45 minutes (+4.20 cm) post-WBV compared to the baseline, indicating a lasting positive effect for at least 45 minutes after a single WBV session. Similar findings have been observed in elderly people with Parkinson's disease, in whom flexibility increased by 3.86 cm immediately after WBV[9]. Another study showed that middle-aged healthy females had a 3.6 cm flexibility improvement following two months of WBV[26]. A 2.5 cm improvement in the sit and reach test is considered clinically meaningful[27]. A single WBV session likely increases flexibility by enhancing stretch reflex sensitivity through Ia inhibitory neurons, altering muscle activity patterns, reducing braking forces, and decreasing muscle stiffness[9]. WBV also stimulates Golgi tendon organs via the Ib pathway, inducing muscle relaxation and inhibiting contractions[9]. Improved blood circulation, thermoregulation, and neural mechanisms during WBV contribute to enhanced flexibility by increasing vasodilation, elevating blood flow and muscle temperature, reducing tissue thickness, and promoting muscle elasticity while minimizing discomfort[28].

The current findings revealed a significant 7.91 mmHg reduction in ankle SBP at 15 minutes compared to the baseline, remaining within the normal range. This indicates that the acute effect of a single WBV session on ankle SBP persisted for a minimum of 15 minutes. Previous research has also demonstrated a decrease in ankle SBP by 9.8 mmHg in healthy adults after 30 minutes of a single WBV session[10]. Another study reported a 6.68 mmHg decrease in ankle SBP after 50 heel raises in a standing position among healthy elderly individuals[29]. Furthermore, a more substantial 24 mmHg reduction in ankle SBP was observed in postmenopausal women with high baseline ankle SBP (≥ 175 mmHg) after 12 weeks of WBV, likely due to the longer training duration and higher initial SBP levels of participants[11].

A previous study has suggested that a reduction in ankle SBP exceeding 30 mmHg post-treadmill exercise indicates peripheral arterial disease[30]. However, our participants, with an average diabetes duration of 2.32 years, might not have progressed to that PAD stage[31]. WBV exercise in a high squat position enhances lower limb muscle activation, relaxing vascular smooth muscles, reducing arterial stiffness, and promoting local vasodilation through nitric oxide production, thus lowering ankle SBP[10]. Conversely, a NWBV intervention increases ankle SBP due to muscle contractions during static high squat exercises performed without WBV, constraining blood capillaries and obstructing circulation[32].

In this study, significant ABI reductions were observed post-WBV intervention: a 7.56% decrease at 15 minutes and 5.88% at 45 minutes, which all remained within the normal range. This finding suggests that the effect of a single session of WBV on the ABI persists for at least 45 minutes. Figueroa and colleagues observed a 3.85% reduction in the ABI after 12 weeks of WBV in postmenopausal women with increased ankle SBP[11]. Another study reported a 9.62% ABI reduction after 50 heel raises in a standing position for healthy elderly people[29]. Our findings align with research indicating a 5% reduction in the ABI following a single exercise session in healthy individuals[33]. In this study, the observed ABI reduction may be attributed to the following mechanisms: 1) increased central aortic

pressure and decreased peripheral BP at the ankles during exercise, delivering more oxygenated blood to meet leg muscle metabolic demands, leading to a small reduction in the ABI, and 2) high shear stress, such as during WBV exercise, triggering endothelial substance release and vasodilation[10]. This study observed non-significant increases in ankle DBP, brachial SBP, and brachial DBP after both interventions, indicating that the increased parameters were within the normal range according to American Heart Association standards[34]. Previous studies found that a single WBV session did not result in significant decreases in ankle DBP or brachial SBP or DBP in healthy young adults[10] and adults with obesity[35]. Another study found that a high squat position reduced vibration transmission to the upper extremities, resulting in insignificant vasodilation[36]. Holding the WBV machine handles to maintain this position during both interventions also caused a pressor rise in brachial BP, which is vital for muscle perfusion during prolonged contraction[37].

Regarding limitations, the findings of our study may not be generalizable to different populations, such as obese individuals with T2DM. Future research should include individuals with T2DM across various age groups, especially those with longer diabetes duration (> 10 years) and higher ankle SBP (>175 mmHg), with a focus on potential clinically significant improvements. Furthermore, our study did not extend its assessment of the acute effects of WBV beyond the 45-minute recovery period. Thus, future research should investigate the effects of WBV over longer durations. Additionally, relying solely on the sit and reach test may be insufficient for accurately evaluating changes in lower extremity flexibility. Despite these limitations, the strength of our study lies in its use of a crossover design, which allowed for a more comprehensive evaluation of treatment impact by comparing outcomes within each participant, thus mitigating individual differences, and potentially reducing the influence of covariates.

Conclusions

A single 25 Hz, 2 mm, 12-minute WBV session can significantly enhance flexibility and lower ankle SBP and the ABI in middle-aged T2DM patients without any adverse effects or complications.

Take home messages

WBV offers a safe and promising alternative exercise method with the potential to mitigate cardiovascular risk in middle-aged individuals with T2DM. Nevertheless, it is crucial to exercise caution, especially for those with hypertension, as the high squat exercise without WBV can raise both brachial and ankle BP levels.

Conflicts of interest

The authors declare no conflict of interest.

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Effects of Qigong combined with Muay Thai on cardiorespiratory responses and exercise intensity in sedentary older participants

Guang Yang[1,2,3], Narisara Premsri[1,2], Terdthai Tong-un[2,4], Orathai Tunkamnerdthai[2,4], Apiwan Manimmanakorn[2,4], Rujira Nonsa-ard[5], Ploypailin Aneknan[2], Naruemon Leelayuwat[1,2,*]

[1] Exercise and Sport Sciences Program, Graduate School, Khon Kaen University, Khon Kaen, Thailand.
[2] Exercise and Sport Sciences Development and Research Group, Khon Kaen University, Khon Kaen, Thailand.
[3] Faculty of Physical Education, Henan institute of economics and trade, Zhengzhou, China.
[4] Department of Physiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.
[5] Faculty of Public Health, Mahasarakham University, Mahasarakham, Thailand.

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Exercise; Ventilation; Endurance; Physical activity; Aging.

ABSTRACT

Khon Kaen Qigong (KKQ) is a new type of exercise that combines Qigong (Baduanjin and Wuqinxi) with Muay Thai. No studies have demonstrated its effects on exercise intensity and cardiorespiratory responses. We aimed to investigate the intensity of the exercise using the cardiorespiratory responses in sedentary older adults. This was a randomized, controlled, pre-and post-test parallel-group study. The participants were randomly assigned to one of the two groups (n=30 each): the exercise or the control group. There were three phases (30 min each) for each activity, including before (baseline), during, and after (recovery) reading a book in the control group or performing KKQ in the exercise group. Heart rate and blood pressure were measured before, immediately after, and 30-min after the activities. Expired gas was collected to measure the respiratory responses and ventilatory efficiency throughout the experiment. Compared with reading, KKQ increased heart rate (p-value < 0.05) and respiratory responses and decreased ventilatory efficiency (All were p-value < 0.01). Markers indicating exercise intensity indicated very low-intensity exercises. This study suggests that a single bout of KKQ can be classified as a very light-intensity exercise according to very low increased cardiorespiratory responses in sedentary older participants. It also decreases ventilatory efficiency, which is related to cardiovascular risk factors. Further studies on KKQ training may confirm its impact on cardiovascular disease interventions.

***Corresponding author:** Naruemon Leelayuwat, PhD. Exercise and Sport Sciences Program, Graduate School, Khon Kaen University, Khon Kaen, Thailand. Email address: naruemon@kku.ac.th; naruemon.leelayuwat@gmail.com
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Introduction

The world's population is aging; the number of older people aged ≥60 years will soon exceed the younger population, and the proportion of older people will reach 21% by 2050[1]. Aging leads to an increased incidence of cardiorespiratory disease, as well as increases in morbidity and mortality[2,3]. Therefore, exploring interventions to prevent these diseases is crucial to promote the health of older adults. Exercise-based rehabilitation programs prevent comorbidities and decrease mortality[4,5].

We invented a novel exercise called Khon Kaen Qigong (KKQ) for sedentary older adults. This could be an interesting choice for them because it is modified from two popular cultural exercises: traditional Qigong (Baduanjin and Wuqinxi) and Muay Thai (Wai Khru session)[6]. Both Qigong types are the most widely practiced types of traditional Chinese Qigong, which are mind-body exercises, whereas Wai Khru is a pre-session of Muay Thai, the most popular martial sport in Thailand[7-9].

Both Qigong and Wai Khru provide meditation and gentle and smooth movements, which are appropriate for the older population[7-10]. Taken together, the popularity and modified beautiful movements of the KKQ may motivate older people to adhere to KKQ practice. Our previous study demonstrated that acute KKQ in sedentary older adults led to sympathetic dominance, as evidenced by increasing heart rate (HR) and respiratory rate (RR)[6]. However, this previous study was a pilot trial requiring further investigation with more participants and cardiorespiratory variables to explore more knowledge of acute KKQ before exploring the training effect.

Exercise intensity is an important component of exercise prescriptions. This is indicated by cardiorespiratory responses. Literature reporting the responses to each component of KKQ documented that only one study was done investigating Baduanjin in older participants and found an acute increase in oxygen consumption (VO_2) and a moderately increased HR[11]. However, the participants were patients with chronic heart failure and cardiac dysfunction, and their hearts worked harder than those of healthy people as shown in the report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines[12]. Thus, healthy older adults without heart disease may yield different results. Data on the effect of the KKQ and its components on exercise intensity as indicated by cardiorespiratory variables in healthy, sedentary older people are not yet available.

Therefore, this study aimed to determine the intensity of the KKQ and its single-session effects on cardiorespiratory variables in sedentary older adults. For the response to a single bout of KKQ, we chose reading a book as the control activity because a 30-min reading was reported to have no stimulation on the cardiopulmonary responses[6]. Thus, compared to reading, the effect of a single bout of KKQ on the cardiopulmonary responses should be clearly observed. We hypothesized that a single bout of KKQ is a low-intensity exercise, as indicated by the low response of the cardiorespiratory system in sedentary older participants.

Materials and methods

Participants

This study was conducted from June 2021 to February 2022 in the Khon Kaen Province, Thailand. Participants aged 60–75 years were recruited. Participants received verbal and written explanations before signing the consent form. They were screened through body composition, anthropometry, physical examinations, electrocardiography, blood chemistry, baroreceptor reflex, and questionnaires for health status and readiness to exercise (using the Physical Activity Readiness Questionnaire, PAR-Q). Participants who had no kidney, liver, or cardiac disease, obesity, and exercise limitation were recruited. Moreover, those who had no regular (longer than 1 hour/week) long-term (>2 years) experience with meditation, Qigong, or other types of exercise were included. However, participants with these diseases or chronic

infection were excluded. Ethical approval was obtained from the Ethics Committee of Khon Kaen University (HE641163).

Sample size calculation was calculated by G*Power 3.1 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) based on a previous study[11] of the therapeutic effect of Qigong on the VO_2 with effect size of 0.53, a power of 80%, and an alpha of 5%. The sample size in each group was 30 (including a dropout rate of 20%).

Research design, randomized allocation, and blinding

This was a randomized, controlled, pre- and post-test, study. To maintain and guarantee blinding, the outcome adjudicators and data analysts were blinded by using participants' code. However, participants and the researcher who collected gas sample were not blinded because both knew the intervention. Nonetheless, participants were blinded to group allocation. The randomized allocation sequence (1:1) was performed using computer-generated random numbers and kept in sequentially numbered, opaque, sealed envelopes. However, a researcher who gave an envelope to the participant for group allocation is not the one who prepared the envelope.

Protocols

Participants who passed the screening were randomly allocated to one of the two groups (n=30 each): the KKQ group (KKG) and the control group (CG).

The KKG visited the laboratory three times at 8:00 am after an overnight fast. During the first visit, they performed the KKQ (Supplementary Figure S1)[6] for 30 min to familiarize themselves with the exercise. Two days later, they visited the laboratory to collect the expired gases during three phases (30 min each), including resting in a supine position before (baseline), during and after KKQ (recovery in supine position), to measure RR, ventilation rate (V_E), VO_2, and carbon dioxide production rate (VCO_2). HR, BP, rating of perceived exertion (RPE), and dyspnea (RPD) were recorded immediately before and at the end of the KKQ and recovery. The room temperature and humidity were recorded throughout the experiment. Two days later, they again came to the laboratory to measure peak VO_2 ($VO_{2,peak}$) by 6-min walk test (6MWT)[13].

The CG participated during a single visit. They performed the same experimental procedure as during the second visit to the KKG, except that the KKQ was replaced by reading a Dhamma book while sitting. The Dhamma book was the same for all participants in this group.

Participants' measurements of all anthropometry, body composition, and cardiovascular outcomes were assessed as described in a previous study[14]. Furthermore, all respiratory outcomes were collected and analyzed with a gas analyzer (Oxycon CareFusion 234 GmbH, Höchberg, Germany). Then percentage of maximal HR (%HRmax) and $VO_{2,peak}$ (%$VO_{2,peak}$), RPE[15], and RPD[16] were used to indicate exercise intensity. In addition, V_E, VO_2, and VCO_2 were used to calculate ventilatory efficiency[17].

Statistical analysis

All statistical analyses were performed using SPSS version 26.0 (IBM, Armonk, NY, USA). The Kolmogorov-Smirnov test was used to test the normality of the data. The independent t-test was used to compare continuous variables of characteristics with a normal distribution between groups. Repeated-measures ANOVA was used to compare continuous variables with a normal distribution within and between groups. The Bonferroni test was used as a post hoc test. The Mann-Whitney U test was used for ordinal data or unpaired samples that were not normally distributed. A *p*-value of < 0.05 was considered statistically significant. Results were expressed as mean ± standard deviation (SD) or stated elsewhere.

Results

Of the 90 eligible participants, 66 were included in this study (Supplementary Figure S2). The remaining participants were unable to participate because they did not meet the inclusion criteria (n=10), declined to participate (n=10), or for other reasons (n=4). They were then randomly allocated to one of the two groups: the KKG or the CG (n= 33 each). Thirty participants (28 females and two males in each group) completed the experiment. In the KKG, two female participants left the study for family reasons, and one male participant dropped out due to physical discomfort. In the CG, three female participants dropped out of the study for physical reasons. The room temperature and humidity were 24.9±0.9°C and 59.4±4.7%. There were no significant differences in all characteristics and cardiorespiratory outcomes between groups at baseline (Table 1, Figure 1-3).

Table 1 Baseline demography, anthropometry, body composition, hemodynamics, and blood chemistry of participants in both groups

	CG (n=30)	KKG (n=30)
Age (yr)[a]	68±4.6	70±6.04
Sex (male/female)	2/28	2/28
BM (kg)[a]	57.2±9.47	58.8±8.82
BMI (kg/m^2)[a]	24.6±3.54	25.5±3.05
W (cm)[a]	85.5±12.15	87.7±8.65
H (cm)[a]	98.3±7.35	99.3±6.47
W/H[a]	0.89±0.06	0.87±0.06
BF (%)[a]	33.6±4.98	35.2±4.05
FM (kg)[a]	19.1±5.8	21.1±4.3
LBM (kg)[a]	35.9±8.8	36.9±6.2
HR (/min)[a]	74.6±11.3	70.9±8.3
SBP (mmHg)[a]	132.5±15.8	125.9±14.4
DBP (mmHg)[a]	79.4±11.7	72.1±8.9
MAP (mmHg)[a]	98.1±13.9	87.1±12.8
FBG (mg/dL)[a]	112.6±37.2	104.1±31.4
TC (mg/dL)[a]	212.2±35.2	227.9±47.2
TG (mg/dL)[a]	151.6±78.0	148.6±91.4
HDL-c (mg/dL)[a]	51.3±17.4	50.4±14.0
LDL-c (mg/dL)[a]	136.1±34.6	151.5±43.7
Cr (mg/dL)[a]	0.84±0.18	0.83±0.12
SGPT (U/L)[a]	19.3±18.6	15.2±5.79

Note: The data are presented by mean ± SD. [a]The independent t-test was used to compare continuous variables with normal distribution between groups.

Abbreviation: BM, body mass; BMI, body mass index; W, waist circumference; H, hip circumference; BF, body fat; FM, fat mass; LBM, lean body mass; FBG, fasting blood glucose; TC, total cholesterol; TG, triacylglycerol; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; Cr, creatinine; SGPT, serum glutamate pyruvate transaminase.

Cardiovascular outcomes

HR

Compared with baseline, HR significantly increased immediately after KKQ and reading and recovery, with a greater value immediately after KKQ compared with reading (All were *p*-value < 0.05) (Figure 1A).

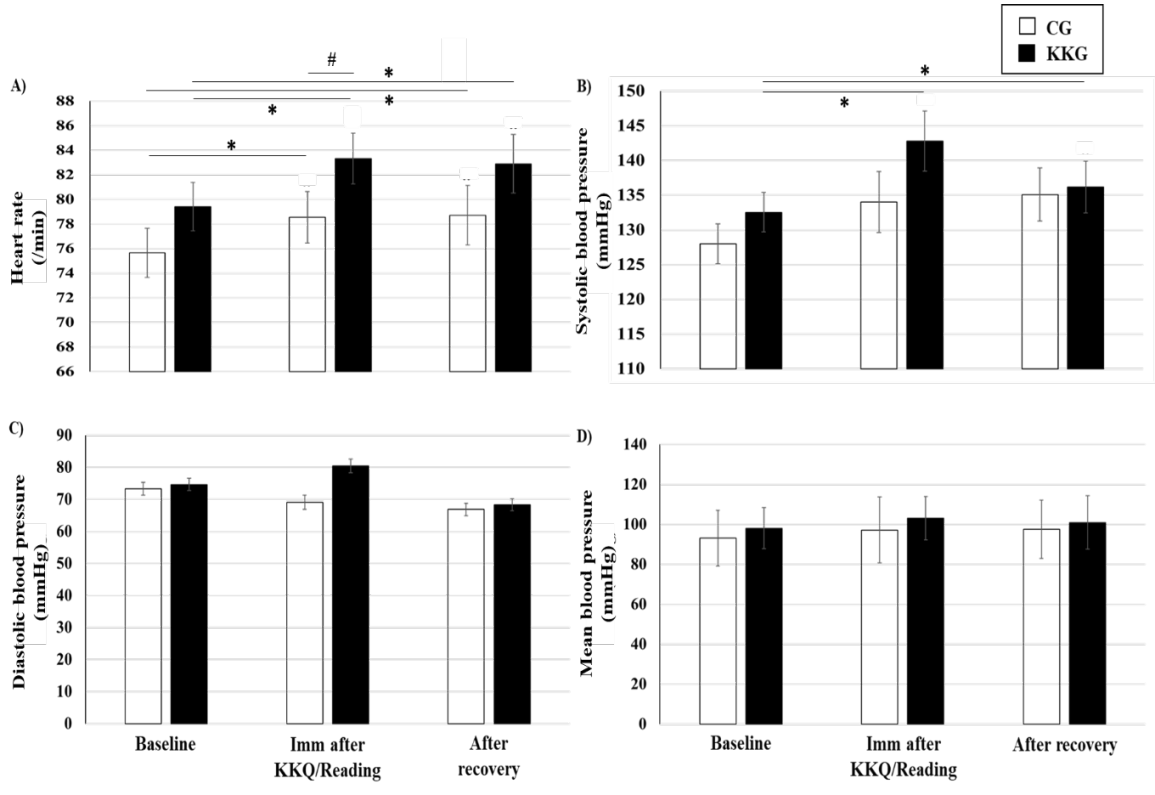

Figure 1 (A) Heart rate (/min), (B) Systolic blood pressure (mmHg), (C) Diastolic blood pressure (mmHg), and (D) Mean arterial pressure (mmHg) at baseline, immediately after KKQ/Reading, and at the end of recovery.

Note: Data are presented as mean±SE (n=30 each group). * within the group (*p*-value < 0.05); # between groups (*p*-value < 0.05).

Abbreviation: CG, control group; KKG, Khon Kaen Qigong group.

BP

Compared to baseline, SBP significantly increased immediately after KKQ and recovery (Both were *p*-value < 0.05) in the KKG (Figure 1B), but no changes were found in the CG. No significant differences in SBP were observed between the groups. Furthermore, no significant differences in DBP and MAP were found within or between the groups (Figure 1C and 1D).

Respiratory outcomes

RR

Compared with the baseline, the RR was significantly increased from 10 to 30 min during KKQ, with greater values in the KKG than in the CG for 20-30 min (All were *p*-value < 0.01) (Figure 2A). Furthermore, the RR was greater than baseline at 5- and 15-min during recovery from KKQ. The RR decreased during the KKQ throughout

recovery and returned to baseline during the last 10 min (All were *p*-value < 0.01). However, there were no significant changes in RR throughout the experiment in the CG.

V_E

Compared with baseline and CG, V_E were significantly greater throughout the KKQ (5-30 min) (All were *p*-value < 0.01) (Figure 2B). Then, the KKG had decreased V_E from during KKQ throughout recovery and returned to baseline during the last 10 min of recovery (All were *p*-value < 0.01). V_E was significantly greater during KKQ than reading at 5-10 min (*p*-value < 0.05) of recovery. V_E did not change throughout the entire experiment in the CG.

VO_2

Compared with baseline and the CG, VO_2 was significantly greater throughout the KKQ (5-30 min) until 5 min into recovery (All were *p*-value < 0.01) (Figure 2C). The KKG had a lower VO_2 during recovery than during KKQ (*p*-value < 0.01) and returned to baseline during the last 25 min of recovery. VO_2 did not change throughout the entire experiment in the CG.

VCO_2

Changes of VCO_2 were the same as those of VO_2, except the KKG had a greater VCO_2 than baseline 15 min into recovery (All were *p*-value < 0.05). VCO_2 did not change throughout the entire experiment in the CG (Figure 2D).

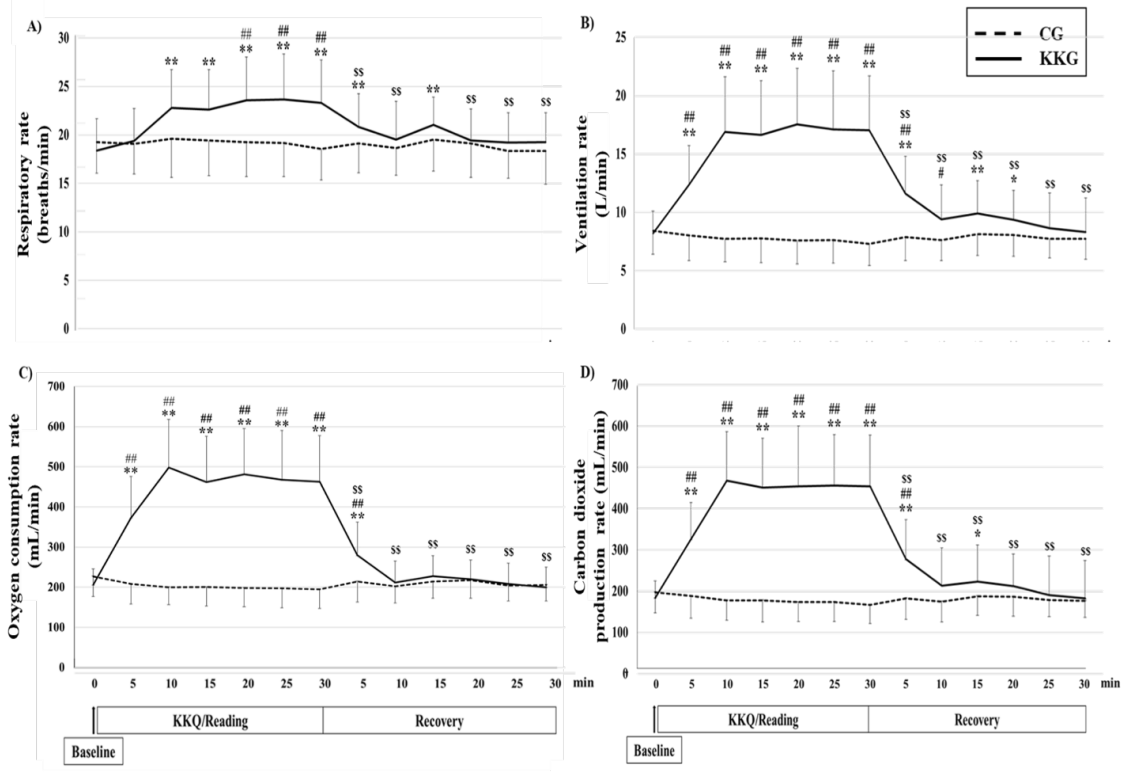

Figure 2 (A) Respiratory rate (breaths/min), (B) ventilation rate (L/min), (C) Oxygen consumption rate (mL/min), (D) Carbon dioxide production rate (mL/min) at baseline, during KKQ/Reading, and recovery in both groups.

Note: Data are presented as mean±SE (n=30 each group). *,** Different from baseline within the group (*p*-value < 0.05, 0.01), $^{\$\$}$ different from that during the KKQ within the KKG (*p*-value < 0.01), $^{\#,\#\#}$ different between groups at the same time point (*p*-value < 0.05, 0.01).

Abbreviation: CG, control group; KKG, Khon Kaen Qigong group.

V_E/VO_2

Compared with baseline, V_E/VO_2 was significantly decreased during KKQ (5-25 min) (All were *p*-value < 0.01 except at 25 min (*p*-value < 0.05)) and increased at 10 min into recovery (*p*-value < 0.01) (Figure 3A). Compared with the CG, V_E/VO_2 in the KKG was significantly lower at 10 min during KKQ (*p*-value < 0.01) and greater at 5-20 min into recovery (All were *p*-value < 0.01). In the KKG, V_E/VO_2 during recovery was greater than during KKQ (All were *p*-value < 0.01). V_E/VO_2 did not change throughout the entire experiment in the CG.

V_E/VCO_2

Compared with baseline and the CG, V_E/VCO_2 was significantly lower throughout KKQ (5-25 min) (All were *p*-value < 0.01, except at 5 min compared with CG (*p*-value < 0.05) (Figure 3B). V_E/VCO_2 of the KKG returned to baseline at 25 min of KKQ until the end of recovery. V_E/VCO_2 did not change throughout the entire experiment in the CG.

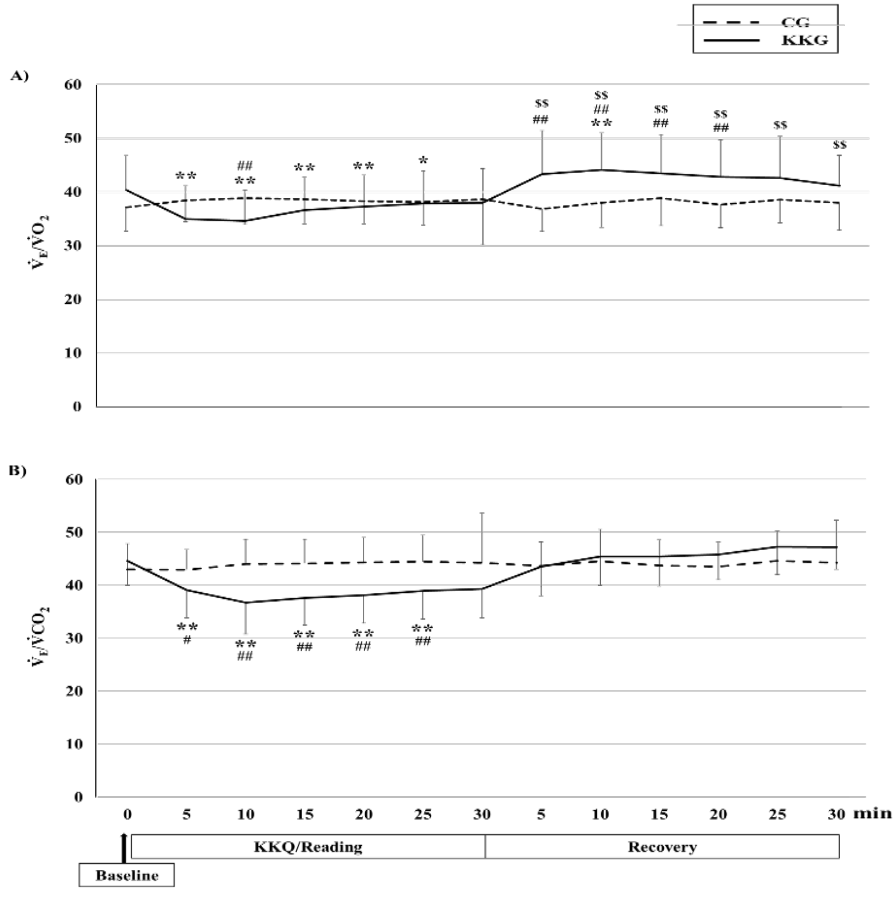

Figure 3 Ventilatory efficiency at baseline, during KKQ/Reading, and recovery in both groups. Data are presented as mean±SE (n=30 each group).

Note: *,**Different from baseline within the group (*p*-value < 0.05, 0.01), $^{\$\$}$ different from that during the KKQ within the KKG (*p*-value <0.01), $^{\#,\#\#}$ different between groups at the same time point (*p*-value < 0.05, 0.01).

Abbreviation: CG, control group; KKG, Khon Kaen Qigong group; V_E/VO_2, ventilatory efficiency relative to VO_2; V_E/VCO_2, ventilatory efficiency relative to VCO_2.

***Intensity of exercise*[16,18]**

%HRmax indicated that KKQ was a very light-intensity exercise (Table 1). Furthermore, the $VO_{2,peak}$ of the participants in KKG was 32.2±4.34 mL/kgBM/min. The $\%VO_{2,peak}$ determined that KKQ was a very light-intensity exercise. The highest $\%VO_{2,peak}$ was during the first round of KKQ (Supplementary Figure S3). The RPE and RPD also increased to a very light to light level of exertion during the KKQ. No participants complained of any discomfort or injury from KKQ.

Table 2 Exercise intensity of KKQ of participants

Variable	Mean±SD	Reference values	Exercise intensity
%HRmax	54.1±9.5	<57	Very-light
$\%VO_{2,peak}$	20.9±5.0	<37	Very-light
Rating of perceived exertion	10.6±1.8	9-11	Very light–fairly light
Rating of perceived dyspnea	2.8±1.6	2-3	Light

Note: The data are presented by mean ± SD (n=30).
Abbreviation: KKQ, Khon Kaen Qigong group; %HRmax, percentage of maximal heart rate; $\%VO_{2,peak}$, percentage of peak oxygen consumption rate.

Discussion

To the best of our knowledge, this is the first study to provide evidence that a single bout of KKQ is a very light-intensity exercise, as indicated by very low responses of the cardiorespiratory system in sedentary older participants. Furthermore, KKQ reduced ventilatory efficiency, whereas the reading was confirmed as resting status.

Unexpectedly, the cardiorespiratory responses determined that KKQ was a very light-intensity exercise. Only two subjective indicators i.e. RPE and RPD indicated it as very light- to light-intensity exercise. Together with the other indicator i.e. %HRmax, $\%VO_{2,peak}$ which is a gold standard indicator of exercise intensity[19] classified it as a very light-intensity exercise. The increase in HR compared to the reading group is consistent with a previous study in our laboratory[6] (a pilot study). We found that KKQ increased HR along with a trend towards an increased low frequency/high frequency ratio of heart rate variability. This reflects the sympathetic dominance induced by KKQ. Sympathetic activity stimulates cardiac frequency, increasing HR[20]. However, it is surprising that KKQ did not increase BP compared with the reading group. The unaltered change in SBP caused by the KKQ was consistent with the response to cycling during low-intensity exercise in a study by Boonthongkaew et al[14]. The increased HR but not SBP may be due to the sinoatrial node, which generates HR and is more sensitive to exercise-induced sympathetic activity or hormonal stimulation than the left ventricular muscle, which increases SBP[20]. In addition, the unchanged DBP may be explained by the fact that KKQ may not stimulate sufficient vasodilators, such as nitric oxide.

All movements of the KKQ included bending forward, backward, sideward, twisting, and walking. This provides good stretching of the chest, waist, arms, and legs. Furthermore, the KKQ included breathing exercises with pursed lips. Together with stretching in the chest area, KKQ enhances thoracic cage flexibility, resulting in increased inspiratory volumes. Therefore, it increases the concentration of inspired oxygen. The increased KKQ-induced VO_2 reflects increased aerobic metabolism possibly led to enhanced aerobic performance[21]. Furthermore, we found that V_E/VCO_2 decreased from baseline throughout

the single bout of KKQ, whereas V_E/VO_2 decreased at 10 min of KKQ compared with the CG. Together with the decreased V_E/VCO_2 and V_E/VO_2 during the KKQ session, the increases in RPE and RPD confirm improved ventilatory efficiency secondary to KKQ. Importantly, it has been shown that exercise-induced decreased ventilatory efficiency are associated with decreased cardiovascular risk and mortality[22,23]. Therefore, we expect that KKQ training may benefit cardiovascular risk and mortality.

Considering the importance of quality of the measurement process, we controlled them throughout. Firstly, this study design is RCT which is a good research design, and we blinded all participants and researchers except those who collected the data during KKQ/Reading. Secondly, the quality of all equipment was controlled by calibration before data collection or having quality assessment during the analysis. Thirdly, we matched all baseline characteristics of participants confirmed by results of no difference between groups (Table 1). Furthermore, the ratio of participants' underlying diseases in CG and KKG was similar (five and three participants with diabetes mellitus type 2; 18 and 17 participants with hypertension, and 27 participants in both groups with dyslipidemia). Therefore, these data were sufficient to confirm the results of this study.

First of our limitations, we did not measure autonomic activity, stress hormone concentration, or vasodilator use. This conceals the mechanism of cardiorespiratory responses to both conditions in older sedentary adults. Furthermore, we did not record the HR during KKQ/reading and recovery every 5 min. We measured the HR before and immediately after activities and recovery. Therefore, we could not show a 5-min change in HR during either activity. Therefore, the HR data were inconclusive. However, other indicators, i.e., $\%VO_{2,peak}$, RPE, and RPD, showed the very light exercise intensity nature of KKQ. In addition, although we did not have a direct measurement of $VO_{2,peak,}$ i.e., cardiopulmonary exercise test (CPET), we used other indirect indicators, i.e., calculated $VO_{2,peak}$ from 6 MWT[24], %HRmax, RPE, and RPD which are standard tools. Measuring $VO_{2,peak}$ from a 6 MWT, a moderate-intensity exercise, is safer for older individuals compared to the direct measurement, i.e., CPET, where participants need to exercise until 85%HRmax or exhaustion[25]. Lastly, most participants were female (28 females in the KKG and CG, respectively). A review article demonstrated that sex influences physiology, pathology, and treatment outcomes[26]. Thus, our results are unlikely to apply to the male population.

Based on previous studies showing beneficial effects of very low-intensity exercise on cardiorespiratory function[27-29], further studies applying KKQ training to investigate cardiorespiratory responses such as heart rate variability, respiratory muscle strength, and dynamic pulmonary functions and cardiovascular risk factors in older adults worth performing. In addition, the training research in other populations, such as male participants, elderly adults, and patients with cardiovascular and pulmonary diseases should be encouraged.

Conclusion

This study demonstrated that a single bout of KKQ is a very light-intensity exercise in sedentary older adults, as indicated by the cardiorespiratory responses to a very low level of effort. Furthermore, it decreases ventilatory efficiency, associated with cardiorespiratory risk factors. Further studies on KKQ training may confirm its impact on cardiovascular disease interventions.

Clinical implication

- Khon Kaen Qigong (KKQ) is a very light-intensity exercise indicated by increased cardiorespiratory responses to very low levels in sedentary older participants.
- KKQ decreased ventilatory efficiency, implying a reduction in cardiorespiratory risk factors.

Conflicts of interest

The authors declare no conflict of interest.

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Supplementary

Figure S1 Postures of Khon Kaen Qigong (Figure reproduced with permission from Liu et al, 2022).

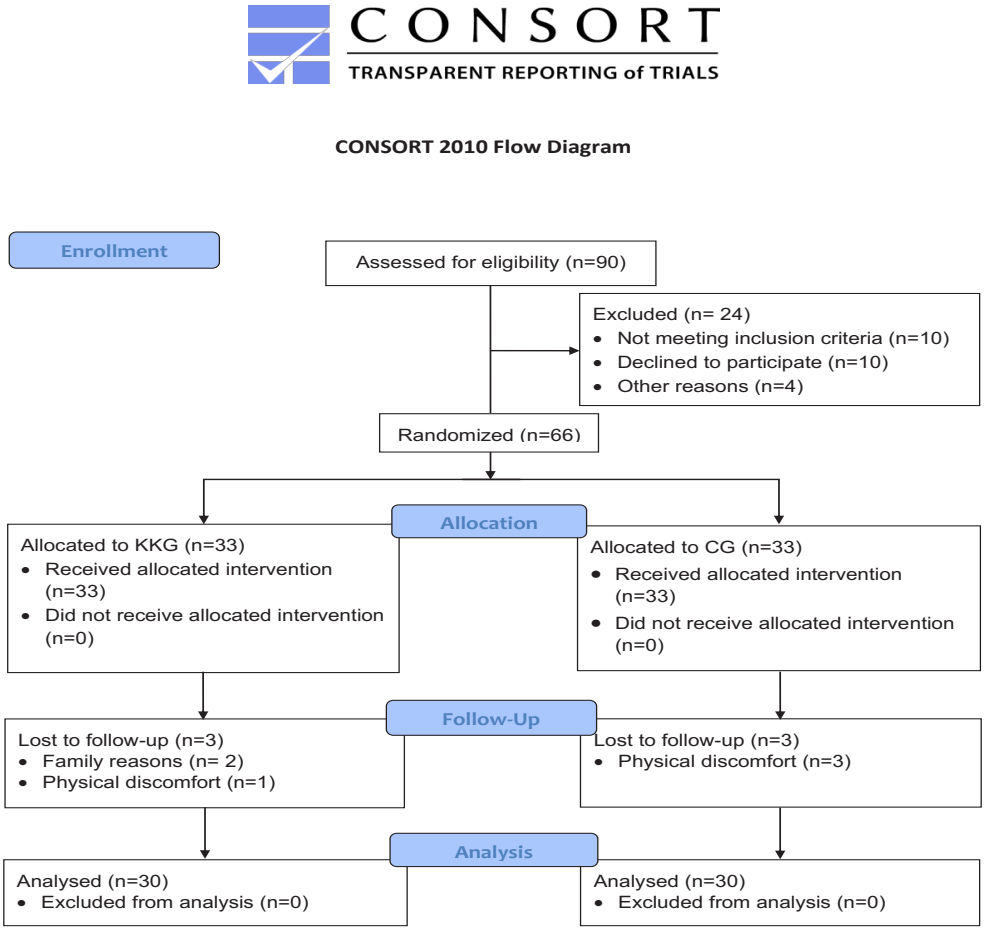

Figure S2 Consort flow diagram of this study.
Abbreviation: KKG, Khon Kaen Qigong group; CG, control group.

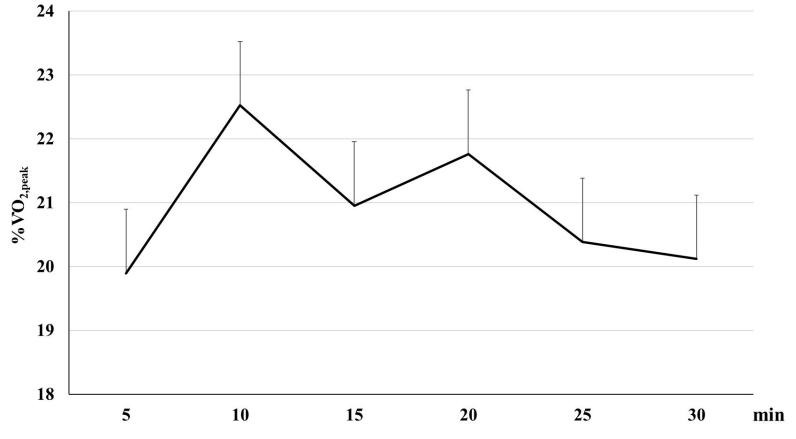

Figure S3 $\%VO_{2peak}$ during Khon Kaen Qigong.
Abbreviation: $\%VO_{2peak}$, percentage of peak oxygen consumption rate.

ORIGINAL ARTICLE

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An Excel Visual Basic for Application worksheet for automatic selection of a sigma statistical quality control procedure, facilitating quality management for laboratories

Pranadta Wontong*

Department of Chemistry, Laboratory, Prasat Hospital, Surin, Thailand.

KEYWORDS
Sigma metric; Statistical quality control; QC plan tool; Quality management.

ABSTRACT
Defining the proper statistical quality control (SQC) procedure and designing the quality control plan provide the analytical quality management (QM) that is essential in laboratory practice, ensuring that reported test results achieve the quality required for medical decisions. The Westgard sigma rules with run size, one of the popular quality control planning tools, is an effective tool for evaluating measurement performance and simplifying an appropriate selection of SQC. To achieve QM, the author established an Excel Visual Basic for Application (VBA) worksheet for automatic sigma scale calculation and automatic selection of SQC procedures. This file applied the Westgard sigma rules with run size concept, developed for a convenient multistage SQC design. In addition, there are more functions for monitoring QC results, documenting, and compiling the corrections utilized to improve QC design. Of 23 assays from our laboratory, only one-fifth of the tests (22%) achieved an optimal level of performance (≥ 6 sigma). Analytes with the highest sigma performance were triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), magnesium (Mg) and creatine phosphokinase (CK). In contrast, one-third of the tests (35%) had a sigma scale of less than 4, requiring them to be solved, improved and have rigorous QC monitoring by primary following in the Data Analysis sheet. Thus, this Excel VBA worksheet is an alternative tool for simplifying analytical QM that is effectively controlled and convenient, with multistage SQC designs.

***Corresponding author:** Pranadta Wontong, MT, BSc. Department of Chemistry Laboratory, Prasat Hospital, Surin, Thailand. Email address: pranadta.lab@gmail.com
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Introduction

Statistical quality control (SQC) is an essential laboratory practice to ensure reported test results achieve the quality required for medical decisions. Laboratories need the optimal SQC to provide a procedure to detect performance changes, potentially causing medically important errors. SQC practice is the evaluation of analytical quality control as a part of quality management. Sigma-metric is the popular quality control planning tool employed for process improvement. In 1986 Bill Smith was the person who applied the six sigma statistic for quality improvement methodology to the Motorola company[1]. Westgard JO is developing QC design and planning tools to support laboratory efforts to select SQC procedures, such as the "Westgard sigma rule for QC design and Run size"[2].

Rosenbaum MW et al carried out a survey about quality control practices for chemistry and immunochemistry in a cohort of 21 large academic medical centers in America in 2018, which revealed that most hospitals (76%) used a rule such as 2 SD to monitor QC results, which is not recommended because of causing a high probability a false rejection, and only 10% used multi-Westgard rules based on the performance of an assay[3]. Westgard JO discusses that this survey is a disappointing finding, but not entirely unexpected because there may be a variety of explanations, such as the guideline is too expensive, does not provide a practical methodology to implement the recommended principles and approach, is too difficult to understand because of the statistical and theoretical nature of the subject, or laboratories are not interested in a quantitative SQC planning methodology. They are still making available new graphical tools and worksheets that are simple recommendations for running QC[4].

In 2021 Westgard et al announced the report of the Global QC Practice survey, which was used in more than 600 laboratories from more than 100 countries. Most laboratories still used 2 SD as the primary rule for QC techniques and Westgard rules for observing QC that utilized those limits for all assays. For determining the control limit, the majority of laboratories calculated the actual mean and the actual SD to create Levey-Jennings control charts, which is the proper procedure. However, the others perform using the manufacturer's range, which is quite wide for detecting the error. In determining control material, most laboratories use the controls provided by manufacturers. Although the recommendation from CLSI is a third-party process, it is the second most popular control type. Concerning the frequency of running QC, most laboratories follow the standard from CLSI, which is once-a-day QC, followed by running twice a day, and three times a day. Even though more frequent running QC has earlier error detection, it comes with a higher budget in the process[5].

From a survey in 2018 to the Global QC practices survey in 2021, Westgard opined that "Laboratories know they should do the right thing, whereas they are unable to utilize them routinely. We think one the reason for this gap between theory and practice is the complexity of the theory and the lack of practical tools to help laboratories apply the evidence-based approach". The author took up this challenge to create practical tools, such as an Excel VBA worksheet, to simplify the theory for alternative implementation customizing the QC for each assay's sigma performance, thus improving QC planning as a part of the quality management system (QMS).

Materials and methods

Materials

In this study, control results were analyzed with Mindray ClinChem Multi Control level 1 and level 2 by Mindray BS-800 analyzer that was used to perform 23 routine biological assays: sodium (Na), potassium (K), chloride (Cl), glucose (Glu), urease (Urea), creatinine (Crea), uric acid (UA), total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein

(LDL), total protein (TP), albumin (ALB), total bilirubin (T-Bili), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), calcium (Ca), magnesium (Mg), phosphorus (P), amylase (AMY), creatine kinase (CK), and lactate dehydrogenase (LDH). The protocol was approved by the Ethics Committee of Prasat Hospital (PSH REC No. 004/2023).

Study design and participants

Brew6sigma, an implementation of an Excel VBA worksheet that is used in this study, used Microsoft Excel 2016, integrated with the Westgard sigma rule for QC design and Run size, which provides simplicity of sigma metric calculation and the design of statistic quality control (SQC) tools to support analytical quality management (Figure 1). The SQC procedure selects the optimized control rules and the number of control measurements to detect medically important errors. Designing a QC plan to integrate SQC is needed to monitor failure modes in analytical methods or instrument systems. Brew6sigma is the alternative of the practical tool with the PDCA cycle concept, to help laboratories apply the complicated six sigma quality management system that adheres to the Thai medical technology standard 2022, corresponding to ISO 15189 standards. The components of a Brew6sigma VBA worksheet include the Index sheet, typically serving as a table of contents for the program, Data Analysis sheet, Summarize sheet, Control level 1 sheet, Control level 2 sheet, Bias sheet, Corrective Action sheet, and Test sheet.

The Data Analysis sheet asks the user to enter the data of TEa, defined from three source recommendations for setting a quality goal or quality requirement, CLIA CAP and Rico, and fill up in-house data that consists of mean, SD and bias in each test for sigma metric calculation. From in-house data, mean and SD are determined on a replication experiment. The CV refers to the "coefficient of variation", which describes the standard deviation as a percentage of the mean, as shown in the following equation:

$$CV\% = (SD/mean) \times 100$$

The CLSI guideline defines the criteria for acceptable CV from the repeatability that the experimental product has at least 20 replicates collected over 20 days (between-runs) and should be less than or equal to thirty-three percent of TEa[6].

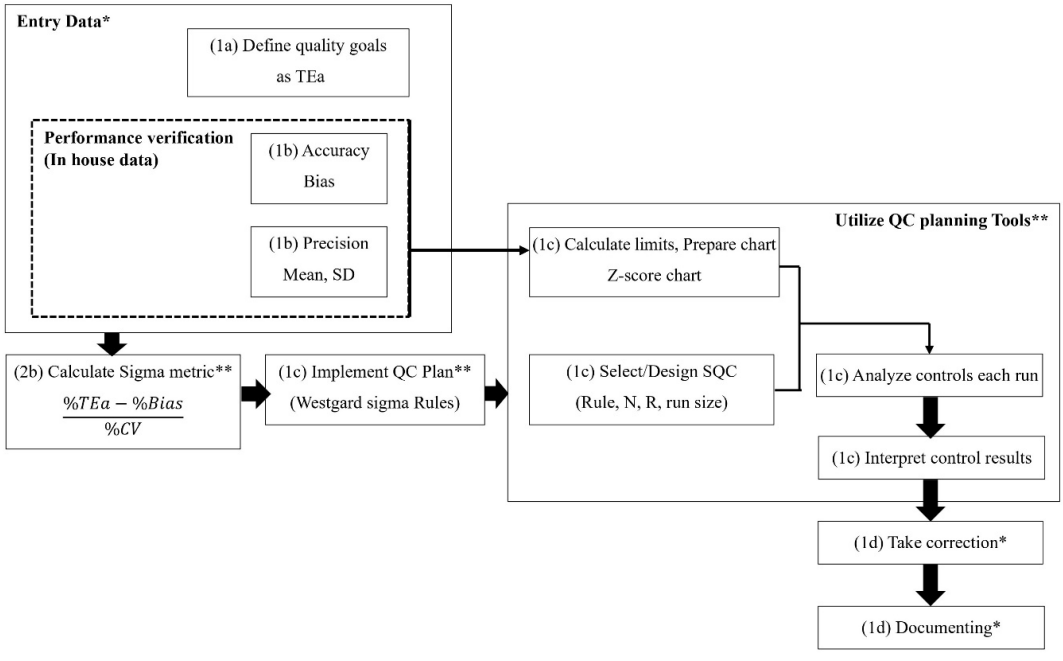


Figure 1 Flow diagram illustration of how the automatic SQC selection process works.
Note: * The part for the user to enter data and documentation of correction, ** The part of the Excel VBA worksheet that automatically calculates the sigma metric and automatically selects the proper SQC procedure.

In this program, the sigma metric was calculated with the following equation:

$$SM = (TEa\% - Bias\%) / (CV\%)$$

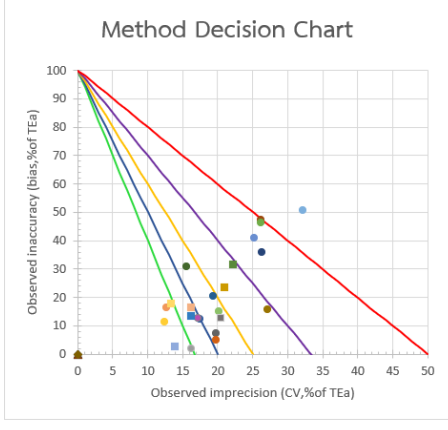
Where TEa represents the allowable total error. Bias and CV represent systemic and random errors, respectively. Thus, the Excel VBA will select an appropriate SQC from the calculated sigma metric or sigma scale, referenced from the Westgard sigma rule for QC design and run size performance of method decision level, Westgard rules, run size (number of patients), number of control measurements and frequency of runs (Table 1). In addition, if the sigma scale is less than six, which may result in more defects, the program will calculate the quality goal index (QGI) by evaluating the root of causing errors, by the following expression:

$$QGI = Bias / 1.5\ CV$$

The QGI ratio represents bias or precision that achieves its quality goals. The quality goals chosen for use are 1.5*TEa/6 for bias and TEa/6 for precision. A high QGI ratio means that bias exceeds its accuracy goal, while imprecision meets its precision goal. On the contrary, a low QGI ratio means that bias meets its accuracy goal while imprecision exceeds its precision goal. The criteria are for interpreting QGI when the sigma metric is less than six, as the calculated QGI is less than 0.8 and more than 1.2, presenting the cause of the problem by imprecision and inaccuracy, respectively, while QGI between 0.8-1.2 presents the cause of the problem by both imprecision and inaccuracy[7].

The Summarize sheet performs the individualized sigma metric, method decision level, and optimal SQC procedure (consisting of the control rules, number of controls, and run size of patient

needed) in each test along with an automatic pie chart of sigma proportion. The user will provide the individual normalized method decision chart by filling in the test name in the field (Figure 2). In the Control level 1 and Control level 2 sheets, the user must input control data to prepare to create Levey-Jennings control charts. In addition, this Excel VBA calculates the cumulative mean, SD and CV. The cumulative CV is a long-term estimate of the central tendency observed for a control material, based on a large number of control measurements collected over a long period (≥ 6 months). Comparing the monthly CV to the cumulative CV, if the monthly CV is more than twice the cumulative CV, then it should be investigated and documented. Any significant change may indicate a change in instrument calibration or a fault in its function.



test_name	%CV of TEa	%Bias of TEa
Na	26.22	46.40
K	26.32	36.00
Cl	26.24	47.40
Glucose	19.74	7.25
Urea	27.16	15.67
Creatinine	19.39	20.50
Uric Acid	15.64	30.80
Cholesterol	25.27	41.00
Triglyceride	12.70	16.40
HDL	16.28	2.05
LDL	12.50	11.30
Total Protein	32.16	50.50
Albumin	20.24	15.00
Total Bilirubin	17.47	12.30
AST	19.75	4.80
ALT	17.24	12.80
ALP	21.04	23.45
Ca	16.28	13.20
P	22.30	31.60
Mg	13.92	2.53
Amylase	16.29	16.25
LDH	20.43	12.73
CK	13.33	17.70

Figure 2 The automatically plotted operating point when entering the named test in the table.
Note: "Normalized" Method decision chart observed inaccuracy is calculated as 100*bias/TEa and imprecision is calculated as 100*CV/TEa, where original parameters are all in units of %.

The Bias sheet collects monthly bias data and is convenient for summary and usage. Bias, inaccuracy, trueness or systemic error is determined during method validation studies from method experiment comparison. The laboratories should perform experiments to verify a manufacturer's claim after installation. After initial validation, laboratories require monitoring bias using EQA/PT samples with target values or assigned values, established by reference methods or the mean of the survey group (peer group). The user must fill up this sheet with their results and the assigned result, which is measured by the same method and instrument for bias calculation. In the calculation

of the sigma metric, this worksheet calculates bias with the following equation:

$$\%Bias = (Your\ result - Assigned\ result)/(Assigned\ result \times 100)$$

To establish the corrective action, the Corrective Action sheet documents and collects corrections that solve the error or are out of control from all the operating tests.

Test sheets specify the standard quality control chart or the Levey-Jennings chart, which is computed from the mean and SD determined in the laboratory by a method operating under stable conditions. The Levey-Jennings chart provides monitored and interpreted control results under the right SQC. This sheet presents a control chart as a z-score chart in which individual control results are calculated for the z-score and plotted on the y-axis versus time on the x-axis. The z-score shows the standard deviation of a control result from the expected mean value, which is determined by the following expression:

$$z\text{-}score = (value - mean) / SD$$

A z-score chart is typically created as the mean (z-score is 0) plus or minus a certain multiple of the SD, commonly ± 3SD, ± 2SD or and ± 1SD. It is expected that 99.7% (i.e. almost all) control results fall within the mean ± 3 SD limits, whereas about 95% are expected within the mean ± 2 SD limits, and 67% within the mean ± 1 SD[8]. As a result, this worksheet interprets control results using optimal SQC procedure from the calculated data in the Data Analysis sheets (as shown beside the z-score chart). In addition, it can interpret control results as violations based on the fully cataloged number of ways that can break the "Westgard rules"[9] and record corrections to establish corrective action. Doing the proper SQC observation and monitoring control results are components of the quality control plan, which is helpful for quality management.

Results

The performances, sigma values and right SQC of the 23 assays in the Mindray BS800 analyzer are used in the Excel VBA worksheet for automatic calculation of the sigma scale and automatic selection of the SQC procedure presented by in-house data of the laboratory at Prasat Hospital, as shown in the Data Analysis sheet (Table 1).

The summarized sigma metric in each test is divided by class, performed in table 2, and shown as a pie chart from the proportion of sigma in the supplement part. Only one-fifth of the test (22%) achieved an optimal level of performance (≥ 6 sigma). Analytes with the highest sigma performance were triglyceride, HDL, LDL, Mg and CK. The assays with sigma ≥ 5 (17.39%) are excellent, and sigma ≥ 4 (26.09%) are good. In contrast, one-third of the tests (35%) with a sigma scale of less than 4 need to be fixed, improved and have rigorous QC monitoring by primarily following the Data Analysis sheet (Table 1).

Table 1 In-House data, individual calculated sigma metric and optimal SQC display in Data Analysis sheet

Test	TEa	33%TEa	mean_1	SD_1	CV1*	mean_2	SD_2	CV2*	Precision check	bias	Sigma1*	Sigma2*	Six Sigma*	Normalized** Method Decision	N, R**	Rules**	Run Size ** (Patient samples)	QGI1***	QGI2***	Problem
Na	5	1.65	114.4	1.5	1.31	137.5	1.8	1.31	/	2.32	2.04	2.05	2.04	Poor	N;6,R;1 (N;2,R;3)	13s; 22s; R4s; 41s; 8x	45	1.18	1.18	Imprecision & Inaccuracy
K	6	1.98	3.80	0.06	1.58	6.978	0.11	1.58	/	2.16	2.43	2.44	2.43	Poor	N;6,R;1 (N;2,R;3)	13s; 22s; R4s; 41s; 8x	45	0.91	0.91	Imprecision & Inaccuracy
Cl	5	1.65	92.8	1.14	1.23	109	1.43	1.31	/	2.37	2.14	2.00	2.00	Poor	N;6,R;1 (N;2,R;3)	13s; 22s; R4s; 41s; 8x	45	1.29	1.20	Inaccuracy
Glucose	8	2.64	101	1.44	1.43	245	3.87	1.58	/	0.58	5.20	4.70	4.70	Good	N;4,R;1 (N;2,R;2)	13s; 22s; R4s; 41s	200	0.27	0.24	Imprecision
Urea	9	2.97	19.8	0.46	2.32	58.5	1.43	2.44	/	1.41	3.27	3.11	3.11	Marginal	N;6,R;1 (N;2,R;3)	13s; 22s; R4s; 41s; 8x	45	0.40	0.38	Imprecision
Creatinine	10	3.3	0.877	0.017	1.94	3.52	0.065	1.85	/	2.05	4.10	4.31	4.10	Good	N;4,R;1 (N;2,R;2)	13s; 22s; R4s; 41s	200	0.70	0.74	Imprecision
Uric Acid	10	3.3	5.14	0.07	1.36	10.87	0.17	1.56	/	3.08	5.08	4.42	4.42	Good	N;4,R;1 (N;2,R;2)	13s; 22s; R4s; 41s	200	1.51	1.31	Inaccuracy
Cholesterol	10	3.3	91	2.3	2.53	182	3.17	1.74	/	4.10	2.33	3.39	2.33	Poor	N;6,R;1 (N;2,R;3)	13s; 22s; R4s; 41s; 8x	45	1.08	1.57	Imprecision & Inaccuracy
Triglyceride	15	4.95	113	1.6	1.42	210	4	1.90	/	2.46	8.86	6.58	6.58	World Class	N;2,R;1	13s	1000			
HDL	20	6.6	27.65	0.9	3.26	60	1.5	2.50	/	0.41	6.02	7.84	6.02	World Class	N;2,R;1	13s	1000			
LDL	20	6.6	58	1.3	2.24	120	3	2.50	/	2.26	7.91	7.10	7.10	World Class	N;2,R;1	13s	1000			
Total Protein	8	2.64	4.68	0.12	2.56	8.55	0.22	2.57	/	4.04	1.54	1.54	1.54	Unacceptable	N;6,R;1 (N;2,R;3)	13s; 22s; R4s; 41s; 8x	45	1.05	1.05	Imprecision & Inaccuracy
Albumin	8	2.64	3.03	0.046	1.52	5.25	0.085	1.62	/	1.20	4.48	4.20	4.20	Good	N;4,R;1 (N;2,R;2)	13s; 22s; R4s; 41s	200	0.53	0.49	Imprecision
Total Bilirubin	20	6.6	1.15	0.04	3.48	4.58	0.16	3.49	/	2.46	5.04	5.02	5.02	Excellent	N;2,R;1	13s; 22s; R4s	450	0.47	0.47	Imprecision
AST	15	4.95	51	1.5	2.94	162	4.8	2.96	/	0.72	4.86	4.82	4.82	Good	N;4,R;1 (N;2,R;2)	13s; 22s; R4s; 41s	200	0.16	0.16	Imprecision
ALT	15	4.95	58	1.5	2.59	144	3.7	2.57	/	1.92	5.06	5.09	5.06	Excellent	N;2,R;1	13s; 22s; R4s	450	0.49	0.50	Imprecision
ALP	20	6.6	84.5	3.5	4.14	202	8.5	4.21	/	4.69	3.70	3.64	3.64	Marginal	N;6,R;1 (N;2,R;3)	13s; 22s; R4s; 41s; 8x	45	0.75	0.74	Imprecision

Table 1 In-House data, individual calculated sigma metric and optimal SQC display in Data Analysis sheet (Cont.)

Test	TEa	33%TEa	mean_1	SD_1	CV1*	mean_2	SD_2	CV2*	Precision check	bias	Sigma1*	Sigma2*	Six Sigma*	Normalized** Method Decision	N, R**	Rules**	Run Size ** (Patient samples)	QGI1***	QGI2***	Problem
Ca	10	3.3	8.6	0.14	1.63	12.9	0.17	1.32	/	1.32	5.33	6.59	5.33	Excellent	N;2,R;1	13s; 22s; R4s	450	0.54	0.67	Imprecision
P	10	3.3	4.30	0.09	2.09	8.07	0.18	2.23	/	3.16	3.27	3.07	3.07	Marginal	N;6,R;1	13s; 22s;	45	1.01	0.94	Imprecision
															(N;2,R;3)	R4s; 41s; 8x				& Inaccuracy
Mg	15	4.95	2.03	0.04	1.97	3.35	0.07	2.09	/	0.38	7.42	7.00	7.00	World Class	N;2,R;1	13s	1000			
Amylase	20	6.6	85.7	2.5	2.92	221	7.2	3.26	/	3.25	5.74	5.14	5.14	Excellent	N;2,R;1	13s; 22s; R4s	450	0.74	0.67	Imprecision
LDH	15	4.95	149	4	2.68	261	8	3.07	/	1.91	4.88	4.27	4.27	Good	N;4,R;1	13s; 22s;	200	0.47	0.42	Imprecision
															(N;2,R;2)	R4s; 41s				
CK	20	6.6	150	4	2.67	258	5.7	2.21	/	3.54	6.17	7.45	6.17	World Class	N;2,R;1	13s	1000			

Note: * The automatically calculated values from in-house data are presented by CV and the sigma metric, ** The automatic functions used to select the optimal SQC are established from individual sigma metrics and presented by normalized method decision, number of controls (N), number of runs (R), rules and the number of patient samples (Run size), *** If sigma scale is less than 6, the calculated value from CV and bias is presented by the QGI ratio defining the root of the error.

Table 2 Summary number of sigma metric classifications by the decision method

Sigma	Test (n)	%	Test
6	5	21.74	Triglyceride, HDL, LDL, Mg, CK
5	4	17.39	Total-bilirubin, ALT, Ca, Amylase
4	6	26.09	Glucose, Creatinine, Uric, Albumin, AST, LDH
< 4	8	34.78	Sodium, Potassium, Chloride, Urea nitrogen, Cholesterol, Total protein, ALP, P

A summary bias table in the Bias sheet supports collecting and monitoring accuracy or frequency of EQA/PT in each test. There are user-editable bias value choices for sigma scale calculation. The Corrective Action sheet performs all of the corrections from all of the tests that utilize implementation and records the violation of QC results in each test sheet by the user for improving QC. Summarized corrections are shown as a table for creating owner laboratory guidelines to solve the problem.

Each test sheet presents a z-score chart and summary data, including mean, SD, CV, bias, sigma metric, method decision, rules, N, R and Run size from table 1, to interpret the QC result for monitoring precision or detecting random error. The QC results as 2 levels are documented in the Control level 1 sheet and Control level 2 sheet for creating a z-score chart and calculating cumulative CV that monitors the shift or drift of control results (Figure 3).

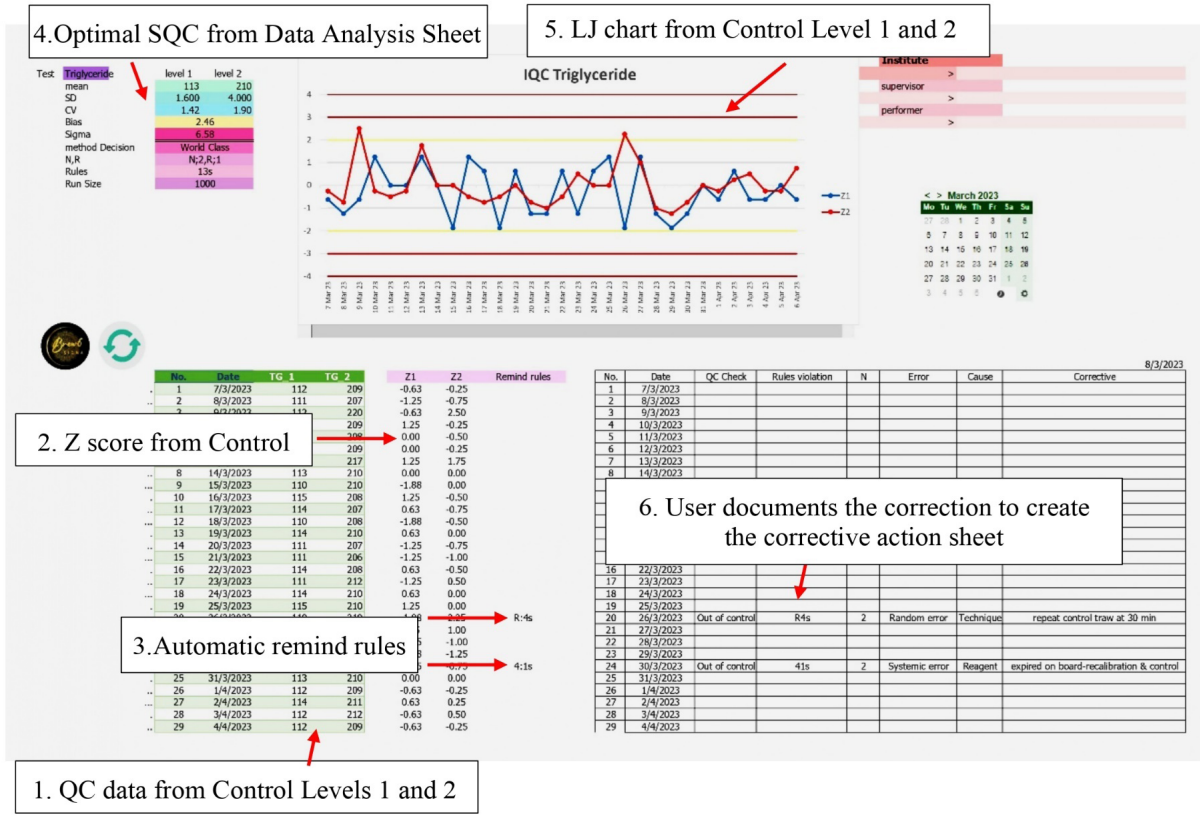


Figure 3 The display of the triglyceride sheet (test sheet).

Discussion

There are several main reasons to explain the differences in sigma metric found in this research, such as 1) the difference of source selected for the TEa target, 2) the difference between the algorithms used to evaluate CV and bias, and 3) the different selection sigma metric between 2 or more control levels.

For the Sigma metric, determining the TEa goals should be made carefully, as neither standardization nor harmonization of the existing resources for TEa goals exists[10]: Clinical Laboratory Improvement Amendments (CLIA), College of America Pathologists Participant (CAP), Royal College of Pathologists of Australasia and the Australasian Clinical Biochemist Association Quality Assurance Program (RCPA), Ricos' biological variability. Each TEa has a direct impact on the sigma metric.

The coefficient of variation (CV%) describes the variation of a test that is expressed as a percentage of the mean and calculated as CV% = (SD/mean) x100. When the SD increases in proportion to concentration, the CV will increase. Likewise, the level of concentration relates to CV as in lower concentrations the CV may be higher, and at higher concentrations, the CV may be lower[11]. Thus, the right target values or mean concentrations should be close to medical decision levels (MDLs), and the right sigma metric should be calculated from the CV at the concentration that hits the MDLs[12]. However, multianalyte controls with 20 or more analytes will be unlikely to hit the MDLs for all of them. In addition, the real concentration of control will be less or over the MDLs. The guideline for choosing the CV to calculate the sigma metric is if all of the controls in each test have a concentration near MDLs, the mean of all CV is used, and if any value is nearest to MDLs, then its CV concentration is used.

Considering the selection sigma metric between 2 or more control levels, for example, Peng S et al calculated the sigma metric and selected the optimal SQC for each control level, then monitored the quality control following each optimal SQC. It is difficult and complicated for the operator because of the differences in sigma value between the levels of control[13]. From Kumar and Mohan, the CV of individual control level used in the sigma metric was from the average CV value in 12 months. They calculated the sigma metric of each control level with the different sigma metrics. The introduction should be evaluated with discretion, which strictly complies with Westgard multi-rules to abolish discrepancy[14]. In conclusion, this study calculated the sigma metric in each test from all concentration levels, then chose the least sigma metric for the strongest criteria to monitor QC.

Lastly, The traditional error model as the Plan-Do-Check-Act (PDCA) cycle described by Deming[15] provides the basic process for developing, implementing and operating a quality management system (QMS). The Excel VBA worksheet can facilitate the PDCA cycle concept and sigma metric tools for analytical quality management as shown in figure 1.

Plan: (1a) Define quality goals as an allowable total error (TEa). TEa guides the selection of analytic measurement procedures, or examination procedures in ISO terminology.

Do: (1b) Validate safety characteristics (precision and bias) using experimental studies and statistical data analysis. Acceptable performance can be evaluated by determining quality on a Sigma scale using the method decision chart. (2b) Assuming the sigma metric indicates acceptable performance (that is greater than 3, preferably at least 4 and, better yet, 5 or 6) proceed to implement the analytical method.

Check: (1c) The SQC procedure optimizes the control rules, number of controls, number of runs, and number of patient samples (Run size) to detect medically important errors. Design a QC plan to integrate SQC with other control mechanisms that are needed to monitor specific failure modes that may occur with a particular analytic method or instrument system.

Act: (1d) Monitor the quality of the testing process over time to characterize performance, identify failures, and improve the QC plan[16].

Conclusion

The Excel VBA worksheet, which employs Westgard sigma rules with run size, is an alternative tool simplifying analytical QM, including specifying quality goals, judging the acceptability of performance of examination procedures, designing statistical quality control (SQC) procedures to detect significant medical errors that are effectively controlled and convenient with multistage SQC designs. Moreover, this file has a function for monitoring QC results, evaluating quality from external quality assessment and proficiency testing surveys, and establishing corrective action for improving the QC plan.

Take home messages

This Excel VBA worksheet is suitable for any hospital starting to apply the sigma SQC designs for analytical QM.

Conflicts of interest

The author declares no conflict of interest.

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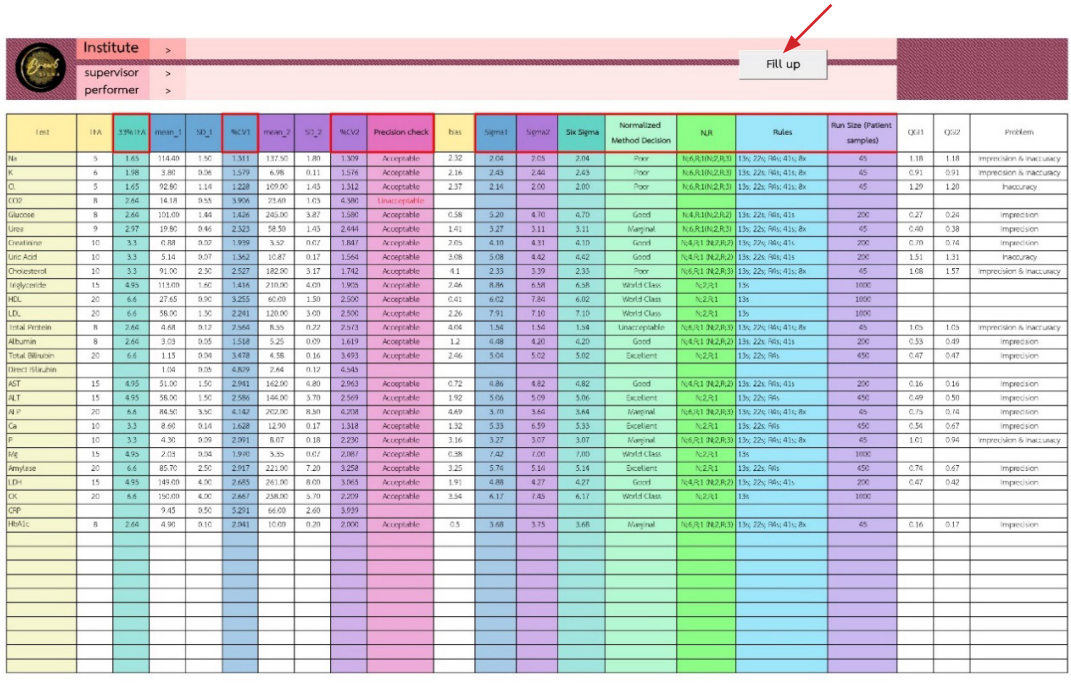
Supplementary

Program interface

The components of a Brew6sigma VBA worksheet include the Index sheet, typically serving as a table of contents for the program, Data Analysis sheet, Summarize sheet, Control level 1 sheet, Control level 2 sheet, Bias sheet, Corrective Action sheet, and Test sheet. When the user clicks each button, the program will run to that page (sheet).

Input the in-house data for the Data Analysis sheet, click the “Fill up” button, and then pop up the entry data window.



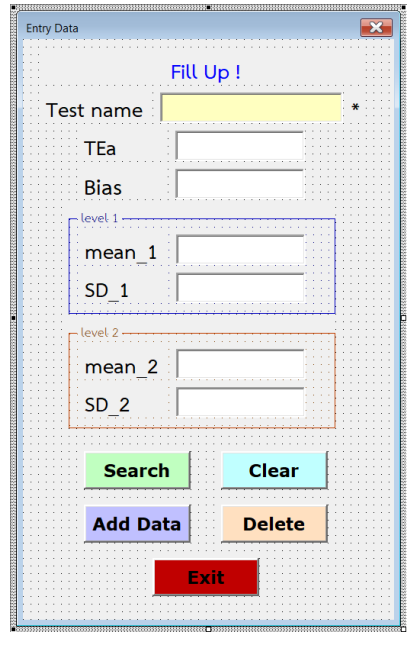


Figure S1 Data Analysis sheet and entry data window.

Click the “Add Data” button for the calculation sigma metric. Thus, the Excel VBA will select an appropriate SQC from the calculated sigma metric or sigma scale, referenced from the Westgard sigma rule for QC design and run size performance of method decision level, Westgard rules, run size (number of patients), number of control measurements and frequency of run.

The Summarize sheet calculates the individualized sigma metric, method decision level and optimal SQC procedure (consisting of the control rules, number of control results, and run size of patients needed) in each test along with a pie chart of sigma proportion. The user will provide the individual normalized method decision chart by filling in the test name in the field.

Test	Six Sigma ammari	Normalized Method Decision	N,R	Rules	Run Size (Patien
Na	2.04	<4	Poor	N;6,R;1(N;2,R;3)	13s; 22s; R4s; 41s; 8x	45
K	2.43	<4	Poor	N;6,R;1(N;2,R;3)	13s; 22s; R4s; 41s; 8x	45
Cl	2.00	<4	Poor	N;6,R;1(N;2,R;3)	13s; 22s; R4s; 41s; 8x	45
Glucose	4.70	4	Good	N;4,R;1(N;2,R;2)	13s; 22s; R4s; 41s	200
Urea	3.11	<4	Marginal	N;6,R;1(N;2,R;3)	13s; 22s; R4s; 41s; 8x	45
Creatinine	4.10	4	Good	N;4,R;1 (N;2,R;2)	13s; 22s; R4s; 41s	200
Uric Acid	4.42	4	Good	N;4,R;1 (N;2,R;2)	13s; 22s; R4s; 41s	200
Cholesterol	2.33	<4	Poor	N;6,R;1 (N;2,R;3)	13s; 22s; R4s; 41s; 8x	45
Triglyceride	6.58	6	World Class	N;2,R;1	13s	1000
HDL	6.02	6	World Class	N;2,R;1	13s	1000
LDL	7.10	6	World Class	N;2,R;1	13s	1000
Total Protein	1.54	<4	Unacceptable	N;6,R;1 (N;2,R;3)	13s; 22s; R4s; 41s; 8x	45
Albumin	4.20	4	Good	N;4,R;1 (N;2,R;2)	13s; 22s; R4s; 41s	200
Total Bilirubin	5.02	5	Excellent	N;2,R;1	13s; 22s; R4s	450
AST	4.82	4	Good	N;4,R;1 (N;2,R;2)	13s; 22s; R4s; 41s	200
ALT	5.06	5	Excellent	N;2,R;1	13s; 22s; R4s	450
ALP	3.64	<4	Marginal	N;6,R;1 (N;2,R;3)	13s; 22s; R4s; 41s; 8x	45
Ca	5.33	5	Excellent	N;2,R;1	13s; 22s; R4s	450
P	3.07	<4	Marginal	N;6,R;1 (N;2,R;3)	13s; 22s; R4s; 41s; 8x	45
Mg	7.00	6	World Class	N;2,R;1	13s	1000
Amylase	5.14	5	Excellent	N;2,R;1	13s; 22s; R4s	450
LDH	4.27	4	Good	N;4,R;1 (N;2,R;2)	13s; 22s; R4s; 41s	200
CK	6.17	6	World Class	N;2,R;1	13s	1000

Sigma	Test (n)	%
6	5	22%
5	4	17%
4	6	26%
<4	8	35%
Σ	23	100%

test_name	%CV of TEa	%Bias of TEa
Na	26.22	46.40
K	26.32	36.00
Cl	26.24	47.40
Glucose	19.74	7.25
Urea	27.16	15.67
Creatinine	19.39	20.50
Uric Acid	15.64	30.80
Cholesterol	25.27	41.00
Triglyceride	12.70	16.40
HDL	16.28	2.05
LDL	12.50	11.30
Total Protein	32.16	50.50
Albumin	20.24	15.00
Total Bilirubin	17.47	12.30
AST	19.75	4.80
ALT	17.24	12.80
ALP	21.04	23.45
Ca	16.28	13.20
P	22.30	31.60
Mg	13.92	2.53
Amylase	16.29	16.25
LDH	20.43	12.73
CK	13.33	17.70

Figure S2 The Summarize sheet and the Westgard sigma rule for QC design and run size.

In the Control level 1 and Control level 2 sheets, the user must input control data to prepare to create Levey-Jennings control charts. In addition, this Excel VBA calculates the cumulative mean, SD and CV. The cumulative CV is a long-term estimate of the central tendency observed for a control material based on a large number of control measurements collected over a long period (≥ 6 months). Comparing the monthly CV to the cumulative CV, if the monthly CV is more than twice the cumulative CV, then it should be investigated and documented. Any significant change may indicate a change in instrument calibration or a fault in its function.

The Bias sheet collects monthly bias data and is convenient for summary and usage. The Corrective Action sheet is a document that collects corrections that solve the error or are out of control from all the operating tests.

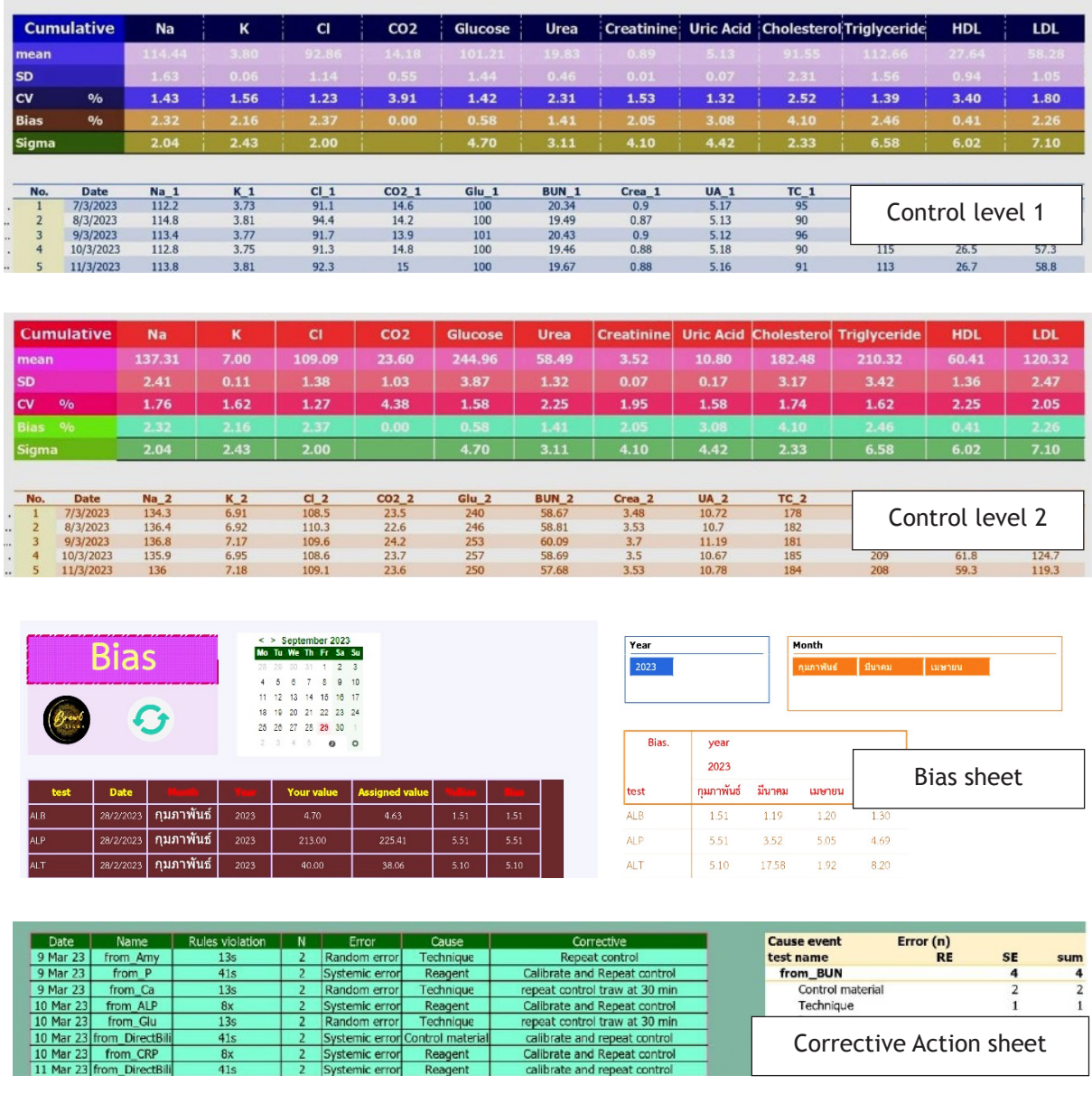


Figure S3 The Control level 1, level 2, Bias and Corrective Action sheet.

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ORIGINAL ARTICLE

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Least significant change as an essential tool for monitoring of bone mineral density using dual energy X-ray absorptiometry

Thantip Pholwattana[1,*], Sirinthorn Sridubdim[2], Sirinya Nanthanangkul[3]

[1] Department of Nuclear Medicine, Udonthani Cancer Hospital, Udonthani, Thailand.
[2] Department of Radiology, Udonthani Cancer Hospital, Udonthani, Thailand.
[3] Department of Nursing Academic Officer, Udonthani Cancer Hospital, Udonthani, Thailand.

KEYWORDS
Least significant change;
Precision error;
Bone mineral density;
Dual-energy absorptiometry.

ABSTRACT
Dual-energy X-ray absorptiometry (DXA) scans are the gold standard for measuring bone mineral density (BMD). It is accepted that precision error is crucial in monitoring BMD measurements. The least significant change (LSC) signifies the minimum difference between two consecutive BMD measurements that can confidently indicate a genuine biological change. This value provides direct benefit to patients by aiding clinicians in making clinical decisions based on real change or stability of BMD. This study aimed to determine the LSC for DXA scan used at Udonthani Cancer Hospital. We conducted a cross-sectional study in 150 patients undertaking DXA scans performed by one of our five radio-technologists from March 2023 to September 2023. Each technologist assessed BMD study of 30 participants twice, obtaining paired BMD measurements for the lumbar vertebrae, hip, and forearm. We utilized the copy of region of interest (ROI) software to replicate the ROI. The LSC was calculated with a 95% CI using both the RMS SD and RMS %CV formulas. The obtained LSC were 3.26% for the L1-L4 vertebrae, 4.40% for the femoral neck, 2.30% for the total proximal femur, and 5.30% for the 33% radius, meeting 2019 International Society for Clinical Densitometry (ISCD) standards. Nevertheless, the ISCD 2019 guidelines do not provide acceptable value for determining the LSC at the 33% radius. The higher variability in measurements at the femoral neck and the 33% radius emphasizes the need for continuous professional development and enhanced reproducible methods to improve the precision of BMD measurement using DXA scans.

***Corresponding author:** Thantip Pholwattana, MD. Department of Nuclear Medicine, Udonthani Cancer Hospital, Udonthani, Thailand. Email address: thantipnm@gmail.com.
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Introduction

Dual-energy X-ray absorptiometry (DXA) scan is the gold standard method for measuring bone mineral density (BMD), playing a vital role in diagnosing osteoporosis, assessing risk of fracture, and monitoring changes in BMD over time[1-4]. The core principle of DXA is the measurement of transmission of X-ray with high- and low-energy photons through the body[2]. Precision error becomes particularly critical especially in the monitoring of consecutive BMD measurements using DXA[1].

The least significant change (LSC) represents the least amount of BMD change that can be considered statistically significant. In simpler terms, it signifies the minimum difference between two consecutive measurements that can confidently indicate a genuine biological change, exceeding precision error of the method[3,5]. The LSC helps clinicians make clinical decisions based on real change or stability of BMD. Several factors affect this value, including the instrument used, the characteristics of the patient population, the measurement site, and the skill of the radio-technologist in positioning the patient (radio-technologist's precision). Notably, the radio-technologist's precision is the key factor in determining the LSC[3]. In addition, although the manufacturer-provided LSC is available in each BMD machine, it cannot be accurately applied and used for different settings due to variable skills of patient positioning by different technologists[1]. We aimed to determine the LSC for DXA scan utilized at Udonthani Cancer Hospital.

Materials and methods

Study design and participants

During March 2023 to September 2023, we enrolled new participants referred for DXA scans at Udonthani Cancer Hospital. Inclusion criteria were age ≥ 18 years with good cooperation, whereas exclusion criteria included pregnant women, individuals with disabilities, and those exceeding 159 kg in body weight which is over the machine capacity. Ethical approval for the study was obtained from the local Ethics Committee, and informed written consent was obtained from all participants.

A cross-sectional study was conducted using DXA scan (Lunar Prodigy, GE) to analyze bone mineral density results from 150 participants, with examinations performed by five radio-technologists. Following the 2019 International Society for Clinical Densitometry (ISCD) guidelines[6], each radio-technologist assessed 30 participants twice. Prior to undergoing a second DXA scan, participants were asked to step down from the densitometer and then be repositioned. Paired measurements of BMD were acquired for the lumbar vertebrae, hip, and forearm[6]. In addition, we utilized the copy of region of interest (ROI) software to replicate the ROI from the initial set of images to the subsequent set. The ROIs are shown in figure S1 (supplement data).

We assessed the individual LSC at L1-L4 vertebrae, femoral neck, total proximal femur, and 33% radius for each radio-technologist, as well as our institute LSC. The LSC was calculated with a 95% confidence interval (95% CI) using both the root mean square standard deviation (RMS SD) and root mean square percentage coefficient of variation (RMS %CV) formulas[6].

Research protocol

Participant data, including age, sex, ethnicity, menopausal status, body weight, height, BMI, underlying diseases, and current medications were collected. The characteristics of all participants are summarized in table 1. Table 2 classifies the characteristics of the groups studied by each individual radio-technologist. Table 3 presents details about the radio-technologists, such as their age, duration of experience with DXA, and the number of prior DXA cases before their participation in this study.

Statistical analysis

Continuous variables such as age, weight, height, and BMI were shown as mean ± SD and median (min-max). Categorical variables such as gender, ethnicity, menopausal status, underlying diseases, and current medications were demonstrated in both numbers and percentages. The RMS SD, RMS%CV, and LSC at the 95% confidence interval were computed employing the ISCD Advanced Precision Calculating Tool[7]. This calculator expresses precision error as RMS SD (absolute value in g/cm^2), CV or %CV and LSC with a range of confidence levels. It is exclusively indicated for advanced bone densitometrists and should be used in particular clinical practice scenarios or clinical research.

Results

Among the 150 participants, ranging from 20 to 87 years of age, with the mean age of 52.5 years, the majority, 80.7%, were female. Menopausal status was reported in 67.8% of the female participants, while male accounted for 19.3% of the total. More than half of the participants, 96 cases (64%), had underlying diseases, predominantly thyroid cancer and breast cancer, undergoing thyroid hormone suppression, and aromatase inhibitor treatments, respectively. The remaining participants were healthy, as detailed in table 1.

Table 1 Participant characteristics

Variable	Value
Age: years	
Mean ± SD	52.5±11.5
Median (min-max)	52.0 (20.0-87.0)
Sex: (n, %)	
Male	29.0 (19.3)
Female	121.0 (80.7)
Menopausal status (n, %)	
Premenopausal	39.0 (32.3)
Menopausal	82.0 (67.8)
Ethnics (n, %)	
Thai	150.0 (100.0)
BMI: kg/m^2	
Mean ± SD	24.5±4.0
Median (min-max)	23.9 (17.3-37.6)
< 18.5 (Underweight)	8.0 (5.3)
18.5 – 24.9 (Normal weight)	80.0 (53.3)
25.0 – 29.9 (Pre-obesity)	47.0 (31.3)
30.0 – 34.9 (Obesity class I)	13.0 (8.7)
35.0 – 39.9 (Obesity class II)	2.0 (1.3)
≥ 40.0 (Obesity class III)	-

Table 1 Participant characteristics (Cont.)

Variable	Value
Underlying disease (n, %)	
Healthy	54.0 (36.0)
Thyroid cancer	50.0 (33.3)
Breast cancer	23.0 (15.3)
Hyperthyroidism	3.0 (2.0)
Hyperparathyroidism	2.0 (1.4)
Others	18.0 (12.0)
Current medication (n, %)	
No medication	54.0 (36.0)
Thyroid hormone	50.0 (33.3)
Aromatase inhibitor	16.0 (10.7)
Others	30.0 (20.0)

Abbreviation: SD, standard deviation; BMI, Body mass index.

Table 2 illustrates participant characteristics divided into five groups by each radio-technologist. Baseline clinical and demographic characteristics were well balanced among the groups.

Table 2 Participant characteristics divided by each radio-technologist (A, B, C, D, E)

Variable	Radio-technologist				
	A	B	C	D	E
Age (years)					
Mean ± SD	50.2±14.8	52.9±9.6	49.0±9.2	54.3±10.5	55.9±12.1
Median	47.5	52.0	50.0	55.5	55.0
(min-max)	(28.0-87.0)	(34.0-71.0)	(20.0-64.0)	(32.0-85.0)	(23.0-85.0)
Sex:					
Female (n, %)	24.0 (19.8)	22.0 (18.2)	30.0 (24.8)	26.0 (21.5)	19.0 (15.7)
Weight (kg)					
Mean ± SD	59.6±14.2	66.1±11	60.4±12.7	61.3±11.1	60.1±9.8
Median	57.3	66.8	55.1	60.0	59.0
(min-max)	(40.0-96.0)	(44.6-87.0)	(39.5-98.6)	(42.0-87.0)	(42.3-78.0)
Height (cm)					
Mean ± SD	157.4±6.8	160.1±9.2	157.3±5.6	157.2±7.8	160.0±7.2
Median	155.0	158.5	157.0	156.0	160.0
(min-max)	(148.0-175.0)	(143.0-179.0)	(147.0-170.0)	(139.0-174.0)	(145.0-174.0)

Table 2 Participant characteristics divided by each radio-technologist (A, B, C, D, E) (Cont.)

Variable	Radio-technologist				
	A	B	C	D	E
BMI (kg/m^2)					
Mean ± SD	23.9±4.8	25.8±3.5	24.3±4.7	24.8±3.9	23.3±2.7
Median	22.8	25.5	23.1	24.2	23.6
(min-max)	(17.3-35.2)	(19.1-32.7)	(18.3-37.6)	(17.9-32.1)	(17.8-29.1)

Abbreviation: SD, standard deviation; BMI, Body mass index.

The characteristics of each radio-technologist are displayed in table 3. The duration of their work experience with DXA ranges from two to three years. Radio-technologist A has the most experience, with 178 previous DXA cases, while radio-technologist C has the lowest, with 62 previous cases.

Table 3 Characteristics of radio-technologists (A, B, C, D, E)

Variable	Radio-technologist					Mean
	A	B	C	D	E	
Age: years	40	52	48	46	56	48.4
Duration of work experience with DXA scan: years	3	3	2	2	2	2.4
Number of previous DXA cases	178	97	62	63	69	93.8

Abbreviation: DXA, Dual-energy X-ray absorptiometry.

Table 4 The LSC by RMS%CV formula

Site	LSC (%)					
	A	B	C	D	E	Average
L1-L4 vertebrae	3.57	3.14	3.21	3.58	2.80	3.26
Femoral neck	4.91	2.93	5.71	4.07	4.37	4.40
Total proximal femur	2.06	1.62	2.80	2.21	2.81	2.30
33% Radius	4.96	1.62	6.40	4.78	8.75	5.30

Abbreviation: LSC, Least significant change; RMS%CV, root mean square percentage coefficient of variation.

Table 5 The LSC by RMS SD formula

Site	LSC (g/cm^2)					
	A	B	C	D	E	Average
L1-L4 vertebrae	0.037	0.034	0.037	0.038	0.032	0.036
Femoral neck	0.050	0.026	0.054	0.035	0.034	0.040
Total proximal femur	0.018	0.015	0.028	0.019	0.025	0.021
33% Radius	0.041	0.015	0.052	0.037	0.066	0.042

Abbreviation: LSC, Least significant change; RMS SD, root mean square standard deviation.

Discussion

The LSC determined using the RMS%CV formula were as follows: 3.26% for the L1-L4 vertebrae, 4.40% for the femoral neck, 2.30% for the total proximal femur, and 5.30% for the 33% radius. Notably, each of these values falls within the acceptable thresholds established by the ISCD 2019 guidelines, which specifies 5.3% for the L1-L4 vertebrae, 6.9% for the femoral neck, and 5.0% for the total proximal femur[6]. However, there are no standard criteria for the 33% radius as this site is not typically included in the routine DXA scan.

A peer review by Wilson et al[8] reported the LSC of 1.22% at the L1-L4 vertebrae and 1.97% at the femoral neck[8], which were lower than those observed for both L1-L4 vertebrae and femoral neck in our study. Moreover, apart from the total proximal femur, the LSC values for nearly all sites in our study were higher than those reported by Nelson et al[9]. The LSC values they provided for the L1-L4 vertebrae, the femoral neck, and the total proximal femur were 0.028, 0.030, and 0.021 g/cm^2, respectively[9]. Even though Nelson et al[9] analyzed LSC results from eight radio-technologists, which potentially caused larger variability, their LSC results were still better than those observed in our study. This might be due to the relatively less experience of our radio-technologists.

Additionally, the LSC for nearly all sites in our study were higher than those recommended by the manufacturer which specify LSC values of 0.010, 0.014, 0.012, and 0.020 g/cm^2 for the L1-L4 vertebrae, the femoral neck, the total proximal femur, and the 33% radius, respectively. However, there is no disclosure of the sources of the process in obtaining these numbers.

Conclusion

This study determined the LSC among five radio-technologists, with half of participants were cancer patients. The results showed that the LSC values across various sites —specifically the L1-L4 vertebrae, the femoral neck, and the total proximal femur—met ISCD standards. Nevertheless, the ISCD 2019 guidelines do not provide acceptable criteria for determining the LSC at the 33% radius. The higher variability in measurements at the femoral neck and the 33% radius emphasizes the need for ongoing professional development through re-training to improve reproducibility and enhance the precision of BMD measurements using DXA.

Take home messages

Although ISCD 2019 recommends that individual institutions ascertain their own LSC, some face limitations due to the need for sufficient volunteers and additional time required for repeat scans. Therefore, LSC in this study may be a reference standard for institutions sharing patient demographics, numbers, and levels of experience among radio-technologists.

Conflicts of interest

The authors declare no conflict of interest.

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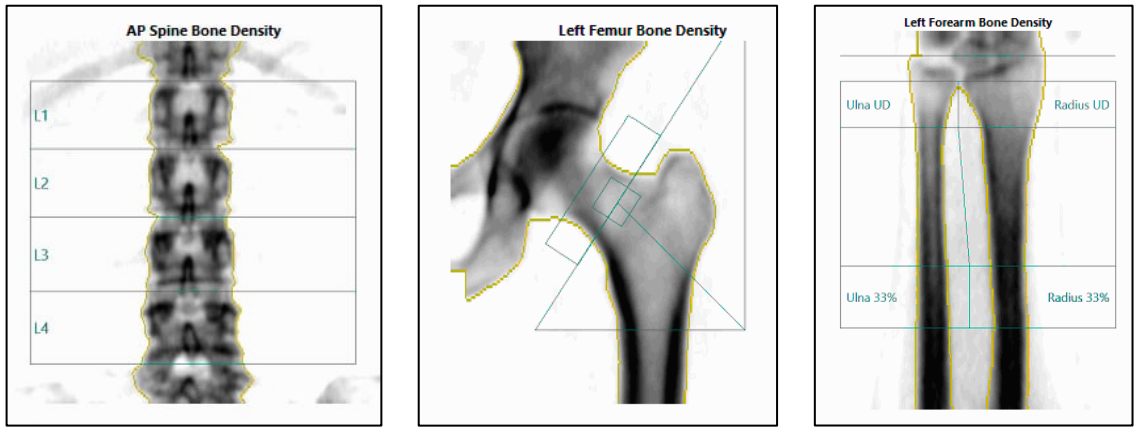
Supplementary



(A) (B) (C)

Figure S1 The ROIs include (A) L1-L4 vertebrae, (B) femoral neck and total proximal femur, and (C) 33% radius.

Abbreviation: ROIs, Region of interest.