

Randomized Controlled Trial on the Effects of Tualang Honey and Hormonal Replacement Therapy (HRT) on Cardiovascular Risk Factors, Hormonal Profiles and Bone Density Among Postmenopausal Women: A Pilot Study

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Abstract

Results of recent trial have shown some negative effects of HRT on postmenopausal women. Therefore, there has been a need to search for an alternative treatment and honey is one of the well known traditional remedies used in minimizing postmenopausal problems. The objectives of the study were to investigate the effects of Tualang honey on the cardiovascular risk factors, changes in hormonal profiles and also effect on the bone. A randomized controlled trial comparing the effects of Tualang honey 20 g/day and HRT for a 4-month intervention period among healthy postmenopausal Malay women aged 45-60 years old was conducted. The primary outcome measures were changes from baseline on the cardiovascular risk profiles, hormonal profiles and effect on bone. Tualang honey compared with low dose HRT, consumed for 4 months by postmenopausal women had no demonstrable effects on the parameters examined such as blood pressure measurement, body mass index and waist circumference. There was no significant difference in the lipid profile, blood sugar profile and bone density between the two groups at the end of the study period.

Keywords: Tualang honey, HRT, Postmenopausal, cardiovascular risk factor, hormonal profiles, bone densitometry

1. Introduction

Menopause is a natural progression of women's physiology. Hormone replacement therapy (HRT) has been the basis of the treatment of menopausal state. The high incidence in cardiovascular disease is due to the increase in the risk factors associated with menopausal state. It is also associated with the emergence of features of metabolic syndrome which includes increase in central or intra abdominal body fat, a change toward more atherogenic lipid profile, with increased low density lipoprotein particles and increased insulin resistance (Knopp, 2002; Eaton & Anthony 2002). Postmenopausal state is associated with a decrease in the bone mineral density

which leads to osteoporosis. There is a widely held belief that the decrease in the estradiol level directly contribute to this. Estradiol directly acts on osteoclast by reducing the rate of bone resorption (Steinweg, 2002).

Despite the proven benefit of hormone replacement therapy (HRT), only 15% of postmenopausal women currently use HRT (Amato & Sylvie, 2002) and of those who started HRT nearly 30% subsequently stopped (Ryan, Harrison & Blake, 1992). The main reasons for not taking HRT were concern over its side effects, safety and efficacy of the treatment. Among the common side effects experienced by women are breast tenderness, edema and breakthrough bleeding. However the major concern regarding HRT relates to the risk of cancer.

The Women's Health Initiative (WHI) Study stated an increase risk in breast cancer, cardiovascular disease, stroke and thromboembolic disease with conjugated equine estrogen plus medroxyprogesterone acetate compared with placebo (Prestwood, 2003). In view of this problem many women are increasingly turning to alternative medicine in an effort to manage their menopausal symptoms (Amato & Sylvie, 2002). However, there are still questions regarding the effectiveness of available alternative medicines in managing menopausal symptoms and complications. A recent result from a RCT indicated that herbal supplements namely black cohosh and soy foods did not relieve vasomotor symptom among menopausal women (Newton, Reed, LaCroix, Grothaus, Ehlich & Guiltinan, 2006).

The use of bee products including honey, pollen, propolis, royal jelly, bee venom and wax in treating illness is known as apitherapy and it can be traced back more than 6000 years to ancient Egypt. The Greeks and the Roman also used bee products for medicinal purpose. This is described by Hippocrates (460–370 BC), Aristotle (384–322 BC) and Galen (130–200 AD), who prescribed the use of honey and bee venom as a cure for baldness (Hellner, Winter, von Georgi & Munstedt, 2007).

Honey is also mentioned in many cultures and religions as an important medicinal product. In Islamic teaching, one chapter in the holy book Quran is named after the bees and the verses in the chapter describe the importance of honey in men's life. In Indian medicine, ayurveda, honey has been used for many centuries in their method for healing and treating illness. Honey in ayurveda is "the highest food" and is referred to as "food for the Gods" (Subrahmanyam, 2007). Honey is also used widely in the Chinese medicine either singly or in combination with other herbs. In Malaysia honey is widely used for treating a multitude of ailments from simple respiratory tract infection to treatment of complicated diabetic foot ulcer. Postmenopausal women are also known to consume honey since it gives them a sense of general wellbeing. However there is limited data regarding the effectiveness of honey in the treatment of specific menopausal symptoms.

Tualang honey is one type of honey which can be found in Malaysia along with, among others Gelam, Belimbing, Durian, and Kelapa. Tualang honey got its name from the Tualang tree where the bees which produce the honey built their nests. The Tualang tree or *Koompassia excelsa* is Asia's largest tree (growing up to 80 metres) and can found in the lowland rainforests of southern Thailand, Peninsular Malaysia, northeastern Sumatra, Borneo and Palawan. Their habitat is the primary tropical rainforest. They prefer damp locations along rivers, in valleys, and the lower slopes of hills. Although common in these forests the Tualang is not naturally abundant therein; they tower above the canopy, their initial branches not occurring until about 30 meters above ground. It is the choice for *Apis dorsata* bees which are the world's largest bees to build their nests. It is presumed that the towering trees afford the bees with safety from the rest of the habitat. Another feature of the Tualang tree is its slippery trunk which prevents the sun bears to climb up the trees and reach the honey combs. A single Tualang tree may contain about 100 *Apis dorsata* nests, and each nest, with the profile of a half-moon and up to 1.5 meters across, may contain about 30,000 bees. Collectively, these bees can produce up to 450 kg of honey from one tree (Oldroyd, Osborne & Mardan, 2000; Itioka, Inoue, Kaliang, Kato & Nagamitsu, 2001).

Research looking at the effect of Tualang honey has shown that it is comparable to manuka honey in terms of its antibacterial activity (Tan et al, 2009). This result suggests that Tualang honey could potentially be used as an alternative therapeutic agent against certain microorganisms, particularly *A. baumannii* and *S. maltophilia*. Other areas where the use of Tualang honey are under investigations are in treatment of radiation mucositis (Biswal, Zakaria & Ahmad, 2003), allergic rhinitis and human immunodeficiency virus (HIV) infection, among others.

There is limited data regarding the use of honey for management of menopausal women. An animal study revealed that administration of honey to ovariectomised rats improves the endometrial and vaginal thickness (Siti Sarah & Siti Amrah, 2010). The vaginal epithelium of honey treated rat showed proliferation and mucination with lack of keratinization. There was also increase in the serum testosterone and progesterone level in the honey treated rats. This study was a pilot study to look at the cardiovascular parameters (blood pressure, waist circumference, total cholesterol, high density lipoprotein, low density lipoprotein, fasting blood sugar), hormonal profiles (follicle stimulating hormone, luteinizing hormone, testosterone and estradiol) and also for bone

densitometry of four months administration of Tualang honey on postmenopausal women.

Ethical consideration:

The study protocol was reviewed and approved by the Universiti Sains Malaysia Human Ethics Committee (USMKK/PPP/JEPeM (198.3(11))).

2. Methods

2.1 study subjects

This was a randomized, prospective, clinical study to evaluate the effects of Tualang honey in comparison with HRT. Subjects will be confined to healthy postmenopausal women who were naturally menopause for more than one year. The study period was four months. A total of 79 patients were recruited.

Group 1: Subjects receiving 20 g/day of Tualang honey. The honey used was from a single batch honey supplied by Federal Agricultural Marketing Authorities (FAMA), Malaysia, evaporated by FAMA to achieve a water content of about 20%, submitted to Sterile Gamma company at Shah Alam, Selangor for sterilization at 25 kGy and packed in 20 g sachet in collaboration with School of Pharmaceutical Sciences laboratory.

Group 2: Subjects receiving hormonal replacement therapy (Femoston®), also known as Femo conti 1/5 (contain 1 mg Estradiol valerate and 5 mg Dydrogesterone) supplied by Solvay Pharma Malaysia.

The choice of the dose of the honey used in the study is based on the animal study using the ovariectomised rat (Siti Sarah & Siti Amrah, 2006). The optimal dose shown to increase the testosterone level was 200 mg/kg/day in the animal model. After taking the average human weight as 60 kg, the dose calculated for human was 12 g (200 mg/kg x 60 kg (average human weight) = 12g). Twenty gram is considered to be medium dose, chosen to study the effect of honey in human being. Furthermore, the dose of the Femo conti is the optimal dose used in the treatment of postmenopausal problem.

Sample size was calculated based on animal study (Siti Sarah and Siti Amrah, 2010) using 2 proportion formula. After considering 20% drop-out and power of 80%, the subjects for each treatment group were 35.

Inclusion criteria were age 45 - 60 years old and naturally menopause for more than one year. No present active medical, surgical and gynecological problems, body mass index 18-35 kg/m², not on HRT for more than 3 months

Exclusion criteria were women whose taking any form of herbal extract in the last 3 months before study entry, history of drug or alcohol abuse, following ovariectomy, history of breast or cervical carcinoma, taking medication that affect bone metabolism, including glucocorticoid, anticonvulsant and methotrexate, clinical relevant cardiovascular, gastrointestinal, hepatic, neurologic, endocrine, hematologic or other major diseases making implementation of the protocol or other interpretation of the study result difficult, endometrial thickness more than 0.5 cm detected from pelvic ultrasonography and mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study.

Informed consent was obtained and the study was explained to the subject by the investigator.

Demographic details including weight and height, physical examination and investigations including pelvic ultrasonography, brief medical history relating to past and current illnesses and concomitant medication was obtained. About 5 mL of fasting blood samples were collected for at baseline and at the end of the study. Subjects were thoroughly examined by Medical Specialists who were part of the Clinical Trial Team at every 2-monthly visits. Randomization was computer-generated .

The investigator may cease study treatment and withdrew the subject or the subject may withdraw herself from participation in the study at any time. Possible reasons for patient withdrawal include the need to take medication, which may interfere with study measurement, patient experiences an intolerable/unacceptable adverse event, patient exhibits non-compliance with the protocol. Patient unwilling to proceed and/or consent was withdrawn and investigator withdraws patient for reasons unrelated to the study drug (e.g., undercurrent illness).

2.2 Safety assessment

2.2.1 Protocol specific clinical assessment

Demographic details were recorded at screening. The subject's body weight and blood pressure were measured at 2 monthly periods. At the screening visit, a physical examination was conducted to determine the patient's current medical conditions and past clinically significant events. This includes all events that have occurred within the last three months and any other earlier event related to the inclusion and exclusion criteria or the subject's disease. This data was recorded at the screening visit. Throughout the study period, subject was directly

questioned about the occurrence of any new signs and symptoms and any changes from baseline was recorded as an adverse event. A physical examination was repeated at the end of the treatment and exit evaluation to assist in determining if there had been any changes to the patient's health during the study period.

2.3 Vital signs

Supine blood pressure and pulse rate was recorded at every visit. Patient was supine or semi-recumbent for five minutes prior to evaluating vital signs.

2.4 Concomitant medication

Concomitant medication included all co-administered drugs and treatment such as analgesics, tonics, herbals or traditional medicines and vitamin and/or mineral supplements. All concomitant medication taken within 7 days prior to commencement of study drug administration and for the duration of the study were recorded in the Clinical Record Form (CRF), including indication, dose, frequency, date and route administered.

2.5 Safety reporting of adverse event and serious adverse event were done

Subjects who are found to be less than 75% compliant with test article usage at any study visit will be withdrawn. Subjects who are found to be taking prohibited medications or supplements without the knowledge of the principal investigator will also be withdrawn. Any major protocol deviations (i.e., those that increase the risk to subjects and/or compromise the integrity of the study or its results) will result in subject discontinuation.

2.6 Statistical analysis

Data was entered, cleaned and analyzed using SPSS version 12. Means and standard deviations for numerical variables and frequency and proportion for categorical variables were reported along with histogram or bar chart when necessary. Level of significance was set at 5% and results were presented with 95% confidence intervals. Repeated measure ANOVA and Multiple Logistic Regression confirmatory analysis were used for analyses.

3. Results

Overall 82 subjects were screened and found to be eligible for the study and were then randomized into two treatment group. However three of them withdraw from the study, leaving a total of 79 participants who actually completed the study. Table 1 and Table 2 showed baseline sociodemographic data.

(Table 1 & Table 2)

The mean age of menopause in this study sample was 49.7 with the overall mean duration of menopause was 5.8 years, with the mean duration in the honey treated group of 5.3 years and 6.3 years in the HRT group. There was no significant difference between the age at menopause and the duration of menopause between the two groups ($p > 0.1$).

The mean parity of these participants was 4.9 with 50.6% having 5 or more children. In term of parity, the honey treated group generally had more children, with 22 of them have more than 5 children compared to 18 with less than 5 children. However when compared with the HRT group the difference was not significant ($p > 0.1$).

In term of gynecological problem, majority of them (64.4%) reported no significant gynecological problem. Those who have positive gynecological and obstetrics history (35.4%) were mainly due to history of miscarriages and caesarean section for delivery (Table 1).

All of the study participant had an educational background, with 25.3% attained tertiary education, 54.4% up to secondary school level and the rest, 20.3% up to primary school level. In term of household income slightly more than half of the participant (53.1%) had an income of less than RM 1000 per month, while 34.2% had an income of between RM 1000-3000 per month, the rest (12.7%) had an income of more than RM 3000 per month. There was a significant differences between the educational level and the income between the two groups with p-value of < 0.05 (Table 2)

Majority of the study (63.3%) participant were healthy with no medical problem, while 36.7% have medical problems but stable or controlled on treatment. Among the medical illness cited were osteoarthritis, hypertension and asthma. There was no statistically significant difference between the honey and the HRT group in term of past medical history (Table 2).

(Table 3 & Table 4)

The baseline clinical findings are presented in Tables 3 and 4 showed the difference between the groups in term the baseline clinical examination findings and baseline biochemical results respectively. The mean systolic and diastolic blood pressures were 132.7 mmHg and 82.0 mmHg respectively, which were within normal limit. There

was a significant difference of systolic blood pressure between the two groups with those treated with honey having a lower reading (127.9 mmHg versus 137.6 mmHg) (p value = 0.002). The mean body mass index and the waist circumference were 27.7 kg/m² and 86.1cm respectively. The BMI was considered to be in the overweight range, while the waist hip circumference was also increase. There was no significant difference between the two groups (p value = 0.907 and 0.717 respectively).

The lipid profile of the participants generally showed dyslipidaemic feature with a mean total cholesterol of 5.7 mmol/L and LDL 3.7 mmol/L. The HDL and TG were in normal range (Table 4). There was no significant difference of all the lipid profile between the groups except for LDL level. There was a significant difference between the groups in term of the LDL -C level, with the group treated with honey having lower LDL level (3.4 mmol/L vs 3.9 mmol/L) ($p < 0.05$).

(Table 5)

The hormonal profile of the study participants was comparable at baseline, with a very high mean FSH value of 73.7 μ IU/ml which indicate late menopausal stage (Table 5). There was no significant difference between the two groups in term of the hormonal profile ($p > 0.05$).

(Table 6)

Table 6 showed the result of the bone densitometry at baseline for both groups. The mean bone densitometry of the study participants was 0.96477 g/cm² and the BMD at the lumbar spine was 1.02565 g/cm². There was no difference between the two groups in term of the baseline bone densitometry at the femur ($p = 0.906$) and at the lumbar spine ($p = 0.625$).

(Table 7 & Table 8)

There is a significant increase in the waist circumference at 4 months in the HRT group when compared with the baseline value after analysis with paired t- test (86.56 cm versus 89.13 cm) ($p < 0.05$). No other significant changes were seen in any of the groups in the other parameters (Table 7). There was no significant difference between the two groups in term of the clinical findings at four months of the study even after performing ANCOVA test and controlling the baseline values (Table 8). The adjusted mean of the blood pressure in HRT group was 134.5 mmHg and 132.5 mmHg in the honey group ($p = 0.587$). In term of the body mass index, the adjusted value in the HRT and honey group was 27.9 and 27.3 kg/m² ($p = 0.246$).

(Table 9)

Referring to Table 9, there was a minimal but significant increase in the level of total cholesterol and LDL-C in the honey treated group after 4 months of treatment ($p < 0.05$). The level of the cholesterol was 5.52 mmol/l and 5.68 mmol/l at baseline and at 4 months respectively. The level of LDL-C was 3.39 mmol/l and 3.66 mmol/l respectively. There was also a significant increase in the level of fasting blood sugar in the honey treated group with a level of 5.25 mmol/l at baseline and 5.68 mmol/l at 4 months ($p < 0.05$).

(Table 10)

There was no significant difference in the lipid profile and blood sugar profile between the two groups at the end of the study period even after analyzing with ANCOVA test and controlling the baseline values (Table 10). The adjusted mean LDL value of the HRT and the honey group were 3.8 and 3.9 mmol/L respectively ($p = 0.487$). Even though there was a significant difference in the baseline value of the LDL between the two groups, the same pattern was not seen at the end of the four months period. There was also no significant change between the blood sugar levels between the groups at the end of the study. The adjusted mean blood sugar reading of the HRT and honey group were 5.4 and 5.8 respectively ($p = 0.218$).

(Table 11)

There were significant changes in the FSH, LH, estradiol and testosterone level in the hormone treated group at 4 months of treatment compared with baseline, while in the honey treated group the only significant change was observed in the LH level (Table 11).

(Table 12)

In Table 12, using the ANCOVA analysis, a significantly lower level of the FSH and LH levels were seen in the HRT group at 4 months of treatment compared with the honey group, with FSH value of 45.3 μ IU/L and LH of 21.7 μ IU/L ($p < 0.001$). The estradiol level meanwhile was significantly elevated with a mean level of 244.0 pmol/L ($p < 0.001$). The findings were still significant after controlling for baseline values, age, BMI, waist circumference and duration of menopause.

(Table 13 & Table 14)

There was no significant changes seen in the bone density between the two groups at four months of study at both femoral and lumbar spine ($p > 0.05$) (Table 13). The adjusted mean of bone density at the femoral site in the HRT and Tualang honey group was 0.960 and 0.938 g/cm² respectively (Table 14). Meanwhile the adjusted mean of bone density at the lumbar spine in the HRT and Tualang honey was 0.999 and 0.996 g/cm² respectively.

4. Discussion

4.1 Sociodemographic characteristic

The mean age at menopause of the study subjects were 49.7 years. A similar result was also attained in a recent study done in Kelantan, which found that the mean age of menopause to be 49.7 years (Dhillon, Singh, Shuib, Hamid & Mahmood, 2006). The age of menopause was also comparable to other countries in the region and the rest of the world. The mean age of menopause of study sample in Singapore was 49.0 years (Foo-Hoe, Lay-Wai, Seang-Mei, Lee & Ken., 2005) and 48.0 years in United Arab Emirates (Rizk, Bener, Ezimokhai, Hassan & Micallef, 1998). In multiethnic sample of US midlife women, the mean age of menopause was around 51.4 years (Gold *et al.*, 2001). Although there is not much difference in the mean age of menopause, there is still variability seen.

The age of menopause is important in term of its association with cardiovascular disease and stroke. There was overall significant association between younger age at menopause and higher risk of coronary heart disease among women who experienced natural menopause and never used hormone therapy (Hu *et al.*, 1999). Similar association between stroke risk was seen with earlier onset of menopause, where age at natural menopause before age 42 was associated with increased ischemic stroke risk (Lisabeth *et al.*, 2009).

The mean duration of menopause of the study subjects were 5.8 years. Based on the Stages of Reproductive Aging Workshop (STRAW) classification for menopausal stage (Soules *et al.*, 2001), this is considered as late menopause. Menopausal women in this stage of menopause are more at risk of the long term sequelae of menopause such as osteoporosis and cardiovascular disease.

The majority of the study participants had a mean household income of less than RM 1000, denoting low socioeconomic income. The socioeconomic status of the participants was also reflected in their educational level, where majority of them (74.7%), did not continue their education until tertiary level. This is comparable to a study looking at sexual function in postmenopausal women in Kelantan which showed 23% had no education, 25% only had primary school education with only 10% were from professional groups (Dhillon *et al.*, 2006).

This is also similar to a study done in Sarawak looking at menopausal symptoms in menopausal women (Syed Alwi, Siti Rubiah & Verna, 2010). However, a study done in urban area showed a different finding where a majority of the women were working (Nik Nasri, 1994). This may reflect on the distribution of the country's population.

4.2 Cardiovascular parameters and risk factors

Cardiovascular parameters measured in this study include both the clinical examination and blood investigations for the lipid profile and fasting blood sugar. The average BMI of the study participants was 27.7 kg/m² which was considered to be in the overweight range. This is in keeping with the finding of the Malaysian Adults Nutrition Survey (MANS) carried out between 2002 and 2003. This survey found that nearly one third of nearly 11,000 of the survey sample were overweight (Azmi *et al.*, 2009). This survey also found that significantly more women was obese compared to the men.

In term of the waist circumference, the mean waist circumference was 86.1 cm which was high according to the International Diabetes Federation criteria for Asian women (IDF, 2006). The mean waist circumference of this study participant was also in line with the finding of the Third National Health Morbidity Survey 2006 which quoted a high prevalence (17.4%) of abdominal obesity in Malaysian population especially in women (Kee *et al.*, 2008). The finding of the current study was in contrast with the Pan Asia Menopause (PAM) study, which found a lower mean BMI of between 23.4 to 24.0 in Asian women (Haines *et al.*, 2005). The difference between these two studies could be due to differences in life style, dietary and socio economic factors.

The result for baseline lipid profile of the study participants generally showed dyslipidaemic pattern with a mean total cholesterol of 5.7 mmol/L and LDL 3.7 mmol/L. The normal value stated by the Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III) for total cholesterol is less than 5.2 mmol/L, LDL of less than 2.6 mmol/L, HDL of more than 1.1 mmol/L and TG of less than 1.7 mmol/L (NCEP, 2001). The HDL and the TG values of the study participants were within normal limit. There

was no significant difference between the two groups at baseline. This result was in line with the current knowledge regarding the association of menopause with dyslipidaemia (Knopp, 2002). The increase at menopause is partly because of advancing age and partly because of the loss of estrogen. Postmenopausal status is also known to be associated with the emergence of metabolic syndrome which is characterized by central adiposity, insulin resistance and lipid abnormality (Carr, 2003). This is due to the changes in the body composition, characterized by an increase in weight and fat mass and a decrease in lean body mass. Metabolic syndrome is well known risk factor for cardiovascular disease.

The result of the clinical examination which includes blood pressure, waist circumference and BMI showed no significant differences between the two groups at the end of the study period. However, there was a statistically significant increase in total cholesterol, LDL-C, and fasting blood sugar level in the honey treated group at 4 months of study compared with baseline.

The result of this study differed from a few studies which looked at the effect of honey on the lipids and glucose level. A study looking at the effect of natural honey on cardiovascular parameters involving 55 overweight or obese, but otherwise healthy individuals showed beneficial effect of honey on the cholesterol, LDL and TG level (Yaghoobi *et al.*, 2008). Even though the findings were statistically significant the clinical relevance was questionable since the changes from baseline were generally between 3 – 6% only. Another study looking at the effect of honey on diabetic patients also showed an improvement in the level of the lipid profile after 2 months of treatment (Mohsen *et al.*, 2009).

The differences between this study and the previous studies could be explained by a few factors.

First, these studies used different study populations which limit the comparability with the recent study. The trials involving men might not hold the same result for postmenopausal women. Second, the type of honey used was different from honey used in the current study. As discussed earlier there are differences in the honey component based on the surrounding flora and fauna from where the bees fed on. It is highly possible that this difference could account for the different effect seen in the different studies. Thirdly, the differences in the dosage used. The previous study used higher dose of 70 g (Yaghoobi *et al.*, 2008) compared with current study which only use 20g. The dose chosen for the current study was based on the previous animal study and even then it was nearly double the dose calculated.

The increase in the fasting blood sugar in the honey treated group raises concern regarding the use of honey especially in diabetic patient. One of the ways to assess the suitability of certain food for diabetic patient is by looking at the glycaemic index. Glycaemic index (GI) is the measurement of the body blood glucose response after a carbohydrate load. According to the international table of glycemic index, honey has a GI value ranging between 32 and 87 (Foster & Miller, 2002). The GI value of table sugar is around 68. Hence, honey can be substituted for table sugar because of its additional health benefits. A study looking at the glycaemic index of Tualang honey however, has categorized the honey as intermediate GI food having a value of 65 (Roberta & Al-Safi, 2009) which was slightly lower than the average table sugar. The study which looked at the effect of honey on diabetic women showed no differences in the fasting blood glucose level of the honey treated group (Mohsen *et al.*, 2009). However this study noted an increase in the HbA1C level in the participant. Therefore caution still need to be practiced in the use of honey in diabetic patient.

Investigations on the effects of other herbal treatments used in the management of menopause showed fairly similar result on the cardiovascular parameters. A randomized controlled trial using soy isoflavones in postmenopausal women showed no significant beneficial effect on the plasma concentrations of lipids, glucose, or insulin (Hall *et al.*, 2006). Other studies which used black cohosh (Wuttke, Gorkow & Seidlov-Wuttke., 2006) and wild yam (Komesaroff, Black, Cable, & Sudhir, 2001) in menopausal symptoms also failed to show any additional beneficial effect on the lipid profile.

It would be remiss if the effects of hormonal replacement therapy particularly Femo conti on the cardiovascular parameters are not discussed. This study showed no significant changes in the lipid profile or other cardiovascular parameters after the four month use of the hormone therapy. However previous studies showed beneficial effect of the combined low dose hormone therapy 17 β estradiol plus 5 mg dydrogesterone especially on increasing the HDL level (de Kraker *et al.*, 2004, Stevenson, Teter & Lees., 2001). The possible difference of the result could be due to the study population and the duration of the study. Previous studies were conducted for longer duration, at least 1 year compared with this study. The duration of this study might not be sufficient to see the effect of the treatment on the cardiovascular parameters.

4.3 Hormonal level

The baseline value of the hormonal level of the study participants showed very high FSH and LH level which indicated late menopause. This was supported by the mean duration of menopause of the study participants which was on average of 6 years. The findings of the hormonal level in this study was similar to the pattern of hormonal changes observed during the late postmenopause stage in various studies (Sowers et al., 2008a; Hall, 2004). The estradiol level was also noted to be low in this study participant as observed in a study looking at the changes in estradiol level in relation to the final menstrual period in a population-based cohort of women (Sowers et al., 2008b).

There was a significant change in the hormonal level in the hormone treated group at four months of treatment with reduction in the FSH, LH and increment of the estradiol level. Similar decrease in the LH and testosterone was seen in the honey treated group. However no significant changes was observed in the FSH and estradiol level. The significance of this finding needs further clarification. Further studies need to be done to see the effect of honey on the hormonal profile especially with the inclusion of vaginal and endometrial cytology. As mentioned previously, the vaginal and endometrial cytology of the honey treated ovariectomised rats showed improvement in the endometrial and vaginal epithelial thickness even though there was no effect on the estradiol and FSH level (Siti Sarah & Siti Amrah, 2006).

4.4 Bone density

The mean bone density measurement at baseline for the study participant was 0.9477 g/cm² and the BMD at the spine was 1.02565 g/cm². This result was comparable to the finding of a study done locally to see the relationship of body composition and bone mineral density in healthy postmenopausal women in Malaysia (Siew Swee et al., 2009). In this study 8% of the study population had osteoporotic changes in the vertebral spine. The major difference with these two studies was a significantly higher percentage (80%) of the study population had osteopenic changes compared with 34.2% in the current study. The difference could be attributed to the difference in the race of study population where our study was predominantly of Malay race while the other study was done among Chinese women only. Another possible factor was the higher BMI of the study population. Our study participants were on average belongs to the overweight group. It is well known that high BMI is a protective factor for bone loss. Other lifestyle factors which played a role in the onset of osteoporosis in postmenopausal women are the smoking status and exercise level. None of these factors were evaluated in the current study.

The result at four months of treatment showed no significant change in term of bone mineral density when compared at baseline and between the two groups. This study was unable to produce the same result seen in animal study where there was a significant change in the bone mass and weight after treatment with honey (Siti Sarah, 2006). The difference with the animal study could be due to the species difference in the metabolism of the honey. The timing of the supplementation could also play a role. In our study, the average duration of menopause was around 6 years; in the rat model honey was given shortly after ovariectomy. Late supplementation may not restore bone loss or prevent further loss of bone. It is well known that prevention of bone loss is easier than reversing them when the loss had already occurred. Another probable reason why this study failed to show any effect on the bone is the study duration, which was only for four months. Previous studies using different treatment modalities either hormonal treatment or alternative treatment were conducted for longer duration, at least 6 months to see the beneficial effect on the bone.

There was conflicting result regarding the bone protective effect of other alternative treatment. A meta analysis concluded that using soy isoflavone for at least 6 months showed reduction in bone loss at the spine of post menopausal women (De-Fu, Li-Qiang, Pei-Yu & Ryohei., 2008). However, a randomized clinical trial conducted following the meta analysis failed to show the protective effect even after one year of use (Brink et al., 2008). Effects of the other alternative treatment on bone metabolism for example black cohosh were less well documented.

5. Conclusions

Tualang honey compared with low dose HRT, consumed for 4 months by postmenopausal women had no demonstrable effects on the parameters examined such as blood pressure measurement, body mass index and waist circumference. There was no significant difference in the lipid profile and blood sugar profile between the two groups at the end of the study period. A significantly lower level of the FSH and LH and increase estradiol level were seen in the HRT group at 4 months of treatment compared with the honey group. There was no significant changes seen in the bone density between the two groups at four months of study.

Recommendation

- (1). A larger study should be done involving all the various ethnics in Malaysia with a proper randomized sampling method to ensure higher generalizability and a more significant effects.
- (2). Multiple doses strength of honey should have been used instead of just one dose, with the inclusion of higher doses as appropriate.
- (3). An attempt should be made to devise a method whereby honey can be formulated in ways which allow blinding of the procedure for example in tablet form. However attempts should be made beforehand to ensure the formulation does not change the honey major active constituents.
- (4). Duration of the study should be lengthened to at least 6 months to 1 year to ensure effect on the bone density is maximized.
- (5). A future study on use of honey in post menopausal women should include the effect of honey on postmenopausal symptoms, an area where alternative medicine is highly studied.

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Table 1. Baseline demographic data

Characteristics	All ^a (n=79)		Trial groups ^a				P-value ^b
			HRT (n=39)		Tualang honey (n=40)		
Demographic data							
Age (years)	55.4	(3.15)	55.3	(3.04)	55.6	(3.29)	0.735
Age of menarche (years)	13.6	(1.62)	13.9	(1.66)	13.3	(1.56)	0.135
Duration of menopause (years)	5.8	(3.96)	6.3	(4.54)	5.3	(3.28)	0.273
Mean age at menopause (years)	49.7	(4.03)	49.2	(4.90)	50.2	(2.93)	0.265
Number of parity							
< 5	39	(49.4)	21	(53.8)	18	(45.0)	0.432 ^c
≥ 5	40	(50.6)	18	(46.2)	22	(55.0)	
Past obstetrics and gynaecology history							
Absent	51	(64.6)	26	(66.7)	25	(62.5)	0.699 ^c
Present	28	(35.4)	13	(33.3)	15	(37.5)	

^a Values are expressed as mean (standard deviation, SD) unless otherwise specified

^b Independent t test

^c Chi-squared test.

Table 2. Baseline Demographic data and past medical history

Characteristics	All ^a (n=79)		Trial groups ^a				P-value ^b
			HRT (n=39)		Tualang honey (n=40)		
Race							
Malay	78	(98.7)	35	(100)	39	(97.5)	0.320 ^d
Non Malay	1	(1.3)	0	(0.0)	1	(2.5)	
Education level							
Primary school	16	(20.3)	9	(23.1)	7	(17.5)	0.041 ^c
Secondary school	43	(54.4)	25	(64.1)	18	(45.0)	
Institution/University	20	(25.3)	5	(12.8)	15	(37.5)	
Income per month							
≤ RM 1000	42	(53.1)	25	(64.1)	17	(42.5)	0.019 ^d
RM 1000 – 3000	27	(34.2)	13	(33.3)	14	(35.0)	
≥ RM 3000	10	(12.7)	1	(2.6)	9	(22.5)	
Past medical history							
Absent	50	(63.3)	28	(71.8)	22	(55.0)	0.122 ^c
Present	29	(36.7)	11	(28.2)	18	(45.0)	

^a Values are expressed as mean (standard deviation, SD) unless otherwise specified

^b Independent t test

^c Chi-squared test, ^d Fisher Exact test.

Table 3. Baseline clinical findings of women treated with HRT and Tualang honey

Characteristics	All ^a (n=79)		Trial groups ^a		P-value ^b		
			HRT (n=39)	Tualang honey (n=40)			
Clinical examinations							
Systolic BP (mmHg)	132.7	(13.8)	137.6	(13.9)	127.9	(12.10)	0.002
Diastolic BP (mmHg)	82.0	(8.73)	83.6	(9.48)	80.4	(7.75)	0.111
Body mass index (kg/m ²)	27.7	(4.35)	27.6	(4.56)	27.3	(4.20)	0.907
Waist circumference (cm)	86.1	(11.6)	85.6	(11.3)	86.5	(12.07)	0.717

^a Values are expressed as mean (standard deviation, SD) unless otherwise specified

^b Independent t test.

Table 4. Baseline fasting lipids and blood sugar level in HRT and Tualang honey groups

Characteristics	All ^a (n=79)		Trial groups ^a		P-value ^b		
			HRT (n=39)	Tualang honey (n=40)			
TC (mmol/L)	5.7	(1.62)	5.9	(1.77)	5.4	(1.42)	0.108
TG (mmol/L)	1.7	(1.03)	1.8	(1.13)	1.6	(0.92)	0.511
LDL-C (mmol/L)	3.7	(1.04)	3.9	(0.98)	3.4	(1.04)	0.025
HDL-C (mmol/L)	1.5	(0.37)	1.6	(0.38)	1.4	(0.36)	0.154
FBS (mmol/L)	5.4	(1.78)	5.6	(2.13)	5.3	(1.36)	0.405

^a Values are expressed as mean (standard deviation, SD) unless otherwise specified

^b Independent t test.

Table 5. Baseline hormonal profiles in HRT and Tualang honey groups

Characteristics	All ^a (n=79)		Trial groups ^a		P-value ^b		
			HRT (n=39)	Tualang honey (n=40)			
FSH (μIU/ml)	73.7	(28.99)	72.2	(29.12)	75.1	(29.17)	0.665
LH (μIU/ml)	31.8	(13.08)	30.2	(12.45)	33.4	(13.63)	0.270
Estradiol (pmol/L)	58.4	(97.72)	57.4	(75.44)	59.4	(116.40)	0.927
Testosterone (nmol/L)	0.9	(0.53)	0.8	(0.48)	0.9	(0.58)	0.723

^a Values are expressed as mean (standard deviation, SD) unless otherwise specified

^b Independent t test.

Table 6. Baseline value of bone densitometry between HRT and Tualang honey

Bone densitometry	All ^a (n=79)		Trial groups ^a		P-value ^b		
			HRT (n=39)	Tualang honey (n=40)			
Femur (g/cm ²)	0.9477	(0.1603)	0.9625	(0.1386)	0.9667	(0.1807)	0.906
Lumbar (g/cm ²)	1.0256	(0.1663)	1.0163	(0.1547)	1.0346	(0.1785)	0.625

^a Values are expressed as mean (standard deviation, SD) unless otherwise specified

^b Independent t test.

Table 7. Cardiovascular outcome in term of clinical findings at baseline and 4 months of intervention in both treatment groups

Trial group	Mean (SD)		t statistics (DF)	P value ^a
	Baseline	4 months		
BMI (kg/m ²)				
Honey	27.73 (4.20)	27.34 (4.13)	1.13 (39)	0.264
HRT	27.62 (4.60)	27.83 (4.56)	9.83 (38)	0.332
WC (cm)				
Honey	86.53 (12.07)	89.18 (9.20)	1.734 (39)	0.91
HRT	85.56 (11.39)	89.13 (11.37)	3.02(38)	0.04
SBP (mmHg)				
Honey	127.95 (12.10)	130.88 (14.04)	1.153 (39)	0.256
HRT	137.63(13.99)	136.18 (10.03)	0.539 (38)	0.593
DBP (mmHg)				
Honey	80.43 (7.75)	79.75 (10.03)	0.378 (39)	0.708
HRT	83.56 (9.48)	81.08 (8.92)	1.283 (38)	0.207

^a Paired t test.

Table 8. Cardiovascular parameters in term of clinical findings at 4 months of study

Study variables	Crude mean (SD ^a)		Adjusted mean (95% CI ^b)		Adjusted mean difference (95% CI ^b)	F stat ^c	P-value ^d
	Placebo (n=39)	Tualang honey (n=40)	Placebo (n=39)	Tualang honey (n=40)			
Cardiovascular disease risk factors							
Systolic BP (mmHg)	136.2 (14.10)	130.9 (14.04)	134.5 (129.85, 139.09)	132.5 (127.94, 137.03)	-1.92 (-8.96, 5.11)	0.29	0.587
Diastolic BP (mmHg)	81.1 (8.92)	79.7 (10.03)	80.2 (77.03, 83.43)	80.6 (77.42, 83.73)	0.35 (-4.53, 5.23)	0.02	0.886
BMI (kg/m ²)	27.8 (4.56)	27.3 (4.13)	27.9 (27.23, 28.54)	27.3 (26.64, 27.94)	-0.59 (-1.59, 0.42)	1.37	0.246
WC (cm)	89.1 (11.37)	89.2 (9.20)	88.9 (86.87, 91.05)	89.3 (87.28, 91.40)	0.38 (-2.80, 3.57)	0.05	0.812

^a Standard deviation

^b Confidence interval

^c F statistic

^d Analysis of covariance (ANCOVA) after adjusted for baseline values, age, BMI, WC and duration of menopause.

Table 9. Biochemical profile for cardiovascular findings at baseline and 4 months of intervention for both treatment groups

Trial group	Mean (SD)		t statistics (DF)	P value ^a
	Baseline	4 months		
TC (mmol/L)				
Honey	5.52 (1.35)	5.68 (1.45)	-2.39 (39)	0.021
HRT	5.92 (1.77)	6.28 (1.30)	-1.16 (38)	0.252
TG (mmol/L)				
Honey	1.65 (0.91)	1.58 (1.11)	0.52 (39)	0.606
HRT	1.80 (1.13)	1.70 (1.00)	0.73 (38)	0.472
LDL-C (mmol/L)				
Honey	3.39 (1.01)	3.66 (1.18)	-2.21 (39)	0.033
HRT	3.98 (1.05)	4.01 (1.280)	-0.16 (38)	0.874
HDL-C (mmol/L)				
Honey	1.45 (0.35)	1.46 (0.27)	-0.34 (39)	0.739
HRT	1.58 (0.38)	1.56 (0.37)	0.22 (38)	0.822
FBS (mmol/L)				
Honey	5.25 (1.35)	5.68 (1.45)	-3.69 (39)	0.001
HRT	5.61 (2.12)	5.38 (1.70)	0.77 (38)	0.442

^a Paired t test.

Table 10. Cardiovascular in term of biochemical profile at 4 months of intervention

Study variables	Crude mean (SDa)		Adjusted mean (95% CIb)		Adjusted difference (95% CIb)	F statc	P-valued
	HRT (n=39)	Tualang honey (n=40)	HRT (n=39)	Tualang honey (n=40)			
TC (mmol/L)	6.0 (1.64)	5.7 (1.35)	5.7 (6.06)	(5.43, 5.9 (6.31)	0.25(-0.23,0.74)	1.1	0.298
TG (mmol/L)	1.6 (0.92)	1.6 (1.12)	1.6 (1.85)	(1.26, 1.6 (1.89)	0.04(-0.40,0.49)	0.03	0.848
LDL-C (mmol/L)	4.1 (1.24)	3.7 (1.14)	3.8 (4.06)	(3.54, 3.9 (4.20)	0.14 (-0.260,53)	0.48	0.487
HDL-C (mmol/L)	1.6 (0.37)	1.5 (0.27)	1.6 (1.66)	(1.48, 1.5 (1.55)	-0.12(0.26,0.03)	2.59	0.112
FBS (mmol/L)	5.5 (1.68)	5.7 (1.45)	5.4 (5.79)	(4.96, 5.8 (6.19)	0.40(-0.24,1.04)	1.54	0.218

^a Standard deviation

^b Confidence interval

^c F statistic

^d Analysis of covariance (ANCOVA) after adjusted for baseline values, age, BMI, WC and duration of menopause.

Table 11. Hormonal profile at baseline and 4 months of intervention for both treatment groups

Trial group	Mean (SD)		t statistics (DF)	P value ^a
	Baseline	4 months		
FSH (μ IU/ml)				
Honey	75.07 (29.17)	78.76 (28.90)	-1.29 (39)	0.204
HRT	72.22 (29.16)	45.31 (29.03)	4.86 (38)	0.000
LH (μ IU/ml)				
Honey	33.42 (13.62)	36.55 (12.71)	-2.86 (39)	0.007
HRT	30.16 (12.45)	21.75 (13.96)	3.14 (38)	0.003
Estradiol (pmol/L)				
Honey	59.39 (116.4)	41.53 (23.87)	1.02 (39)	0.314
HRT	57.36 (75.44)	244.02 (300.5)	-3.39 (38)	0.000
Testosterone (nmol/L)				
Honey	0.87 (0.57)	0.64 (0.49)	3.88 (39)	0.000
HRT	0.85 (0.47)	0.48 (0.34)	5.19 (38)	0.000

^a Paired t-test.

Table 12. Hormonal profile at 4 months of intervention

Study variables	Crude mean (SD) ^a		Adjusted mean (95% CI) ^b		Adjusted mean difference (95% CI) ^b	F stat ^c	P-value ^d
	Placebo (n=39)	Tualang honey (n=40)	Placebo (n=39)	Tualang honey (n=40)			
Hormonal profile							
FSH (μ IU/ml)	45.3 (29.04)	78.8 (28.91)	46.1 (38.10, 54.05)	78.0 (70.15, 85.89)	31.94 (20.48, 43.41)	300.88	0.000
LH (μ IU/ml)	21.7 (13.96)	36.6 (12.71)	22.7 (18.86, 26.53)	35.6 (31.85, 39.41)	12.94 (7.42, 18.45)	21.92	0.000
Estradiol (pmol/L)	244.0 (300.51)	41.5 (23.88)	242.3 (170.63, 314.00)	43.2 (-27.54, 113.94)	-199.12 (-302.18, -96.05)	14.85	0.000
Testosterone (nmol/L)	0.5 (0.34)	0.6 (0.49)	0.5 (0.40, 0.61)	0.6 (0.52, 0.73)	0.12 (-0.03, 0.27)	2.48	0.120

^a Standard deviation^b Confidence interval^c F statistic^d Analysis of covariance (ANCOVA) after adjusted for baseline values, age, BMI, WC and duration of menopause.

Table 13. Bone density at baseline and 4 months of intervention for both treatment groups

Trial group	Mean (SD)		t statistics (DF)	P value ^a
	Baseline	4 months		
Femur (g/cm ²)				
Honey	0.9669 (0.1807)	0.9421 (0.1324)	1.222 (39)	0.229
HRT	0.9629 (0.1283)	0.9559 (0.1283)	0.867 (38)	0.391
Lumbar spine (g/cm ²)				
Honey	1.0347 (0.1785)	0.9999 (0.1528)	1.970 (39)	0.056
HRT	1.0163 (0.1547)	0.9941 (0.2259)	0.698 (38)	0.490

^a Paired t test.

Table 14. Bone density at 4 months of intervention

Study variables	Crude mean (SD ^a)		Adjusted mean (95% CI ^b)		Adjusted mean difference	F stat ^c	P-value ^d
	HRT	Tualang honey	HRT	Tualang honey			
	(n=39)	(n=40)	(n=39)	(n=40)			
Femur (g/cm ²)	0.9559 (0.1283)	0.9420 (0.1324)	0.960 (0.937,0.984)	0.938 (0.915, 0.962)	0.022 (-0.011, 0.056)	1.849	0.178
Lumbar spine(g/cm ²)	0.9941 (0.2259)	0.9999 (0.1528)	0.999 (0.949,1.049)	0.996 (0.9464, 1.0464)	0.03 (-0.68, 0.074)	0.007	0.943

^a Standard deviation

^b Confidence interval

^c F statistic

^d Analysis of covariance (ANCOVA) after adjusted for baseline values, age, BMI, and duration.