

Heart rate variability in normal-weight patients with polycystic ovary syndrome

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ABSTRACT

Objective: Polycystic ovary syndrome (PCOS) is an endocrine disease closely related to several risk factors of cardiovascular disease. Obese women with PCOS show altered autonomic modulation. The results of studies investigating cardiac autonomic functions of normal-weight women with PCOS are conflicting. The aim of the study was to assess the reactivity of cardiac sympathovagal balance in normal-weight women with PCOS by heart rate variability analysis.

Methods: We examined the heart rate variability in 60 normal-weight women with PCOS and compared them with that in 60 age-matched healthy women having a similar metabolic profile. Time and frequency domain parameters of heart rate variability were analyzed based on 5-min-long continuous electrocardiography recordings for the following 3 periods: (1) during rest in supine position, (2) during controlled breathing, and (3) during isometric handgrip exercise.

Results: Time and frequency domain parameters of heart rate variability for the 3 periods assessed were similar in the two groups. Although modified Ferriman–Gallwey score and serum testosterone and luteinizing hormone levels were significantly higher in women with PCOS, homeostatic model assessment-insulin resistance (HOMA-IR) was not different between the PCOS and control groups. There were no significant correlations between serum testosterone levels and heart rate variability parameters among the study population.

Conclusion: The findings of this study suggest that the reactivity of cardiac sympathovagal balance is not altered in normal-weight women with PCOS having a normal HOMA-IR. (*Anatol J Cardiol* 2017; 17: 404-9)

Keywords: autonomic nervous system, heart rate variability, polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is the most frequent endocrine disorder during the reproductive years of women. It is characterized by menstrual irregularities, infertility, biochemical or clinical hyperandrogenism, and polycystic ovaries (1). PCOS is closely related to several cardiometabolic risk factors such as central obesity, dyslipidemia, insulin resistance (IR), type 2 diabetes mellitus, metabolic syndrome, and hypertension (2, 3). Women with PCOS have an estimated 4–11-fold increased risk of coronary heart disease than those without (4). Approximately 50% of these women are either overweight or obese (1). Obesity is known to result in an increased sympathetic activity (5). Previous studies investigating cardiac autonomic control in these women were mainly concentrated on heart rate variability (HRV). Women with PCOS who are overweight or have an impaired glucose metabolism were included in most of these studies. Moreover, in some studies, there was a statistically significant difference in terms of body mass index (BMI) between

women with and without PCOS (6). The cause of HRV alteration in women with PCOS may be related to concomitant metabolic abnormalities such as central obesity and IR. Therefore, the aim of this study was to assess HRV in normal-weight women with PCOS and normal glucose metabolism in comparison with age-matched healthy controls.

Methods

Study design

The study was designed as case control study.

Study population

The study groups comprised 60 normal-weight women newly diagnosed with PCOS (age 18–37 years) and 60 healthy, no hirsute volunteers (age 18–40 years) with regular and proven ovulatory cycles. A sample size of 60 patients per group would have provided 80% power using a type 1 error rate of 0.05. We defined normal weight as BMI between 18.50 and 24.99 kg/m² according

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to the World Health Organization criteria. PCOS was diagnosed using the Rotterdam criteria comprising the presence of at least two of the following three features: anovulation/menstrual irregularity, clinical and/or biochemical signs of hyperandrogenism, or presence of polycystic ovaries after exclusion of other etiologies (7). Hirsutism was defined as a modified Ferriman–Gallwey score ≥ 8 (7). Exclusion criteria for the study were as follows: (i) a BMI of <18.5 or ≥ 25 kg/m², (ii) waist circumference of >88 cm, (iii) any arrhythmia, (iv) smoking or alcohol abuse, (v) drug usage affecting autonomic balance or interfere with hormonal levels, (vi) a systemic disorder affecting autonomic modulation, and (vii) IR or diabetes mellitus. Written informed consent was obtained from all the subjects prior to inclusion into the study. Our study complies with the World Health Organization Declaration of Helsinki and the World Psychiatric Association, Good Clinical Practices, and Good Laboratory Practice rules. An independent Ethics Committee approved the study protocol.

Anthropometric measures

Anthropometric measurements including weight, height, waist circumference, and hip circumference were obtained. The height of the subjects was measured by portable stadiometers. Body weight was measured by trained healthcare professionals with participants standing without shoes in light indoor clothing using a digital scale. Waist circumference was measured midway between the lowest border of the rib cage and the upper border of the iliac crest at the end of normal expiration. Hip circumference was measured at the widest part of the hip at the level of the greater trochanter. BMI was calculated as the ratio of body weight in kilograms to the square of the height in meters.

Assay

Metabolic and hormonal assessments were made between days 2 and 10 of the menstrual cycle or on any day if the woman was amenorrheic. After an overnight 12-h fasting, venous blood samples were obtained between 9 and 10 am. Serum glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were measured using the Beckman Coulter AU680 analyzer (Beckman Coulter, Miami, FL, USA) based on enzymatic colorimetric methods using original assay reagents (Beckman Coulter, Miami, FL, USA). Serum hormone levels were measured using the Beckman Coulter UniCel Dxl 800 immunoassay analyzer (Beckman Coulter, Miami, FL, USA) by chemiluminescence immunoassay using original assay reagents (Beckman Coulter, Miami, FL, USA). The insulin level in serum was measured using a radioimmunoassay method. IR was measured using the homeostatic model assessment (HOMA-IR):fasting insulin (μ IU/mL) \times fasting glucose (mg/dL)/405. IR was defined as an HOMA-IR score higher than 2.7.

HRV analysis

The study was conducted during the follicular phase of the menstrual cycle in control subjects to avoid the influence of

ovarian hormones on autonomic function and HRV (8). In the PCOS group, the test was conducted during the amenorrheic period (9). Participants were evaluated in the morning following at least 8 h sleeping and after having a light breakfast free of caffeine-containing beverages. To test the change in sympathetic and parasympathetic parameters of HRV, isometric handgrip exercise and controlled breathing was used. After an adaptation period for at least 15-min rest in supine position, electrocardiograms were recorded to calculate HRV parameters for the following 3 periods: (1) during rest in supine position for 5 min, (2) during controlled respiration (15 breaths per minute) in supine position for 5 minutes, and (3) during handgrip exercise in sitting position for 5 min by an investigator blinded to the patient's status. Between each 5-minute recording period, it was left for 5 min to prevent the effect of potential rapid changes in the heart rate on HRV analysis. Participants performed an isometric handgrip exercise at 25% of their predetermined maximum volunteer capacity in a manner of 45-s contraction and 15-s resting per minute using the Jamar hydraulic hand dynamometer (Sammons Preston, Bolingbrook, IL, USA). Blood pressure measurements were obtained using a sphygmomanometer after each period.

Table 1. Clinical features and metabolic characteristics for women with PCOS, and healthy controls

Variables	PCOS (n=60)	Control (n=60)	P*
Age, years	25.4 \pm 5.9	25.9 \pm 6.6	0.791
Weight, kg	58.0 \pm 10.7	57.0 \pm 7.9	0.790
Height, cm	161.4 \pm 6.3	163.6 \pm 4.5	0.411
BMI, kg/m ²	21.2 \pm 2.7	22.3 \pm 2.1	0.579
Waist, cm	76.2 \pm 7.1	74.3 \pm 9.6	0.510
Hip, cm	90.4 \pm 11.4	92.1 \pm 7.2	0.824
Waist/hip ratio	0.8 \pm 0.1	0.8 \pm 0.1	0.341
FGS	11.0 \pm 4.6	4.0 \pm 2.8	0.002**
FSH, μ IU/mL	4.2 \pm 1.7	4.1 \pm 1.3	0.845
LH, μ IU/mL	8.9 \pm 4.3	5.2 \pm 2.8	0.032**
Estradiol, pg/mL	78.3 \pm 37.8	88.0 \pm 13.4	0.437
Testosterone, ng/dL	88.6 \pm 57.3	52.3 \pm 47.8	0.042**
Fasting glucose, mg/dL	79.6 \pm 9.0	72.4 \pm 7.3	0.245
Fasting insulin, μ IU/mL	5.21 \pm 2.36	4.12 \pm 2.14	0.485
HOMA-IR	1.84 \pm 0.61	1.61 \pm 0.52	0.348
Total cholesterol, mg/dL	168.8 \pm 38.9	155.8 \pm 34.2	0.362
Triglyceride, mg/dL	140.5 (90.8–165.2)	140.5 (78.0–164.2)	0.798
HDL cholesterol, mg/dL	53.0 \pm 11.9	55.8 \pm 17.7	0.580
LDL cholesterol, mg/dL	103.5 (86.5–126.0)	108.0 (85.2–133.5)	0.509

Data are presented as mean \pm standard deviation or median with 25th and 75th percentiles where indicated. *Student's t-test and Mann–Whitney U test were used for statistical analyses. P** values are statistically significant (<0.05).

BMI - body mass index; FGS - Ferriman Gallwey Score; FSH - follicle-stimulating hormone; HDL - high-density lipoprotein; HOMA-IR - homeostatic model assessment insulin resistance; LDL - low-density lipoprotein; LH - luteinizing hormone

Electrocardiographic data were transferred to a computer and digitalized via an analog-to-digital conversion board (Norav Medical Ltd., Yokneam, Israel). Both time and frequency domain of HRV analysis were performed using the HRV Software (Norav Medical Ltd., Yokneam, Israel). Mean of RR intervals (mean RR), standard deviation of R–R interval (SDNN), and the root mean square of successive R–R interval differences (RMSSD) were measured by assessing time domain parameters. Time domain parameters generally reflect the total HRV. Extremely low values indicate autonomic dysfunction, whereas higher values for these measures could reflect a more healthy autonomic function. For the frequency domain parameters, power spectral analysis based on the fast Fourier transformation algorithm was used. Two components of power spectrum were computed with the following bandwidths: high frequency (HF) (0.15–0.4 Hz) and low frequency (LF) (0.04–0.15 Hz). The LF–HF ratio and the normalized unit of LF (LFnu) and HF (HFnu) were also calculated [LFnu=LF/(LF+HF), HFnu=HF/(LF+HF)]. HF, HFnu, and RMSSD represent the cardiac parasympathetic drive (10). LF and LFnu represent both sympathetic and vagal influences (10). The LF–HF ratio depicts the sympathovagal balance (10). SDNN reflects slow heart rate fluctuations; thus, it is considered as a marker of overall autonomic modulation.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 for Windows statistical software (IBM SPSS Statistics,

Chicago, IL, USA). The results for variables were expressed as mean±standard deviation or median with interquartile range (25th and 75th percentiles) for continuous variables. The differences between groups were compared using Student’s t-test for normally distributed data and Mann–Whitney U test for non-parametric data. Pearson’s coefficient of correlation was used to determine correlations between serum testosterone level and HRV indices. For comparing repeated variables within groups, two-way repeated measurements analysis of variance (ANOVA) test (2:3 factorial design) was used for normally distributed data and Friedman’s two-way ANOVA test was used for non-parametric data. For all analyses, p<0.05 was considered statistically significant.

Results

Table 1 shows the anthropometric, metabolic, and hormonal profiles for all PCOS and control participants. Modified Ferriman–Gallwey score and serum testosterone and luteinizing hormone levels were significantly higher in PCOS group compared to those in the control group, whereas other parameters, including HOMA-IR, were similar in the two groups.

Figure 1 shows the relationships between testosterone and HRV parameters (RMSSD, LF, and LF–HF ratio) at rest in women with PCOS women, and Figure 2 shows in the same parameters in the control group. There was no significant relationship between testosterone levels and HRV indices in both groups (Table 2).

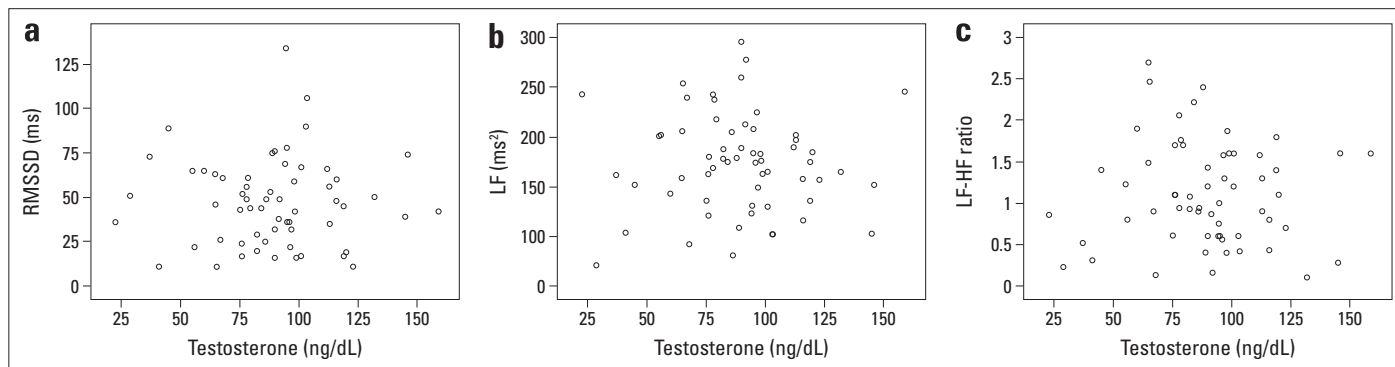


Figure 1. Relationships between testosterone level and HRV parameters: (a) RMSSD, (b) LF, and (c) LF–HF ratio at rest in normal-weight women with PCOS

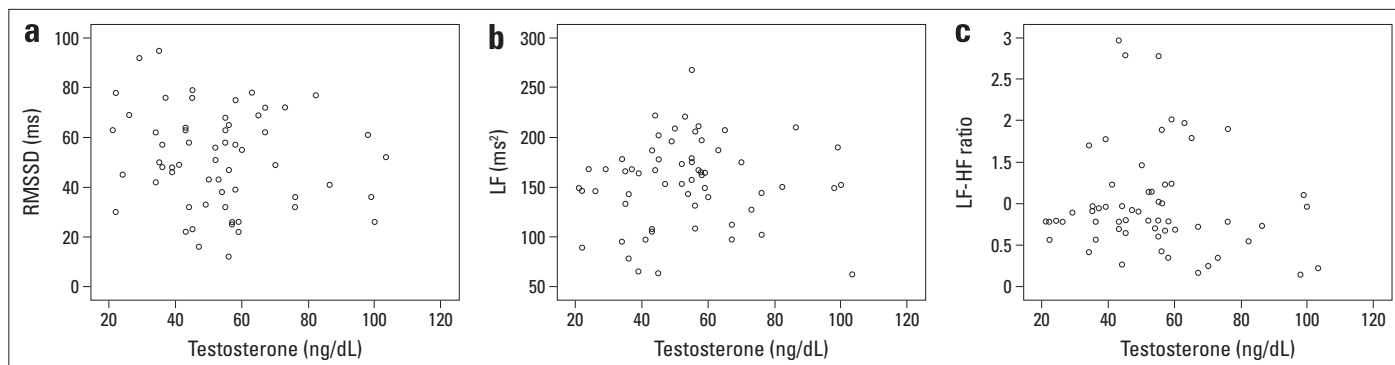


Figure 2. Relationships between serum testosterone levels and HRV parameters: (a) RMSSD, (b) LF, and (c) LF–HF ratio at rest in the control group

Table 2. Relationship between serum testosterone level and HRV indices

Variables	Pearson's correlation coefficient	P*
RMSSD, ms		
PCOS	-0.12	0.167
Control	-0.16	0.412
LF, ms ²		
PCOS	0.09	0.380
Control	0.05	0.680
LF-HF ratio		
PCOS	0.18	0.248
Control	-0.11	0.398

*Pearson's correlation was used for statistical analyses.
HF - high frequency; LF - low frequency; RMSSD - the root mean square of successive R-R interval differences

Controlled respiration in supine position promoted a significant increase in HFnu and a significant decrease in LFnu and the LF-HF ratio in the PCOS and control groups, indicating significant vagal stimulation and sympathetic withdrawal (Table 3). Handgrip exercise promoted a significant decrease in HFnu and a significant increase in LFnu and the LF-HF ratio in all groups, indicating significant vagal withdrawal. However, there was no difference between the groups in terms of blood pressures and HRV parameters at rest during controlled respiration and isometric handgrip exercise.

Discussion

This study suggests that the cardiac autonomic modulation as assessed by HRV might not be altered in normal-weight women with PCOS having normal HOMA-IR. The control of heart rate depends on the interaction between the sympathetic and parasympathetic branches of the autonomic nervous system (11). There are several methods by which the autonomic modulation of the cardiovascular system can be assessed. HRV has been used as a non-invasive method to evaluate heart rate regulation by the parasympathetic and sympathetic divisions of the autonomic nervous system (10). Decreased HRV depicts decreased cardiovagal modulation and is a potential risk for cardiovascular health (12). Reductions in HRV may also occur in patients with metabolic syndrome or diabetes mellitus, even in the absence of established cardiovascular disease (13). There is an association between IR and cardiovascular risk reflected by changes in HRV in patients with hyperinsulinemia and diabetes mellitus regardless of age (14, 15). At rest, HRV indices mostly reflect vagal modulation and no conclusions can be made regarding sympathetic modulation (16). Efferent vagal activity is a major contributor to the HF component, as seen in clinical and experimental observations of autonomic maneuvers such as electrical vagal stimulation, muscarinic receptor blockade, and vagotomy. During controlled parasympathetic stimulation,

Table 3. Comparison of blood pressures and HRV parameters of the groups

Variables	Rest	Controlled breathing	Handgrip exercise	F	P
SBP, mm Hg					
PCOS	108.9±12.4	107.4±11.3*	126.2±12.9****	72.5	<0.001
Control	107.0±10.7	105.0±9.8*	124.3±11.3****	67.0	<0.001
Interaction				79.1	0.558
DBP, mm Hg					
PCOS	70.5±12.1	68.1±10.5***	87.1±15.5****	68.7	<0.001
Control	66.0±9.5	64.5±9.3*	83.7±12.9****	51.2	<0.001
Interaction				73.3	0.293
Mean RR, ms					
PCOS	811.1±109.4	806.5±114.9*	721.5±90.8****	65.4	<0.001
Control	818.5±104.7	817.6±116.7*	722.2±93.6****	18.0	<0.001
Interaction				68.5	0.925
SDNN, ms					
PCOS	45.0 (33.2–66.5)	60.5±28.5***	56.9±21.1**	7.3	0.003
Control	52.0 (41.0–70.0)	64.1±26.0**	63.2±23.9**	2.6	0.026
Interaction				6.1	0.415
RMSSD, ms					
PCOS	48.0±32.9	50.0 (28.8–85.0)***	39.6±20.9**	12.8	<0.001
Control	52.0±21.4	65.5 (41.0–74.2)**	38.3±20.5***	12.1	0.001
Interaction				16.1	0.585
HF, ms ²					
PCOS	198.4±84.1	284.4±109.9****	114.3±51.6****	30.9	<0.001
Control	212.1±63.1	306.1±112.7***	110.7±57.0****	40.5	<0.001
Interaction				50.8	0.527
LF, ms ²					
PCOS	174.5±58.2	103.0±51.0****	199.2±70.7**	28.3	<0.001
Control	162.0±52.1	120.7±66.9**	210.9±77.6**	9.0	0.016
Interaction				26.3	0.595
HFnu, %					
PCOS	52.0±15.2	71.6±15.1****	36.6±13.5****	63.6	<0.001
Control	56.4±13.4	70.0±19.5**	34.3±12.6****	35.3	<0.001
Interaction				81.0	0.259
LFnu, %					
PCOS	48.0±15.2	28.4±15.1****	63.4±13.5****	63.6	<0.001
Control	43.7±13.4	30.0±19.5**	65.7±12.6****	35.3	<0.001
Interaction				81.0	0.259
LF-HF ratio					
PCOS	1.1±0.6	0.5±0.4****	2.1±1.2****	34.5	<0.001
Control	0.9±0.5	0.6±0.6**	2.3±1.3***	13.3	0.001
Interaction				41.8	0.129

Data are presented as mean±standard deviation or median with 25th and 75th percentiles where indicated. Two-way ANOVA for repeated measures (2x3 factorial design) and Friedman's two-way ANOVA tests were used for statistical analyses. *: P>0.05 compared to the rest, **: P<0.05 compared to the rest, ***: P<0.01 compared to the rest, ****: P<0.001 compared to the rest. DBP - diastolic blood pressure; HF - high frequency; HFnu - normalized unit of high frequency; LF - low frequency; LFnu - normalized unit of low frequency; RMSSD - the root mean square of successive R-R interval differences; SBP - systolic blood pressure; SDNN - standard deviation of all NN intervals

a marked increase in time domain HRV indices and HF spectral component are associated with vagal modulation. During controlled sympathetic stimulation, a marked reduction in time domain HRV indices and HF spectral component are associated with vagal withdrawal (17). The interpretations of LF and LFnu are controversial. They were considered by some authors as markers of sympathetic modulation (especially LFnu) but are now known to include both sympathetic and vagal influences. The increase in LFnu reflects a shift in the interaction as a consequence of the decrease in vagal modulation. The assessment of HRV based on ECG recordings at rest in supine position and during controlled breathing and isometric handgrip exercise allowed us to evaluate parasympathetic modulation and the parasympathetic-sympathetic balance in young women with PCOS and healthy controls.

Metabolic and cardiovascular disorders have been shown to be related with autonomic dysfunction (18, 19). PCOS is a common endocrine disorder associated with long-term health risks, including IR, diabetes mellitus, dyslipidemia, hypertension, and premature atherosclerosis (20). Obesity has long been known to cause derangement in autonomic functions in the form of increased adrenergic and decreased vagal modulation (21). It was reported that the android type of obesity accentuated the autonomic derangement (22). Increased levels of adipokines in obesity were postulated to cause sympathetic overactivity (23). There are reports of decreased HRV in women with PCOS and increased weight gain (24). In women with PCOS, endothelial dysfunction, a surrogate marker of atherosclerosis development, was shown to be related to obesity, IR, and increased sympathetic tone (25, 26). In a study investigating heart rate recovery after maximal cardiopulmonary exercise test in young overweight PCOS women, PCOS women showed a significantly reduced heart rate recovery compared with healthy controls (27). Abnormal heart rate recovery is a measure of autonomic dysfunction and was inversely correlated to BMI in overweight women with PCOS. Giallauria et al. (28) showed that women with PCOS and abnormal heart rate recovery had higher inflammatory markers (C-reactive protein level and white blood cell count) than those that have normal heart rate recovery. Impaired autonomic function and inflammatory pattern could be improved by exercise training in PCOS women (29).

Previous studies evaluating the HRV in PCOS showed impaired cardiac autonomic modulation at rest condition and during 24 h in women with PCOS in comparison with controls (9, 24, 30). However, in most of these studies, women with PCOS had many metabolic disorders, especially obesity (6). Furthermore, in a study performed on non-obese women with PCOS, HRV was not altered (31). The absence of concomitant cardiovascular risk factors in our study patients might partly explain the observed findings. It is well-known that IR and hyperinsulinemia lead to elevated sympathetic outflow through actions in central brain receptors (32). Furthermore, majority of women with PCOS having a BMI index greater than 30 kg/m² have IR and lean women with PCOS may

have normal insulin levels and sensitivity (33) similar to our data. However, even lean patients with PCOS might have IR (34). As previously stated (35), it is probable that the presence, absence, or degree of IR might determine the autonomic nervous activity, with in PCOS. Thus, we can speculate that the observed differences between our results and previous reports could be, at least in part, related to concomitant cardiovascular risk factors such as obesity and IR. Androgens are generally considered to induce IR. The absence of correlation between testosterone and parameters of HRV suggests that testosterone levels might not affect autonomic modulation in normal-weight women with PCOS having normal HOMA-IR, although larger data are needed to confirm this.

Study limitations

The main limitation of our study was the relatively small sample size. Obesity and IR are common in women with PCOS. Therefore, few women with PCOS were included in the study. Furthermore, obese women with PCOS could be included in the study as an additional group. Thus, the effect of obesity on cardiac sympathovagal modulation could have been evaluated.

Conclusion

In conclusion, women with PCOS and normal weight and normal glucose metabolism have a preserved cardiac autonomic modulation at rest and in response to parasympathetic and sympathetic stimulations. Further studies are needed to confirm the clinical relevance of these data.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – C.K.; Study design – C.K.; Supervision – C.K., T.P.K.; Fundings – C.K.; Materials – T.P.K.; Data collection and/or processing – C.K., T.P.K.; Analysis and/or interpretation – C.K., T.P.K.; Literature Review – C.K., T.P.K.; Writer – C.K., T.P.K.; Critical Review – T.P.K.

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