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Correlation between Serum Dehydroepiandrosterone and Cognitive Function in Thai Pre/ Perimenopause Women Aged 40-49 Years Old: A cross-sectional study

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ABSTRACT

Objectives: To determine correlation between serum dehydroepiandrosterone (DHEA) and cognitive impairment as evaluated by the Montreal Cognitive Assessment (MoCA) in premenopausal/ perimenopausal women. The study also evaluated other factors those can affect both cognitive function and DHEA concentrations.

Materials and Methods: A cross-sectional, single population study recruited 101 healthy premenopausal/perimenopausal women aged 40-49 years. The inclusion criteria included participants who did not have i) hormonal treatment including DHEA, ii) previous ovarian operation, and iii) endocrinological, neurological and mental illness. Blood sampling and MoCA test were performed following the written informed consent. The MoCA, a cognitive screening test evaluating 8 compartments of global cognitive function, was all performed by single certified-physician. MoCA < 25 is determined as having cognitive impairment. DHEA concentrations were measured in batch utilizing the deMeditec ELISA kits.

Results: Mean age of the participants was 43.49 ± 2.89 years. Mean DHEA concentration was 16.07 ± 5.45 ng/ml while the MoCA score was 24.12 ± 3.44. Women with impaired cognitive function (MoCA < 25) were 44.6% (45/101). Neither correlation between DHEA-MoCA, Age-DHEA, nor Age-MoCA was observed (r = -0.139, -0.01, -0.12, respectively; $p > 0.05$). Only women's years of education was positively correlated with the MoCA score ($r = 0.469$, $p < 0.001$). Adjusted odd ratio of serum DHEA on low MoCA (< 25) score was 0.98 (95%CI 0.92, 1.06, $p = 0.649$ determined by log-regression analysis).

Conclusion: No correlation between serum DHEA concentration and cognitive function as determined by the MoCA score in the premenopausal/perimenopausal population aged between 40-49 years old.

Keywords: Dehydroepiandrosterone (DHEA), cognitive function, Montreal Cognitive Assessment (MoCA), Thai women.

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การวิจัยแบบตัดขวางเรื่องความสัมพันธ์ของระดับของฮอร์โมน DHEA และภาวะพุทธิปัญญาในหญิงไทย วัยก่อน/ใกล้หมดระดู อายุระหว่าง 40-49 ปี

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บทคัดย่อ

วัตถุประสงค์*: เพื่อศึกษาความสัมพันธ์ระหว่างฮอร์โมน dehydroepiandrosterone (DHEA) และภาวะพุทธิปัญญาบกพร่อง โดยใช้แบบทดสอบ Montreal Cognitive Assessment (MoCA) ในผู้หญิงวัยก่อน/ใกล้หมดระดู ศึกษาปัจจัยอื่นๆ ทีมีผลต่อภาวะพุทธิปัญญา และระดับฮอร์โมน DHEA ในกลุ่มประชากรที่ศึกษา*

วัสดุและวิธีการ*: การศึกษาแบบตัดขวาง เก็บข้อมูลจากหญิงไทยอายุ 40-49 ปี จำนวน 101 ราย เกณฑ์คัดอาสาสมัครเข้า ประกอบด้วย 1. ไม่มีประวัติใช้ยาฮอร์โมน รวมถึง DHEA 2. ไม่มีประวัติผ่าตัดรังไข่ และ 3. ไม่มีโรคทางต่อมไร้ท่อ โรคทางระบบประสาทและโรคจิตเวช โดยทำการเก็บเลือดจากผู้เข้าร่วมวิจัยเพื่อตรวจระดับฮอร์โมน DHEA โดยวิธี ELISA และทำแบบทดสอบ MoCA เพื่อประเมินภาวะพุทธิปัญญา แบบทดสอบจะมีทั้งหมด 8 ส่วน ซึ่งทำการประเมินโดย ผู้ผ่านการฝึกอบรม โดยผลการประเมิน MoCA ต่ำกว่า 25 จะแปลผลได้ว่ามีภาวะพุทธิปัญญาบกพร่อง*

ผลการศึกษา*: ค่าเฉลี่ยอายุผู้เข้าร่วมการศึกษา 43.49±2.89 ปี ค่าเฉลี่ยของระดับฮอร์โมน DHEA 16.07±5.45 ng/ml และค่าเฉลี่ยของ MoCA score 24.12±3.44 คะแนน โดยมีผู้ที่ได้ MoCA score น้อยกว่า 25 คะแนน ซึ่งถือว่ามีภาวะพุทธิปัญญาบกพร่องอยู่ร้อยละ 44.6 จากผลการศึกษาไม่พบความสัมพันธ์ระหว่างฮอร์โมน DHEA กับ MoCA score อายุกับฮอร์โมน DHEA และอายุกับ MoCA score (r = -0.139, -0.01, -0.12 ตามลำดับ; $p > 0.05$) มีเพียงจำนวนปีการศึกษาที่มีความสัมพันธ์กับ MoCA score ($r = 0.469$, $p < 0.001$) Adjusted odd ratio ของฮอร์โมน DHEA กับระดับ MoCA score น้อยกว่า 25 คะแนนคือ 0.98 (95%CI 0.92, 1.06, $p = 0.649$ วิเคราะห์ข้อมูลโดยใช้สถิติ log-regression analysis)*

สรุป*: ไม่พบความสัมพันธ์ระหว่างฮอร์โมน DHEA และภาวะพุทธิปัญญาที่ประเมินโดยใช้แบบทดสอบ MoCA ในประชากรหญิงวัยก่อน/ใกล้หมดระดูอายุ 40-49 ปี*

คำสำคัญ*: Dehydroepiandrosterone, พุทธิปัญญา, แบบประเมินพุทธิปัญญา Montreal Cognitive Assessment*

Introduction

Ageing results in multiple organ deterioration, including cardiovascular, musculoskeletal, cognition, sexual function, etc. There has been a search for decades to explore solutions to fight against the ageing. It is established that a majority of hormonal axes, especially adrenal and gonadal steroids, are diminished with age. Hence, a concept of hormone fountain of youth was created in which hormone supplements and vitamins have been used to rejuvenate an individual's body[1]. One of the most common hormone medications used is dehydroepiandrosterone (DHEA) which can be prescribed over-the-counter in the Unites States as a food supplement to improve general well-being and prevention of ageing in elderly population (both men and women)[1]. DHEA is a steroid hormone mainly produced from the zona reticularis of the adrenal cortex[2]. DHEA level peaks at around age of 20 and decreases by approximately 10% in every 10 years[3]. Despite being under-investigated, previous studies have shown that it is linked to the conversion of sex hormones, i.e. estradiol (E2) and testosterone (T) in the peripheral organs, such as liver[4]. Due to its function as a substrate for potent sex steroid (both E2 and T) conversion, researcher has been determining to establish a link between diminishing DHEA with reproductive ageing. In fact, many subfertility women who are suffered from ovarian ageing either by their age or premature ovarian insufficiency have currently been prescribed DHEA as an adjuvant in their invitro fertilization cycles. Therefore, DHEA is not only used in an elder but also a young individual who is in needs (and is indicated) for 'anti-ageing' medication.

One of conditions mostly seeks for anti-ageing intervention is impaired cognitive function or dementia/Alzheimer's disease. Cognitive function is an intellectual process which includes contemplation, comprehension, reasoning and recollection of a domain of information, and it is affected by number of various factors, but the most recognizable one is aging. There are multiple tools accepted for the assessment of the cognitive function, including the Montreal Cognitive Assessment (MoCA), which can be used to detect early impairment in cognition. The MoCA relatively demonstrates higher sensitivity with a comparable specificity when compared to other tests such as the Mini-Mental State Examination (MMSE). MoCA assesses various domains of cognition such as visuoconstructional skills, naming, memory, attention, verbal fluency, abstraction and delay recall. The total score is 30, in which a score of greater than or equal to 25 is considered normal[5]. Previous studies demonstrated a correlation between DHEA and cognitive function in postmenopausal women, aged of more than 50, and showed a conflicting study results. The neuroprotective mechanisms of DHEA can be described by that i) studies has shown that E2 and T play a beneficial role in the cognitive function[6-9]. ii) neural tissue can synthesize DHEA. In addition, the DHEA is partially produced by the brain, and functioning as a neuroprotective hormone[10]. Nonetheless, current studies on menopausal women group with age of more than 50 have shown that the administration of DHEA is not associated with the improvement of cognitive function[11].

Currently, there is no study investigating the relationship between serum DHEA and cognitive function in the premenopausal population. As previously mentioned, conflicting findings were noted in the postmenopause and elderly population, those some studies observed an association between serum DHEA and cognitive function[12, 13] but supplying DHEA medication did not improve the cognitive function[11]. The inconclusive result thus makes it worth evaluating the association in the pre-/peri-menopausal women. DHEA constantly declines throughout women's life, thus may support or deny the positive correlation that some papers had suggested. Besides aging, hypoestrogenic state also negatively affects the cognitive function[6-9]. Thus, in this study, we focused on the pre/perimenopausal women who have decreased DHEA level, while the estrogen level still maintained. Moreover, we should

be able to gain information as a reference for future research whether serum DHEA can predict early cognitive impairment and may suggest patients for the supplementation. The objective of this study was therefore to evaluate a correlation between DHEA and cognitive function determined by the MoCA, specifically focusing on pre-/peri-menopause women aged between 40-49 years old. Correlations between age and either serum DHEA or the MoCA were also investigated. Finally, factors influencing the impaired cognitive function were determined using the multivariate model.

Materials and Methods

This cross sectional study recruited pre/perimenopausal women aged between 40 to 49 years, who visited the general gynecology department at the HRH Princess Maha Chakri Sirindhorn Medical Center (MSMC) during 2016 to 2017. This study received financial support from Faculty of Medicine, Srinakharinwirot University and was approved by the institutional ethical committee. The inclusion criteria consisted of female aged as described above who had i) their last menstrual period within one year before enrolled into the study, ii) no current hormone or steroid use, iii) no history of DHEA hormone supplement, iv) no history of ovarian surgery, v) no history of endocrinological disorder; such as polycystic ovarian syndrome (PCOS) or adrenal gland disorder, vi) no history of severe head injury or neurological diseases such as Alzheimer's disease, and vii) no history of mental disorders. Upon written informed consent obtained, participants were asked to provide their demographic information. Then cognitive function assessment was performed using the Thai version MoCA. Participant who could not complete the MoCA due to any reason, for example, illiteracy, would be excluded from the study.

MoCA is used to detect early impairment in cognition. On the other hand, scoring less than previously stated, is considered as impaired cognitive function[5]. The Thai version MoCA test have the sensitivity to detect mild cognitive impairment (MCI) of 80% and to detect a mild Alzheimer's disease (AD) of 98%, with the specificity of 80%[14]. In this study, the MoCA was done by the principal investigator (P.E.) who had been trained and certified through the MoCA official website, http://www.mocatest.org. Participants with an abnormal MoCA score should then be appointed for the neurological examination by the consultant neurologist (M.W.). Finally, 3-5 ml blood sample was collected by a qualified nurse for later DHEA analysis. Serum was separated from the blood sample by centrifugation at 4,000 rpm for 10 minutes and stored at -20°C until assay. Enzyme-linked immunosorbent assay (ELISA) of serum DHEA was carried out in batch once recruitment completed utilizing the DeMeditec ELISA kit (Germany). The intra- and inter-assay correlation coefficients were 7% and 10%, respectively.

Statistical analysis

The calculation of the sample size was done using a formula of single population, cross-sectional survey[15]. Because there had no data of a prevalence of impaired cognitive function in pre/peri-menopausal women from previous studies, neither Asian nor Western population, thus the prevalence of mild impaired cognitive function reported in the post-menopausal population was alternately entered in the formula[16]. The target population required 88 participants. A Total of 101 participants were recruited in this study. The descriptive data were shown as mean ± SD. The correlation between DHEA and MoCA score and other factors, were analyzed using linear regression analysis. Meanwhile, the correlation between DHEA and impaired cognitive function considering when MoCA score less than 25 was analyzed using the log regression analysis. Finally, for other factors and variables, including DHEA levels, that can influence the impairment of cognitive function, was analyzed using multivariate regression analysis.

Results

Table 1 demonstrates patient demographic

data. Mean ± SD age and body mass index (BMI) of the participants were 43.49 ± 2.89 years and 23.39± 3.50 kg/m^2, respectively. Approximately half of the participants was in the normal BMI range (18.5-22.9 kg/m^2). Mean years of education was 12.32 ± 4.64 years in which 57.4% of the cohort received > 12 years of education. Correspondingly, the most educational level was Bachelor degree or higher (56.4%). In the study population, mean ± SD serum DHEA concentration was 16.07 ± 5.45 ng/ml. A level of 5.17 and 26.97 ng/ml were considered as a lower and upper limit for normal DHEA concentration in this study. Mean ± SD MoCA score was 24.12 ± 3.44. MoCA score screening positive for impaired cognitive function (MoCA < 25) was observed in 44.6% of the total number of participants. Mean DHEA concentrations between the low (< 25) and normal (≥ 25) MoCA score were similar (16.35 ± 5.38 vs. 15.85 ± 5.54, p = 0.649). Adjusted odd ratio, determined by logistic regression analysis, of the serum DHEA concentrations in the low MoCA score over the normal group was 0.98 (95%CI 0.92, 1.06, p = 0.649) (Table 2).

Various correlations were determined. Regarding the MoCA score, neither serum DHEA concentration nor participant's age was observed to be correlated with the cognitive function (Pearson correlation coefficient, r=0.139, 0.120; p=0.167, 0.233, respectively). As expected, women's years of education was positively correlated with the MoCA score, r=0.469, p<0.001) (Table 3). Concerning serum DHEA levels, there is no significant correlation between either age or BMI and the DHEA concentrations (r=0.01, 0.144; p=0.920, 0.151, respectively). Adjusted correlation coefficients in the multivariate model is present in Table 3 and 4.

Table 1. Demographic data.

	n (%)	**Mean ± SD**
Age (years)		43.49 ± 2.89
• 40 - 44	68 (67.3)	
• 45 - 49	33 (32.7)	
BMI (kg/m^2)		23.39 ± 3.50
• < 18.5	4 (4)	
• 18.5 - 22.9	51 (50.4)	
• 23 - 24.9	23 (22.8)	
• 25 - 29.9	17 (16.8)	
	6 (6)	
Years of education (years)		12.32 ± 4.64
• ≤ 6	25 (24.8)	
• 7 - 12	18 (17.8)	
• > 12	58 (57.4)	
Highest educational level		
• Primary school	25 (24.8)	
• Secondary or vocational school	19 (18.8)	
• Bachelor or higher	57 (56.4)	

BMI: body mass index

Table 2. Subgroup analysis regarding DHEA concentrations, age and years of education between participants with normal cognitive function (MoCA score ≥ 25) and cognitive impairment (MoCA score < 25).

	Normal cognitive function MoCA ≥ 25	Cognitive impairment: MoCA < 25	p value
Total n (%)	56 (55.4)	45 (44.6)	
DHEA concentration (mean ± SD; ng/ml)	15.85 ± 5.54	16.35 ± 5.38	0.65
Age (mean ± SD; years)	43.49 ± 2.51	44.07 ± 3.23	0.08
Years of education (mean ± SD; years)	13.18 ± 4.53	10.89 ± 4.83	< 0.01

DHEA: dehydroepiandrosterone, MoCA: Montreal Cognitive Assessment

* Overall MoCA score in the population was 24.12 ± 3.44

** Adjusted odd ratio of serum DHEA on low MoCA (< 25) score was 0.98, 951%CI 0.92-1.06, p = 0.649

Table 3. Demonstrate correlation coefficients between MoCA score and other factors.

	Adjusted correlation coefficient (r)*	p value
DHEA	- 0.139	0.167
Age	- 0.120	0.233
Year of education	0.469	< 0.001

DHEA: dehydroepiandrosterone

Table 4. Demonstrate correlation coefficients between DHEA level and other factors.

	Adjusted correlation coefficient (r)*	p value
Age	0.01	0.920
BMI	0.144	0.151

BMI: body mass index

Discussion

Overall, there was no correlation between serum DHEA and cognitive function determined by the MoCA score. Likewise, a correlation between age and either MoCA or serum DHEA could not be detected in the study. Serum DHEA concentrations were similar between participants with normal and low (< 25) MoCA score. It is important to note that almost half of participants had their MoCA scores less than 25 which were compatible with mild cognitive impairment.

A majority of previous cross-sectional studies determining a correlation between serum DHEA and impaired cognitive function were conducted in either post-menopause or elderly population[10]. Valenti et al (2009) conducted a study in the elderly population, aged > 65 years old using Mini-Mental state examination (MMSE), one of the cognition tests, and they found that DHEA levels were positively related with the higher MMSE score[12]. Davis et al (2008), also studying in the postmenopausal women, found that DHEA concentrations were positively correlated

with the executive function, concentration and working memory[13]. Both studies enrolled a large number, approximately 300 of participants. In contrast, few studies, again in elderly population, failed to demonstrate a significant correlation[17, 18]. Moreover, various studies evaluated the efficacy of DHEA supplementation in post-menopausal women but the results were inconclusive[10]. For example, Merritt et al (2012) could not demonstrate a beneficial effect of 40 mg/day of oral DHEA for 4 weeks on an improvement of short term memory in women aged > 55 years old[19]. These conflicting results lead to our investigation in the younger population. We concluded that serum DHEA could not predict the cognitive impairment as determined by the MoCA test. The findings have also raised concerns over a beneficial effect of DHEA supplementation especially in a young individual. There was a possibility concerning a non-correlation result that our age group was too specific in which the variety of cognitive function among the study population. It can also imply that cognitive deterioration is a long-term, chronic process.

DHEA is secreted mainly to the circulation from the adrenal glands[2]. The original function of DHEA is thought to serve as a substrate for more potent sex-steroid conversion[4]. Estrogen stimulates neuron growth and formation of synapses, neurotransmitter production and functions as an anti-oxidant[20], thus provides a protective effect on the cognitive function[6-9]. In addition, DHEA can be produced and it works locally in the brain. Peripheral conversions as well as local production are believed to be a key explanation of our study, regarding the non-correlation result. In fact, Labrie and colleague reported similar findings in cognitive and other conditions which they then create the 'intracrine theory' supporting that serum DHEA level has a poor predictive factor as the hormone is actively converted at the target organ. The action of DHEA is therefore associated with rate and efficacy of hormone conversion (to either E2 or T) at the peripheral tissue[21].

Nonetheless, 44.6% of participants in our study had cognitive impairment as determined by the MoCA score. The number was also in accordance with the educational background of the study population in which 43.6% were graduated from lower than the Bachelor degree. Moreover, the study's subgroup analysis demonstrated a significant lower years of education in the participants with impaired cognitive function (MoCA < 25) when compared with the normal group (10.89 ± 4.83 vs 13.18 ± 4.53, $p < 0.01$) (Table 2). An increasing year of education was moderately correlated with higher MoCA score ($r = 0.469$, $p < 0.001$) (Table 3). In literature, it is also evidenced that higher education is significantly associated with better cognitive function[22]. Distribution of participant's education background was therefore a primary determining factor of the higher incidence of cognitive impairment among the study's participants. The unexpectedly high incidence was different from other previous studies especially the one utilized for sample size calculation (prevalence = 5%) and hence may required a bigger sample size to demonstrate a significant correlation. In addition, although the MoCA test demonstrated a better sensitivity, while the specificities were comparable, when compared to other tests such as the MMSE[23], the results were from studies performed in the elderly population Therefore, the accuracy of the test should be further explored in pre/perimenopausal population. In our groups, all participants with abnormal results were referred to the neurologist (MW, the 2nd author). There was no further intervention required for all test-abnormal participants.

Concerning the secondary outcomes, neither association between age and serum DHEA nor between age and cognitive function was observed. On the contrary, previous studies demonstrated a negative correlation between age and serum DHEA levels[3] as well as the cognitive function. The previous studies were performed across multiple age groups. As mentioned earlier, an explanation could be from narrow-range age group in our study. Other explanation included either the intracrine theory, or interference of educational background, or all of reasons

mentioned. Further research is required to dissect the mechanism/function of DHEA prior to encourage the use of DHEA supplementation to prevent impaired cognitive function in women.

Conclusion

In conclusion, there was no correlation between serum DHEA concentration and cognitive function as determined by the MoCA score in the premenopausal population aged between 40-49 years old.

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Potential conflicts of interest

The authors declare no conflict of interest.

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