

## Menopause care for obese and diabetic women

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### Abstract

Women with obesity or/and diabetes form an increasing part of the peri- and post-menopausal women cared for by general practitioners and gynaecologists. Menopausal obese/diabetic women have a different hormonal *milieu* than lean women, with increased exposure to androgens and oestrogens. In spite of this, obese women experience more menopause-related symptoms, particularly vasomotor symptoms and urinary incontinence. Obese and diabetic women also have a higher risk of breast and endometrial cancer, dementia, coronary heart disease (CHD) and venous and arterial thromboembolism. Bone mineral density loss is variable yet diabetic women show a uniformly higher rate of fractures, partly through a greater likelihood of falls. Although oestrogen-progestagen-type hormone therapy (HT) improves glycaemic control and the lipoprotein profile in diabetic women, HT should be used very cautiously in obese and diabetic postmenopausal women because of accrued risks of thrombosis and CHD. Instead, the primary goal is to stimulate physical activity which improves general fitness and body weight control during the menopause transition, and which reduces the risk of breast cancer and osteoporosis. Also, vitamin D sufficiency should be ensured together with a healthy calcium intake, but anti-osteoporosis drugs which strongly suppress bone remodelling should be used with caution.

*Key words:* Diabetes, hormone therapy, menopause, obesity, osteoporosis.

### Introduction

Overweight or obesity and diabetes are 21<sup>st</sup> century epidemics which threaten to reverse hard-won gains in life span obtained in the 20<sup>th</sup> century, both in developed and in transition countries (Prospective Studies Collaboration 2009). While type 1 diabetes mellitus (T1DM) was lethal a century ago, insulin therapy has made postmenopausal life possible for the large majority of women confronted with this disease. Yet type 2 diabetes mellitus (T2DM) is by far the most common form of diabetes in Europe and elsewhere; T2DM is strongly associated with obesity and insulin resistance. While diabetic women can now expect a good disability-free life span, much depends on lifestyle choices and long-term metabolic control, both of which determine the occurrence of microvascular and macrovascular (*ie*, atherosclerotic) complications. General practitioners and diabetologists are primarily responsible for up-to-date and individualised advice on metabolic control. Yet

gynaecologists are also primary care-partners of women during and after the reproductive period. Hence, they need to be aware of the challenges that face postmenopausal women with obesity or/and diabetes. This narrative overview highlights some of these challenges, and offers some recommendations on follow-up and treatment. Hormone therapy (HT) with oestrogens and progestagens after the menopause – hailed in the 1980s and 1990s as a near-miracle therapy with bone, metabolic and cardiovascular benefits – is now reckoned to entail more risks than benefits for the large majority of women with obesity or diabetes. Clearly, the emphasis must be on maintaining a healthy lifestyle and micronutrient provision when necessary. But let's start with the natural menopause and follow a meandering path from there.

### The natural menopause is obesogenic

A six-year longitudinal study in 543 women in midlife, part of the large SWAN project on the

menopausal transition in the U.S.A., showed a gain in body mass index (BMI,  $\sim 0.2$  kg/m<sup>2</sup>/y), waist circumference ( $\sim 0.9$  cm/y) and fat ( $\sim 0.57$  kg/y) but not muscle mass. These changes might be ascribed to ageing *per se*, yet the extra fat mass was related to the rise in FSH inferring that ovarian failure is also partly responsible (Sowers *et al.*, 2007). Importantly, regular physical activity prevents or attenuates these changes (Sternfeld *et al.*, 2004).

Another analysis in 156 midlife women over four years confirmed an increase of total fat mass with ageing, and showed a rapid rise in intra-abdominal (*ie*, visceral) fat in the two years before menopause. This gain in visceral fat is accompanied by a more positive energy balance, since basal (or resting) energy expenditure and physical activity decline in the years before menopause while energy intake remains constant (Lovejoy *et al.*, 2008). The intra-abdominal fat accumulation modifies the secretion of adipose-tissue products (adipokines) and causes an increase in inflammatory markers such as C-reactive protein (Lee *et al.*, 2009).

The SWAN project further demonstrated that the menopausal transition entrains hyperlipidaemia (Derby *et al.*, 2009) and accelerates the development of the metabolic syndrome (see Glossary, Table 1) (Janssen *et al.*, 2008). Interestingly, the drop in the sex hormone binding globulin (SHBG) concentration during the transition and the baseline bioavailable (*ie*, SHBG-corrected) testosterone concentration are the best predictors of incident metabolic syndrome.

### **The hormonal milieu of postmenopausal diabetic women: overexposure to androgens and oestrogens**

No longitudinal data are available on the menopause transition in diabetic women. An accentuation of the previously described changes is anticipated, because women with the metabolic syndrome, impaired glucose tolerance or T2DM (see Glossary) typically show lower circulating SHBG compared to lean women with normal glucose tolerance (Ding *et al.*, 2006; Maggio *et al.*, 2007). In postmenopausal women, SHBG is inversely correlated with the HOMA-IR, an index of insulin sensitivity (see Glossary) (Golden *et al.*, 2007) and SHBG is the principal “hormonal” predictor of the metabolic syndrome (Maggio *et al.*, 2007) or T2DM (Ding *et al.*, 2006). As a consequence of reduced SHBG, free or bioavailable levels of both testosterone and oestradiol are robustly elevated (Ding *et al.*, 2007; Maggio *et al.*, 2007).

In addition, there is probably a boost of androgen and oestrogen secretion, since elevated total andro-

gen (*eg*, DHEA, testosterone) and oestradiol concentrations were documented in some studies (Ding *et al.*, 2006, 2007; Golden *et al.*, 2007). The putative sex steroid hypersecretion may be ovarian, adrenal and/or peripheral in origin. Both ovarian and adrenal androgen secretion remain high up to the menopause in women with a diagnosis of the polycystic ovary syndrome, which is more common among obese and diabetic women (Puurunen *et al.*, 2009). Also, subcutaneous adipose tissue is now recognised to be an androgen- and oestrogen-producing tissue (Blouin *et al.*, 2009).

Yet the cumulative hyperandrogenic exposure appears to prevail. A comparison of T2DM postmenopausal women with age- and BMI-matched controls showed less lower-body (*ie*, gynoid or gluteofemoral) fat in the women with T2DM (Stoney *et al.*, 1998). T2DM women also appear to have higher (facial) hirsutism scores (Korytkowski 2005); in this regard, Achard and Thiers coined the description “*le diabète de la femme à barbe*” back in 1921.

### **Earlier age at menopause in obese and diabetic women?**

Women with T1DM have a substantially increased risk of other autoimmune diseases. A higher incidence of autoimmune oophoritis and primary ovarian insufficiency might therefore be predicted. But the available data are scarce. In one study, age at menopause was 8 years earlier in 143 women with T1DM compared with their sisters, but more research is needed on possible confounding factors (*eg*, previous ovarian surgery) (Dorman *et al.*, 2001).

For obesity and T2DM, there is no physiological basis for an alteration in age at menopause and indeed, no relationship with BMI was found in the SWAN project ( $n = 14,620$ ) (Gold *et al.*, 2001). However, in a multinational European sample ( $n = 5,288$ ), obesity conferred a slightly increased risk of earlier age at menopause (Dratva *et al.*, 2009). To be sure, the effect of obesity, if any, is weaker than that of smoking.

### **More, not less, menopausal symptoms in obese women (Table 2)**

Despite their increased oestrogen concentrations, obese women experience more menopausal symptoms in midlife than lean women do. In the SWAN study ( $n = 16,065$ ), obesity (defined as a BMI  $\geq 32$ , and compared with a BMI of 19-26.9) augmented the risk of vasomotor symptoms (hot flashes and night sweats) by 18%, musculoskeletal symptoms (stiffness/soreness) by 53% and urine leakage by 118% (Gold *et al.*, 2000). In a subgroup of SWAN

**Table 1.** — Glossary

Central obesity	Defined in women as a waist circumference $\geq 88$ cm ( $\geq 80$ cm in some populations such as Asians)
Diabetes mellitus	Defined as a fasting plasma glucose level $\geq 126$ mg/dl (7.0 mmol/l) or a 2-h glucose level of $\geq 200$ mg/dl (11.1 mmol/l) on a 75-g oral glucose tolerance test *
HOMA-IR	Short for homeostasis model assessment for insulin resistance, and a frequently used measure of insulin sensitivity. Defined as (glucose/insulin)/22.5
Impaired glucose tolerance	Defined as a 2-h plasma glucose level of $\geq 140$ mg/dl (7.8 mmol/l) but $< 200$ mg/dl (11.1 mmol/l) on a 75-g oral glucose tolerance test *
Metabolic syndrome	Also called syndrome X or the insulin resistance syndrome, this controversial “syndrome” represents a cluster of cardiometabolic risk factors predictive of both type 2 diabetes and cardiovascular disease. Several gender-specific sets of criteria exist, but the NCEP/ATPIII criteria ** are used most widely. To be labeled with the metabolic syndrome, women should have at least 3 of the following 5 criteria: 1) waist circumference $\geq 88$ cm; 2) blood pressure $\geq 130/\geq 85$ mm Hg; 3) fasting plasma glucose $\geq 110$ mg/dl; 4) triglycerides $\geq 150$ mg/dl; 5) HDL-cholesterol $\leq 50$ mg/dl.

\* American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2009;32(Suppl.1):S62-7.

\*\* Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486-97.

participants ( $n = 461$ ), subcutaneous adiposity showed a better association with hot flashes than did visceral adiposity (Thurston *et al.*, 2008).

Women who experience **hot flashes** have a smaller thermoneutral zone and thus a lower core body temperature threshold at which sweating (or shivering) occurs. The hot flash event is triggered by a temporary, small elevation of body temperature provoked by environmental heat, hot or spicy food or drink, sympathetic activation, etc. (Freedman & Krell, 1999). Because obese women have an “extra coat” with low thermal dissipation, they are better armed against environmental cold - peripheral vasoconstriction keeps core body temperature constant with less need to activate brown adipose tissue for heat generation (Celi, 2009). But they are more vulnerable to heat triggers which include exercise (Aiello *et al.*, 2004).

Several studies have confirmed that obesity and weight gain in midlife are risk factors for **stress**

**incontinence**. A randomised trial showed that symptomatic overweight or obese women in the early postmenopause who lose weight through diet and exercise, experience an improvement of their stress incontinence (Subak *et al.*, 2009).

#### More hormone-related cancers in obese and diabetic women

It is now well established that obesity, and central obesity (see Glossary) in particular, raises the risk of a cancer diagnosis as well as cancer-related death. The excess risk per 2.5 or 5.0 kg/m<sup>2</sup> BMI-category above the normal reference range (*eg*, 22.5-24.9) appears linear (Pischon *et al.*, 2008; Prospective Studies Collaboration, 2009).

Hormone-receptor-positive **breast cancer** is more common among obese women in the postmenopausal period (Ballard-Barbasch *et al.*, 2009); breast cancer risk increases in a linear fashion

**Table 2.** — Risk profile of obese/diabetic postmenopausal women

Symptoms:	<ul style="list-style-type: none"> <li>• More likely to experience vasomotor symptoms</li> <li>• More likely to experience stress incontinence</li> </ul>
Vascular health:	<ul style="list-style-type: none"> <li>• More cardiovascular disease (coronary heart disease, stroke, venous thromboembolism)</li> </ul>
Bone health:	<ul style="list-style-type: none"> <li>• Variable bone density yet consistently more fractures, owing in part to falls associated with central obesity, diabetes complications and poor health in general</li> </ul>
Cognitive function:	<ul style="list-style-type: none"> <li>• More likely to develop dementia (Alzheimer’s and vascular)</li> </ul>
Cancer:	<ul style="list-style-type: none"> <li>• Higher incidence of breast and endometrial cancer</li> <li>• Poorer prognosis after breast or endometrial cancer diagnosis</li> </ul>

according to the weight gain incurred since menopause or even since the age of 18 years (Eliassen *et al.*, 2006). Obesity also worsens the prognosis after a breast cancer diagnosis (Ballard-Barbasch *et al.*, 2009). Diabetes (primarily T2DM) is associated with a 20-25% increased risk of breast cancer, mainly hormone-receptor-positive cancers (Larsson *et al.*, 2007). The magnitude of this risk is in line with the rise in circulating sex steroids (DHEA, testosterone, oestradiol) observed in postmenopausal T2DM women (The Endogenous Hormones and Breast Cancer Collaborative Group, 2002; Ding *et al.*, 2007; Golden *et al.*, 2007), and is comparable to the risk imparted by five years of oestrogen-progestagen-type HT (Chlebowski *et al.*, 2003). Hyperinsulinaemia is another independent hormonal link between obesity or T2DM and breast cancer (Gunter *et al.*, 2009). From a clinical viewpoint, all obese and diabetic postmenopausal women need regular mammograms.

Clinicians have long recognised that obesity and diabetes (both T1DM and T2DM) are major risk factors for a diagnosis of **endometrial cancer**, and epidemiological studies confirm this observation (Hjartåker *et al.*, 2008). The risks conferred by obesity and diabetes are apparently additive, resulting in a sixfold increased risk in obese diabetic women (Friberg *et al.*, 2007). Similar to breast cancer, both hyperoestrogenaemia and hyperinsulinaemia (Nagamani & Stuart, 1998) appear to be hormonal mediators. The best endometrial surveillance practice in these women is unknown: further studies should assess the value of regular endometrial thickness measurements by ultrasound or/and regular progestagen-induced withdrawal bleeding. Obesity may also augment the risk of ovarian cancer (Hjartåker *et al.*, 2008).

Preexisting diabetes increases the risk of death from any cause following a diagnosis of cancer. Although expected, this effect nonetheless appears to be stronger for endometrial and breast cancer than for gastrointestinal or lung cancer (Barone *et al.*, 2008), necessitating further research on the causes thereof.

### **The dementia rate is doubled in obese and diabetic women**

Dementia is a major problem in old age, with 18% of people aged > 75 years afflicted by major cognitive decline. Although two forms exist - Alzheimer's dementia (50-60% of cases) and vascular dementia, there is a broad interface between both forms (Craft, 2009). Obesity, the metabolic syndrome and diabetes in midlife all increase the risk of dementia at an advanced age, with median odds ratios across studies

of 2.0-2.3 (Kloppenborg *et al.*, 2008). Persons who are obese in midlife but lose considerable weight thereafter (an early manifestation of dementia?) appear to carry the highest risk: the term "obesity paradox" was coined to describe this age-dependent relationship between BMI and dementia (Fitzpatrick *et al.*, 2009). The mechanisms involved include  $\beta$ -amyloid accumulation in the brain as a result of hyperinsulinemia, microvascular impairment and atherosclerosis, etc. (Craft, 2009). The value of cognitive screening in obese and diabetic women from age 60-65 years onwards needs further evaluation.

### **More bone fractures and more falls**

Obese women show less bone resorption and bone mineral density (BMD) loss in the early postmenopause than lean women; yet they are still losing bone (Ravn *et al.*, 1999). Although reduced bone loss is protective against osteoporotic fractures, individuals with central obesity fall more often (Shapses & Riedt 2006); more research is needed on the risk factors of falling (*eg*, rapid weight gain, vitamin D deficiency, etc.) and its impact on fracture rate. Better documented is that weight loss in overweight postmenopausal women stimulates bone resorption and accelerates BMD loss (Jensen *et al.*, 2001; Riedt *et al.*, 2005), particularly when losing >10% of initial weight over a short period of time. Mechanistically, this can be explained by a lower oestrogen production in adipose tissue, lower calcium intake and absorption, hypercortisolism, etc. (Shapses & Riedt 2006).

Women with early T2DM have a slightly higher BMD than nondiabetic women (3-5% after adjustment for BMI) but they may lose bone more rapidly with ageing and longer diabetes duration (Schwarz *et al.*, 2005). They also have a 29% higher fracture rate (Bonds *et al.*, 2006), which is explained in part by a fourfold higher likelihood of falling. Indeed, apart from overweight, T2DM individuals may develop microvascular complications that lead to visual impairment, neuropathic foot ulcers and foot fractures, and poor health in general. In addition, diabetic bone quality may be inferior (Verhaeghe & Bouillon, 2008).

But the bone effects are most pronounced in women with T1DM. In contrast to T2DM, they have smaller bones and a reduced BMD, which appears to be dependent on long-term glycaemic control (Danielson *et al.*, 2009). Their vertebral and hip fracture rates are much higher than in T2DM, up to 14-fold higher than in nondiabetics (Verhaeghe & Bouillon 2008). It is unknown whether T1DM modulates menopausal bone loss. Follow-up of bone

health parameters is nonetheless an essential part of menopause care for T1DM women, which includes advice on adequate calcium and vitamin D intake (see below) and a low threshold for regular BMD testing (eg, a personal history of low- or moderate-trauma fracture, a family history of osteoporosis, body weight < 60 kg, smoking, moderate alcohol intake, systemic corticosteroid use, etc.).

### Examining the value of HT in obese/diabetic women: moderate metabolic benefits

In randomised trials from the U.S. such as *PEPI* (Espeland *et al.*, 1997) or *WHI* (Manson *et al.*, 2003; Margolis *et al.*, 2004), **weight gain** and waist expansion were somewhat repressed in HT (conjugated equine oestrogens with or without a progestagen) users compared to placebo users. Small and partly randomised studies suggest that this HT effect applies to obese and T2DM postmenopausal women as well (Kristensen *et al.*, 1999; Samaras *et al.*, 1999). Of potentially greater clinical importance is the observation that HT may improve liver steatosis in overweight or obese women with T2DM, as suggested by a reduction in liver enzymes (McKenzie *et al.*, 2006).

The *PEPI* and *WHI* trials further demonstrate that HT lowers fasting plasma **glucose and insulin** (by 7-16%) and the HOMA-IR index, inferring insulin sensitisation (Espeland *et al.*, 1998; Margolis *et al.*, 2004; Bonds *et al.*, 2006a). By contrast, glucose levels during an oral glucose tolerance test tend to be higher in HT users (Espeland *et al.*, 1998), compatible with delayed glucose clearance. Yet the net effect of HT use on glucose homeostasis is beneficial: the incidence of T2DM was reduced by 12-21% in the *Nurses' Health Study* (Manson *et al.*, 1992) and the *WHI* trial (Margolis *et al.*, 2004; Bonds *et al.*, 2006a), and by 35% in elderly women with coronary artery disease (the *HERS* trial, Kanaya *et al.*, 2003), independently of baseline BMI and HT-induced BMI change.

The finding of lower fasting insulin (or C-peptide) and insulin resistance during postmenopausal HT use extends to women with impaired glucose tolerance or T2DM (Ferrara *et al.*, 1995; Brussaard *et al.*, 1997; McKenzie *et al.*, 2003). Several small trials in postmenopausal women with T2DM document an improvement of glycaemic control after starting oral or transdermal HT, with better fasting or/and postprandial glucose values or/and a reduced hemoglobin(Hb)A<sub>1c</sub> level. The HbA<sub>1c</sub> reduction was modest, however: 0.6% after 6-8 weeks (Brussaard *et al.*; 1997; Samaras *et al.*; 1999; Friday *et al.*, 2001), 0-1.2% after 3 months (Andersson *et al.*, 1997; Samaras *et al.*, 1999; Fenkci *et al.*, 2003; Kernohan *et al.*,

2007) and 0-0.4% after 6 months (McKenzie *et al.*, 2003; Perera *et al.*, 2001). HbA<sub>1c</sub> levels were also lower in HT-treated compared to untreated postmenopausal diabetic women in an observational study (Crespo *et al.*, 2002) but a health-discrepancy bias cannot be excluded. Oral HT may generate more glycaemic benefits than transdermal HT does, since the HT-induced lowering of HbA<sub>1c</sub> was related to the rise in SHBG (Andersson *et al.*, 1997). Preliminary data suggest that the glycaemic benefits of oestrogen-progestagen-type HT do not extend to tibolone (Prelevic *et al.*, 1998).

HT favourably affects the **lipoprotein profile** in T2DM women, yet the *WHI* trial has clearly demonstrated that HT-induced lipid profile changes do not accord with the short-term risk of coronary heart disease (CHD) (Manson *et al.*, 2003). In summary, oral HT reduces LDL-cholesterol, augments HDL-cholesterol in some studies, and does not cause a significant rise in triglyceride levels (Andersson *et al.*, 1997; Brussaard *et al.*, 1997; Samaras *et al.*, 1999; McKenzie *et al.*, 2003); Friday *et al.* (2001) reported a mild elevation in fasting but not postprandial triglycerides. Milder changes occur with transdermal HT (Perera *et al.*, 2001; Fenkci *et al.*, 2003). The favourable lipoprotein profile may be mechanistically related to the reduced carotid wall thickness observed in a sample of T2DM women who used HT for 10 years on average (Dubuisson *et al.*, 1998).

### Harmful effects of HT: a search for interactions with obesity/diabetes

The harmful effects of HT include breast cancer, CHD, stroke, cognitive decline and dementia, venous thromboembolism, urinary incontinence and gallbladder disease.

The *WHI* trial has left no doubt that HT use is one of the risk factors for a breast cancer diagnosis in postmenopausal women, with 24% more incident cases after a mean follow-up of 5.6 years; there was no significant interaction with the BMI ( $p = 0.12$ ) although the risk appeared to be lower in women with a BMI  $\geq 30$  (Chlebowski *et al.*, 2003). Yet in a reanalysis of most observational studies before 1997, the overall excess risk of breast cancer – ie, 35% after  $\geq 5$  years HT use – was confined to women with a BMI < 25 (Collaborative Group on Hormonal Factors in Breast Cancer 1997). In the British *Million Women Study*, there was also an interaction between HT use and BMI with a lower breast cancer risk in HT users with a BMI  $\geq 25$  v < 25 (Million Women Study Collaborators 2003). Thus, the effect of HT on breast cancer risk becomes less apparent with increasing BMI.

CHD accounts for > 25% of all deaths. For each 5 kg/m<sup>2</sup> increase in BMI above 25, there is a 35% increase in mortality from CHD (Prospective Studies Collaboration 2009). In the *WHI* trial, HT increased CHD incidence by 81% in the first treatment year and was subsequently neutral; there was no interaction between HT use and the BMI or the presence/absence of diabetes (Manson *et al.*, 2003). Yet diabetic persons have a substantially increased baseline risk of CHD and some observational studies showed a synergistic interaction with HT. For example, the incidence of CHD was more than fourfold higher in Danish nurses with diabetes (probably both T1DM and T2DM) who used HT compared to diabetic never-users (Løkkegaard *et al.*, 2003); and in an American cohort of diabetic women, recent HT use conferred a fourfold higher risk of myocardial infarction recurrence (Ferrara *et al.*, 2003).

HT use, obesity and diabetes are all risk factors for stroke (Wassertheil-Smoller *et al.*, 2003; Prospective Studies Collaboration, 2009). In the *WHI* trial, there was no interaction between the effects of HT use and diabetes but the interaction with BMI was not examined (Wassertheil-Smoller *et al.*, 2003).

The *WHI* trial has deflated another “HT balloon”: HT does not reduce the incidence of dementia, but rather accelerates cognitive decline and doubles the risk of dementia. While cognitive decline is BMI-dependent, as mentioned previously, there was no interaction between the effects of HT use and obesity/diabetes in the trial (Rapp *et al.*, 2003).

Venous thromboembolism is clearly BMI-dependent, with a threefold increased risk in obese *v* lean postmenopausal women. Importantly, in the *WHI* trial, the effect of HT was additive, thus leading to an almost sixfold increased risk in obese HT users compared to untreated lean women (Cushman *et al.*, 2004).

Contrary to clinical teaching in the 1980-90s, the *HERS* and *WHI* trials showed HT use to be a risk factor, not a treatment, for stress and mixed-type urinary incontinence. While urinary incontinence is BMI-dependent, as mentioned, the effect of HT did not appear to be more pronounced among obese or diabetic women (Hendrix *et al.*, 2005). Gallbladder disease is also more common in HT users, again with no apparent interaction with BMI (Cirillo *et al.*, 2005).

In conclusion, the risks conferred by HT and obesity on venous thromboembolism are additive, while the risk of breast cancer during HT use appears to be reduced in obese women. A synergistic effect of HT use and diabetes on CHD events cannot be excluded at this time.

## **Conclusion: HT is rarely a good choice for obese/diabetic women in clinical practice**

According to a statement from the European Medicines Agency (EMA 2003), the presence of disturbing menopausal symptoms with an adverse impact on the quality of life constitutes the only valid indication for HT. The *EMA* statement is general, and does not make recommendations for use in obese or diabetic women.

While obese women experience more vasomotor symptoms, it is unknown whether HT is as effective for this indication as in lean women, or indeed whether it is more effective than weight loss. In a small open-label cross-over study in overweight/obese T2DM women, HT improved the vitality and energy scores (Samaras *et al.*, 1999). For obese women with severe menopausal symptoms, contraindications (*eg*, a history of CHD, stroke, venous thromboembolism or breast cancer) must be carefully excluded before considering HT. Non-oral HT is to be preferred to oral HT because this mode of treatment appears to carry less thrombotic risk in obese women (Canonica *et al.*, 2008). Because of their increased risk of endometrial cancer, adequate association of a progestagen (a minimum of 12 days per month) is required in obese women with an intact uterus; endometrial surveillance may be valuable. Many obese HT users suffer from gastro-oesophageal reflux symptoms (Nilsson *et al.*, 2003), yet it is uncertain whether non-oral therapy improves these symptoms.

Although oestrogen-progestagen-type HT may benefit the glycaemic control and the lipoprotein profile in T2DM women, making advantage of these actions would require long-term treatment which is incompatible with current recommendations on safe HT use; in addition, these benefits can be achieved by other therapeutic options (see below). Because of the potential adverse effect of HT on CHD, the indications for HT should be very strict in diabetic women, and it might be argued that the benefit-risk balance is rarely if ever positive. Fortunately, clinicians and patients have always known this intuitively; even in the 1990s, diabetic women in the U.S. were 60% less likely to use HT (Crespo *et al.*, 2002).

## **Offering alternatives for HT to obese/diabetic women in the menopause transition and post-menopause (Table 3)**

**Regular physical activity** is the number one intervention. Physical activity improves insulin sensitivity, and large randomised trials have shown that lifestyle intervention including exercise prevents or

**Table 3.** — General recommendations for postmenopausal obese or diabetic women

- Engage in regular physical activity (at least 30 min a day)
- Join a weight loss education program if obese
- Consider a Mediterranean diet for weight control and cardiovascular benefits; avoid foods or drinks with *trans* fatty acids or a high glycaemic index (*ie*, containing sucrose or fructose)
- Avoid smoking; keep alcohol intake at  $\leq 1$  U/day
- Increase vitamin D intake by increasing fish consumption and/or take a vitamin D supplement (800-1000 IU/day)
- Optimize calcium intake at 1200-1500 mg/day (1700 mg/day when losing weight)
- Consider raloxifene use if osteoporosis has been diagnosed

delays a diagnosis of T2DM in high-risk individuals (Diabetes Prevention Program Research Group 2002). Physical activity is beneficial even with no or minimal weight loss, because it reduces visceral fat and improves general fitness (Ross & Bradshaw 2009), and attenuates weight gain in the menopause transition (Sternfeld *et al.*, 2004). Regular (> 5 h/week) physical activity also meaningfully reduces breast cancer risk after menopause (Sprague *et al.*, 2008; Ballard-Barbasch *et al.*, 2009). If the physical activity includes weight-bearing- or resistance-type exercises, early postmenopausal bone loss at the spine is prevented, similarly to or perhaps better than with HT (Maddalozzo *et al.*, 2007). Yet some women may experience an aggravation of vasomotor symptoms by exercise (Aiello *et al.*, 2004).

Weight loss through energy intake restriction is an obvious if secondary (Ross & Bradshaw, 2009) goal in overweight or obese women. Large randomised trials have demonstrated that the composition (low-fat, low-carbohydrate, high-protein, Mediterranean) of an energy-restricted diet is of little importance for the magnitude of medium-term (2 year) weight loss in overweight individuals (Shai *et al.*, 2008; Sacks *et al.*, 2009). In overweight persons with T2DM, weight loss through intensive lifestyle intervention is accompanied by improved glycaemic control and cardiometabolic risk factors (The Look AHEAD Research Group, 2007). But the most difficult task is to maintain weight loss, and those who combine diet and physical activity have the best chances of continuing their weight control; attending weight control treatment sessions is also important (Sacks *et al.*, 2009; Wadden *et al.*, 2009). In overweight postmenopausal women, weight loss decreases the risk of urinary incontinence (Subak *et al.*, 2009) and breast cancer (Sprague *et al.*, 2008; Ballard-Barbasch *et al.*, 2009), the latter probably by reducing circulating oestrogen concentrations; in very obese women, bariatric surgery may also lessen breast cancer risk (Cleary & Grossman, 2009). A further measure to reduce postmenopausal breast cancer risk is to restrict alcohol intake to 1 unit per day or less (Sprague *et al.*, 2008).

Although the trials carried out so far may have been underpowered, low-dose aspirin ( $\leq 100$  mg/day) shows no benefit in the primary prevention of CHD among diabetic individuals (Patel *et al.*, 2009). Therefore, until more data become available, aspirin should not routinely be started in postmenopausal diabetic women. Neither is there a place for routine antioxidant (vitamins C and E) supplementation, which may actually augment the risk of hypertension and death – one possible mechanism is by blocking the beneficial effects of physical activity (Ristow *et al.*, 2009). Instead, a healthy diet should be recommended containing plenty of fish, vegetables and nuts, and avoidance of foods with *trans*-fatty acids and foods or drinks with a high glycaemic index (*ie*, mainly sucrose and fructose, which cause postprandial hyperglycaemia) (Mente *et al.*, 2009). A Mediterranean diet thus offers the double benefit of improved weight control (Shai *et al.*, 2008) and lower risk of CHD. Of course, smoking should be strongly discouraged, and smokers may be referred to a smoking withdrawal program. Further cardiovascular management (blood pressure lowering, statin therapy) is beyond the scope of this overview.

An important task of menopause care is maintaining **bone health**. Numerous studies show that obese individuals have a substantially higher risk of low 25(OH)D concentrations (Macdonald *et al.*, 2008), which is the best marker of vitamin D (in)sufficiency. Vitamin D is fat-soluble and therefore partly sequestered within adipose tissue, rendering it metabolically unavailable; however, weight loss does not appear to raise 25(OH)D levels (Jensen *et al.*, 2001). Many experts advocate a 25(OH)D level of  $\geq 30$  ng/ml ( $\geq 75$  nmol/L) for optimal bone health and muscle function and, potentially, as a boost to natural immunity against microbial pathogens, autoantigens and cancer (Holick, 2007). The methods to improve vitamin D sufficiency are judicious sun exposure, increasing the vitamin D intake (fatty fish such as mackerel, salmon, sardines and tuna, eggs, vitamin D-supplemented dairy products, etc.), and/or a taking a vitamin D supplement (800-1000 IU/day).

Calcium intake should optimally be 1200-1500 mg/day for postmenopausal women, especially in vitamin D-insufficient women (Bischoff-Ferrari *et al.*, 2009). On the other hand, recommending extra calcium to calcium-sufficient women is of little value for their bone health (Jackson *et al.*, 2006). A diet rich in dairy products may be more beneficial to preserve BMD than a calcium supplement, through an effect on oestrogen metabolism (Napoli *et al.*, 2007) or/and because of a concomitant extra intake of protein and phosphate; dietary calcium may also lessen gastrointestinal side-effects. An additional benefit of consuming at least 1200 mg/day of calcium is the small but significant reduction in weight gain in postmenopausal women (Caan *et al.*, 2007), possibly by interfering with fat absorption in the gut. For overweight/obese women who are currently losing weight, a total calcium intake of ~1700 mg/day is recommended to minimize bone loss (Jensen *et al.*, 2001; Riedt *et al.*, 2005); this can rarely be achieved by dietary measures alone. A total calcium intake of > 2000-2500 mg/day should be avoided, because of an increased risk of kidney stones (Jackson *et al.*, 2006).

In case of osteoporosis, specific anti-osteoporosis drugs should be considered. Bisphosphonates such as oral alendronate have been shown to act independently of BMI (Ravn *et al.*, 1999; Kaji *et al.*, 2009) and equally well in T2DM *v* nondiabetic women (Keegan *et al.*, 2004). But there is one worrying preliminary report that osteonecrosis of the jaw, one of the complications of bisphosphonate use, may be more common in diabetics (Khamaisa *et al.*, 2007). Fortunately, osteonecrosis of the jaw is rare among individuals treated with oral bisphosphonates for osteoporosis ( $1/10^4$ - $10^5$ ), in contrast to intravenous bisphosphonates used in malignancies. Another potential complication of long-term bisphosphonate use is a metadiaphyseal chalk-stick type fracture in the femur, possibly occurring as a consequence of chronic low bone remodelling – *ie*, as bones become “frozen”, they cannot properly remedy the “wear and tear” or microdamage (Visekruna *et al.*, 2008). Since diabetic individuals have chronic low remodelling by themselves (Verhaeghe & Bouillon 2008), this type of fracture might be more common among diabetic bisphosphonate users, but no data are available as yet. Until such time, bisphosphonates should be used very cautiously in diabetic women, and a treatment holiday after 2-5 years may be considered depending on the estimated fracture risk. Alternatively, raloxifene 60 mg/day may be preferred which, compared to alendronate 70 mg/week, reduces bone turnover less aggressively (Luckey *et al.*, 2004). Raloxifene does not adversely affect the glycaemic control, lipoprotein profile and microalbuminuria

progression in women with T2DM (Andersson *et al.*, 2002; Hadjadj *et al.*, 2007). When an anti-osteoporosis drug is taken into consideration, vitamin D and calcium sufficiency should be ensured.

## Conclusions

This overview highlighted some challenges faced by postmenopausal women with obesity or/and diabetes. On top of the generally recognised risks of CHD and venous thromboembolism, there is also an increased risk of vasomotor symptoms, urinary incontinence, fall-related fractures, dementia, and breast and endometrial cancer. While HT may offer symptom relief and short-term metabolic benefits, accrued risks of CHD and thrombosis indicate that HT is for the few, not the many. Increasing physical activity should be the pivot of any management program, to repress the amount of visceral fat, improve general fitness and reduce the risks of breast cancer and osteoporosis. Bone health should also be maintained by ensuring vitamin D sufficiency and an optimal calcium intake.

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