The 6th Scientific Meeting of the Asia Pacific Menopause Federation

Singapore | 20 – 23 Apr 2017

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Delivery of holistic care for the postmenopausal woman

Although the average age of menopause is around 50 years, about 10% of women will experience menopause before the age of 45 years, and many women experience iatrogenic menopause. Therefore, the needs of individual women will vary considerably, such that the care of each woman needs to be in the context of her socio-economic circumstances, as well as understanding her other health risks.

In addition to evaluating and managing menopausal symptoms, menopause is the time when other health risks should be evaluated and managed. Over the last decade, cardiovascular disease, diabetes, musculoskeletal disease and cancer, most notably breast cancer, have emerged as leading causes of morbidity and mortality in women.

A major risk factor for all of these diseases is being overweight or obese. Importantly, central adiposity, without obesity or the metabolic syndrome, is in itself a risk factor for each of these chronic diseases. In contrast to developed countries where obesity is associated with poverty, in Asia, obesity is most associated with affluence. The hormonal changes at menopause also contribute to the development of obesity. This is in part due to central brain effects that occur when oestrogen levels fall and also due to effects of oestrogen insufficiency on fat metabolism. In addition, chronic sleep disruption as a consequence of oestrogen deficiency, stress and ageing, results in desynchronization of central and peripheral body clocks. This, in turn, further contributes to metabolic perturbations and increased abdominal visceral fat. Animal models suggest that oestrogen therapy may ameliorate these changes.

Another important component of the holistic care of women at midlife is attention to their musculoskeletal health, which encompasses joint muscle and bone health. The focus should not be on bone health alone, but rather on strength and mobility. Women should be encouraged to incorporate varied physical activities into their daily lives.

Consideration should also be given to nutrition and mental health, as well as common disorders in women unrelated to menopause, such as urinary incontinence, faecal incontinence and pelvic organ prolapse.

Holistic care involves:
• Determining the symptoms of greatest concern to the woman
• Evaluating biological/psychological/social factors
• Alleviating the symptoms of greatest concern to the woman

• Risk reduction for chronic disease
  • Metabolic syndrome (cardiovascular disease, diabetes)
  • Musculoskeletal disease
  • Cancer
  • Depression

• Managing other conditions common in women at midlife

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What's hot in hot flushes

Hot flushes affect up to 70% of peri- or postmenopausal women, may persist for many years and cause a decrease in quality of life for women in midlife. However, the causes of hot flushes have remained elusive.

Menopause is associated with increased gonadotrophin-releasing hormone (GnRH) secretion with increased luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations, which can coincide with hot flushes. Recent evidence suggests that the kisspeptin/neurokinin B/dynorphin (KNDy) signalling system in the hypothalamus is an important stimulus for GnRH secretion. This system is also sensitive to oestrogen withdrawal. There is accumulating evidence that KNDy neurons are involved in thermoregulation, administration of neurokinin B can induce flushes, which are decreased by administration of blockers of this pathway. These are now the subject of early clinical trials.

Hot flushes resemble a heat dissipation response and are characterized by vasodilation and sweating, and as such, cutaneous vessels (key effectors in thermoregulation) may play a role in the mechanism of flushing. Postmenopausal women with severe flushing have been shown, in studies involving the measurement of skin blood flow, to have increased skin blood flow compared with their matched non-flushing contemporaries. Decreased oestrogen at menopause increases the sensitivity of the heat-loss pathway, leading to the activation of heat-loss effectors at lower temperatures.

Vasomotor symptoms and cardiovascular disease (CVD)

Observational data suggesting a link between hot flushing and CVD are conflicting, possibly because obesity,

a significant risk factor for CVD, has an insulating effect due to subcutaneous fat increasing both hot flushing and CVD risk. Although prospective studies linking hot flushes with incident CVD are lacking, a substantial body of evidence supports an association of hot flushing with vascular function, an early marker of atherosclerosis. An example is the decreased reactivity of the large, deep blood vessels of the arm. However, women who flush have an enhanced ability to dissipate heat through the blood vessels in the skin that is proportional to the severity of the hot flushing. Thus, care must be taken when interpreting the findings of studies in this area as much will depend on methodology.

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The hot flush

- Hot flushing is common in many countries, causing reduced quality of life for women. They may also continue for many years into menopause
- Postmenopausal women who flush have enhanced skin perfusion and a stronger vasodilator response in blood vessels in the skin than postmenopausal women who do not, suggesting that a flush is a heat loss response
- Hot flushers have decreased hyperaemic response to shear stress. This is associated with an increase in cardiovascular risk, supporting the hypothesis that women who flush may be at greater risk of having cardiovascular disease
- The kisspeptin/neurokinin receptor pathway that controls the secretion of gonadotrophin-releasing hormone may be important in the aetiology of vasomotor symptoms, creating interesting treatment opportunities for the future
- Early studies with a neurokinin 3 receptor blocker suggest a highly significant effect on flushing when compared with placebo

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Testosterone supplementation for postmenopausal women for sexual dysfunction

Testosterone is an important female hormone with ubiquitous effects in the body. The primary indication for treatment of women with testosterone is presently for the treatment of persistent low desire–arousal, which causes a woman distress. Recent Australian data indicates that approximately 34% of women aged 40–65 years, and 14% of women aged 65–79 years are affected by low desire with associated personal distress.

Studies have shown that physiological testosterone therapy can be effective for restoration of sexual desire and arousal in surgically postmenopausal women on oestrogen only, naturally postmenopausal women on oestrogen plus progestin, postmenopausal women on no hormone therapy and premenopausal women aged 35–45 years.

Before considering treatment a full psychosocial and medical history needs to be taken and modifiable factors need to be addressed. Treatment should be considered a trial. There is no blood level of testosterone that will guide treatment and no cut-off level of testosterone that defines "androgen deficiency".

If considering testosterone therapy for women, oral and injectable testosterone should be avoided as these result in unpredictable levels and may adversely affect lipids. Male formulations are not recommended as it is very difficult to

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measure out a sufficiently low dose for a woman from a product formulated to give a male dose, which may be up to 10-fold higher. The use of compounded formulations is often unavoidable. Transdermal preparations provide the most physiological replacement option.

If a woman has not experienced improvement after 6 months, treatment should cease. Women who respond and, wish to continue testosterone, should have their testosterone levels regularly monitored (6-monthly) to avoid overdosing, and asked about symptoms of androgen excess. It is recommended that total testosterone and sex hormone-binding globulin are measured and free testosterone calculated from these (an online calculator can be used). Ideally, free testosterone should be kept within the normal range for a young woman.

Testosterone supplementation for postmenopausal women for sexual dysfunction

- Testosterone therapy has been shown to improve sexual desire, arousal, pleasure, orgasm frequency and sexual satisfaction in naturally and surgically postmenopausal women using/not using concurrent oestrogen therapy
- Where an approved testosterone formulation for women is not available, use compounded testosterone. Products for men are ideally avoided
- Treatment should be considered a trial of therapy for 3–6 months for properly diagnosed desire–arousal disorder
- Measure testosterone and sex hormone-binding globulin (SHBG) levels at baseline and after 3–6 weeks of initial treatment to check for patient overuse
- Stop treatment if no response by 6 months
- For ongoing users, review testosterone and SHBG levels every 6 months to monitor for excessive use and signs of androgen excess

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Progestins and Breast Cancer

For all its problems, the Women's Health Initiative Randomized Controlled Trials (WHI RCTs) of menopausal hormone therapy (MHT) remain an invaluable source of information.

The original WHI Oestrogen Plus Progestogen RCT was stopped in part because of a non-significant increase in breast cancer risk for users of combined conjugated oestrogens (CE) + medroxyprogesterone acetate (MPA) MHT. The relative risk (RR) was 1.26 (95% confidence interval [CI]: 1.00–1.59). When long-term follow-up data was published in 2014 the RR during the intervention phase was reported as 1.24 (95% CI: 1.01–1.53), whilst overall long-term follow-up was 1.28 (95% CI: 1.11–1.48).[1]

In contrast to this, when the oestrogen-only arm of WHI was released in 2002, the RR of breast cancer for users of CE was 0.77 (95% CI: 0.59–1.01). In other words, a trend to benefit from oestrogen, although not significant. Follow-up of this data found a statistically significant reduction in breast cancer incidence and mortality for users of CE compared with placebo.[2]

The placebo rate in both arms of the WHI trial was very similar, and so it appears as though there is a difference between the effect of oestrogen plus progestogen and oestrogen-only on breast cancer risk.

Subsequent to these findings a number of observational studies have been analyzed, examining the risk of breast cancer among women using oestrogen only or oestrogen plus various progestogens. Synthetic progestins bind not only to progesterone receptors, but also to other steroid receptors including (in the case of MPA) glucocorticoid receptors and (in the case of norethisterone acetate) androgen and oestrogen receptors. It now appears that these non-progesterone receptor-mediated effects may adversely alter a woman's risk of breast cancer. *In vitro* studies show more breast epithelial cell proliferation with oestrogen + MPA plus less breast epithelial cell apoptosis than when oestrogen is combined with micronized progesterone. MPA has been shown to increase breast cell sulphatase activity that promotes conversion of oestrone sulphate to oestrone, thence oestradiol, in the breast.

An observational study found no increased risk of breast cancer after 4 years treatment with oestrogen only or oestrogen plus progestagen whilst for oestrogen plus synthetic progestins the RR was 2.07 (95% CI: 1.26–3.39).[3] Similarly the E3N study found an increase in breast cancer for women using oestrogen + micronized progesterone or oestrogen + dydrogesterone whilst for oestrogen plus synthetic progestins the risk was increased (RR 1.69 [95% CI: 1.50–1.91]).[4] Average duration of treatment was 8.1 years.

Similar data has been reported in a Finnish Study.[5]

A meta-analysis reported that for users of oestrogen plus progesterone compared with oestrogen plus synthetic progestins, the RR of breast cancer was 0.67 (95% CI: 0.55–0.81).[6]

Clearly more research is required. However, it does appear, based on observational data and RCTs, that the increased risk of breast cancer reported with MHT use is associated with the addition of a synthetic progestin and duration of use.

In the absence of other data, it seems prudent to recommend that a natural progestogen, such as micronized progesterone or dydrogesterone, be used when required.

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Different progestogens: Do they matter in breast cancer risk?

- Randomized, controlled trails show a clear difference in breast cancer risk for users of oestrogen only compared with oestrogen plus progestin menopausal hormone treatment
- Long-term follow-up of Women's Health Initiative (WHI) trials found an increased risk for oestrogen plus progestogen users (relative risk [RR] 1.28 [95% confidence interval (CI): 1.11–1.48]) and a reduced risk for oestrogen-only users (RR 0.79 [95% CI: 0.65–0.97])
- Oestradiol plus synthetic progestins, such as medroxyprogesterone acetate (MPA), stimulate breast cell proliferation and block apoptosis more than oestradiol plus natural progestogens
- Observational studies with follow-up of up to 8 years found different effects on breast cancer risk for women using oestrogen plus synthetic progestins compared with women using oestrogen plus micronized progesterone or dydrogesterone
- For women using oestrogen plus synthetic progestins, with up to 8 years follow-up, RR of breast cancer was increased (1.69–2.03), whilst risk with oestrogen plus micronized progesterone or dydrogesterone was not
- A meta-analysis of the effects of oestrogen plus progesterone compared with oestrogen plus synthetic progestins on breast cancer risk found reduced risk for the former (RR 0.67 [95% CI: 0.55–0.81])

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Calcium and vitamin D: Is the debate over?

Both calcium and vitamin D are important to our overall health. Hypocalcaemia leads to increased neuronal membrane permeability to sodium, neuronal hyperexcitability and eventually tetany. Hypercalcaemia causes nervous system depression, sluggish reflexes and cardiac abnormalities.

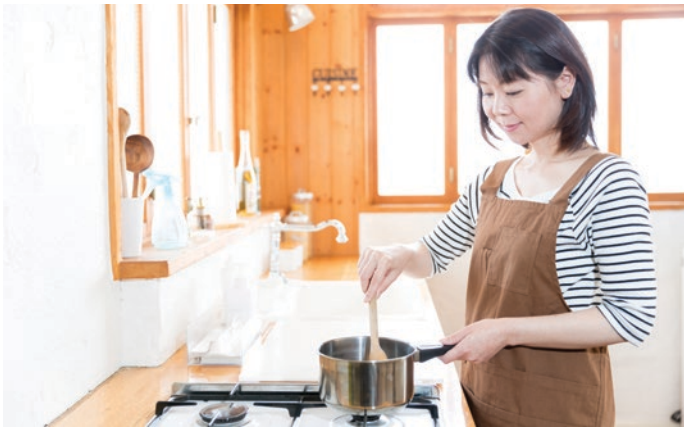
Calcium homeostasis is regulated by three hormones:

- *Parathyroid hormone* increases plasma calcium by mobilizing it from bone, increasing renal reabsorption and increasing formation of vitamin D.
- *Vitamin D* increases calcium absorption from the gut and reabsorption from the kidney. It is also important in bone mineralization.
- *Calcitonin* inhibits bone resorption and increases urinary calcium.

Adequate calcium intake is necessary to minimize mobilization from bone. Adequate vitamin D is necessary to facilitate this process. Calcium requirements vary with age, gender and menopausal status ranging from 600–1200 mg daily. The ideal source of calcium is dietary.

Supplementary calcium is important for those who cannot obtain their daily requirements from diet alone. In general, calcium supplements are safe, although large bolus doses are best avoided. Randomized, controlled trial (RCT) data shows a modest effect of calcium and vitamin D supplementation on fracture risk, but none for vitamin D alone.

Exercise is also important. The minimum exercise requirement for bone health is at least 30 minutes of brisk walking 3–4 times per week. A Cochrane systematic review has reported that exercise, calcium and vitamin D reduced the risk of fracture and improved bone density and muscle strength.[1] Calcium supplementation was associated with a small increase in gastrointestinal symptoms and renal calculi, but not with any increase in coronary heart disease or death.[1]



Vitamin D is obtained from sunlight and from oily fish. Mild vitamin D deficiency is common and the recommended daily intake (RDI) is 800 IU/day. Vitamin D deficiency is associated with proximal muscle weakness, an increased risk of falls and osteomalacia. Vitamin D deficiency has also been linked to an increased risk of colorectal, breast and prostate cancer. Vitamin D has antiproliferative, anti-angiogenic, immunomodulatory and pro-apoptotic effects. However, data on the effects of vitamin D supplementation on cancer risk or cardiovascular health are inconsistent. In the Women's health Initiative (WHI) RCTs no effect of vitamin D supplementation on cancer risk or mortality was found.[2]

No recommendations for vitamin D supplementation beyond bone protection and maintenance of RDI can yet be made as long term efficacy and safety are unproven. Large-scale, general population, high-dose vitamin D trials are ongoing. Results from these trials may yet improve our understanding of the non-skeletal roles of vitamin D.

The jury is still out.

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Calcium and vitamin D: Is the debate over?

- Both calcium and vitamin D, at physiological levels, are important for overall health and well-being
- Calcium has important roles in bone and muscle health, cardiovascular health and neuronal function. Calcium homeostasis is maintained by parathyroid hormone, vitamin D and calcitonin
- Daily recommended calcium intake varies with age and is important for good health
- Increasing dietary calcium should be the first recommendation towards achieving desired daily intake
- There is no benefit seen with supra-physiological intake of vitamin D
- Supplemental calcium should be reserved for those unable to achieve desired daily dietary intake
- Vitamin D is important for calcium absorption and bone mineralization. Extraskeletal effects of vitamin D may include beneficial effects on cardiovascular health and a patient's risk of cancer
- Benefits of vitamin D supplementation beyond normal values for bone health, including effects on cardiovascular health and cancer risk, remain unproven and their safety untested
- Large-scale, general population, high-dose vitamin D supplementation trials are ongoing, which may improve our understanding of non-skeletal roles of vitamin D
- The debate is not over and further research is required

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