Menopause care for obese and diabetic women

Johan Verhaeghe

Department of Obstetrics and Gynaecology, Katholieke Universiteit Leuven, Leuven, Belgium.

Correspondence at: J. Verhaeghe, Department of Obstetrics and Gynaecology, U.Z. Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium. E-mail: johan.verhaeghe@uz.kuleuven.be

Abstract

Women with obesity or 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 21st century epidemics which threaten to reverse hard-won gains in life span obtained in the 20th 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 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, ~0.2 kg/m²/y), waist circumference (~0.9 cm/y) and fat (~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 androgen (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 ≥ 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
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/m² BMI-category above the normal reference range \((eg, \geq 22.5)\) appears linear (Pischon et al., 2008; Prospective Studies Collaboration, 2009). Hormone-receptor-positive breast cancer is more common among obese women in the post-menopausal period (Ballard-Barbasch et al., 2009); breast cancer risk increases in a linear fashion

| 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 \((\text{glucose/insulin})/22.5\) |
| **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 \(\geq 130/\geq 80\) 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.

| Table 2. — Risk profile of obese/diabetic postmenopausal women |
|---------------------|
| **Symptoms:** | More likely to experience vasomotor symptoms More likely to experience stress incontinence |
| **Vascular health:** | More cardiovascular disease (coronary heart disease, stroke, venous thromboembolism) |
| **Bone health:** | Variable bone density yet consistently more fractures, owing in part to falls associated with central obesity, diabetes complications and poor health in general |
| **Cognitive function:** | More likely to develop dementia (Alzheimer’s and vascular) |
| **Cancer:** | Higher incidence of breast and endometrial cancer Poorer prognosis after breast or endometrial cancer diagnosis |
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 post-menopausal 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 β-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 post-menopause 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 (Shaptes & 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. (Shaptes & 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 aging 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)A1c level. The HbA1c 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). HbA1c 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 HbA1c 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 ≥ 30 (Chlebowski et al., 2003). Yet in a re-analysis of most observational studies before 1997, the overall excess risk of breast cancer – ie, 35% after ≥ 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 ≥ 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/m² 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 vs 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 (EMEA 2003), the presence of disturbing menopausal symptoms with an adverse impact on the quality of life constitutes the only valid indication for HT. The EMEA 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, contra-indications (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
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-Barbash 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-Barbash 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 (≤ 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 ≥ 30 ng/ml (≥ 75 nmol/L) for optimal bone health and muscle function and, potentially, as a boost to natural immunity against microbial pathogens, auto-antigens 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 metaphyseal 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 bisphosphate 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.

References

Aiello EJ, Yasui Y, Tworoger SS, Ulrich CM, Irwin ML, Bowen D, Schwartz RS, Kumai C, Potter JD, McTiernan A. Effect of a yearlong, moderate-intensity exercise intervention on the occurrence and severity of menopause symptoms in postmenopausal women. Menopause. 2004;11(4):382-8.
Andersson B, Johansson G, Holm G, Bengtsson B-A, Sashegy A, Pavo I, Mason T, Anderson PW. Raloxifene does not affect insulin sensitivity or glycemic control in postmenopausal women with type 2 diabetes mellitus: a randomized clinical trial. J Clin Endocrinol Metab. 2002;87(1):122-8.
Andersson B, Mattson L-A, Hahn L, Marin P, Lapidus L, Holm G, Bengtsson B-A, Bjørntorp P. Estrogen replacement therapy decreases hyperandrogenicity and improves glucose homeostasis and plasma lipids in postmenopausal women with noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab. 1997;82(2):638-43.
Ballard-Barbasch R, Humsberger S, Alciati MH, Blair SN, Goodwin PJ, McTiernan A, Wing R, Schatzkin A. Physical activity, weight control, and breast cancer risk and survival: clinical trial rationale and design considerations. J Natl Cancer Inst. 2009;101(9):630-43.
Barone BB, Yeh H-C, Snyder CF, Pears KS, Stein KB, Derr RL, Wolff AC, Brancati FL. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA. 2008;300(23):2754-64.
Bischoff-Ferrari HA, Kiel DP, Dawson-Hughes B, Orav JE, Li R, Spiegelman D, Dietrich T, Willett WC. Dietary calcium and serum 25-hydroxyvitamin D status in relation to BMD among U.S. adults. J Bone Miner Res. 2009;24(5):935-42.
Blouin K, Nadeau M, Mailloux J, Daris M, Lebel S, Luu-The V, Tchernof A. Pathways of adipose tissue androgen metabolism in women: depot differences and modulation by adipogenesis. Am J Physiol Endocrinol Metab. 2009;296(1):E244-55.
Bonds DE, Larson JE, Schwartz AV, Strotmeyer ES, Robbins J, Rodriguez BL, Johnson KC, Margolis KL. Risk of fracture in women with type 2 diabetes: the Women’s Health Initiative observational study. J Clin Endocrinol Metab. 2006;91(9):3404-10.
Bonds DE, Lasser N, Qi L, Brzyzki R, Caan B, Heiss G, Limacher MC, Liu JH, Mason E, Oberman A, et al. The effect of conjugated equine oestrogen on diabetes incidence: the Women's Health Initiative randomised trial. Diabetologia. 2006a;49:459-68.

Brussaard HE, Gevers-Leuven JA, Fröhlich M, Klut C, Krans HM. Short-term oestrogen replacement therapy improves insulin resistance, lipids and fibrinolysis in postmenopausal women with NIDDM. Diabetologia. 1997;40:843-9.

Caan B, Neuhouser M, Aragaki A, Lewis CB, Gass M, Lane D, Rodabough RJ, Gilligan MA, Cyr MG, Thomas CA, et al. Influence of estrogen plus progesterin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. JAMA. 2003;289(24):3243-53.

Cirillo DJ, Wallace RB, Rodabough RJ, Greenland P, LaCroix AZ, Limacher MC, Larson JC, Effect of estrogen therapy on gallbladder disease. JAMA. 2005;293(3):330-9.

Cleary MP, Grossman ME. Minireview: obesity and breast cancer. Breast Cancer Research. 2002;25(10):1675-80.

Crespo CJ, Smit E, Snelling P-Y, Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ. 2008;336:1227-31.

Celi FS. Brown adipose tissue: when it pays to be insufficient. N Engl J Med. 2009;360(15):1553-6 (Editorial).

Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, Rodabough RJ, Gilligan MA, Cyr MG, Thomas CA, et al. Influence of estrogen plus progesterin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. JAMA. 2003;289(24):3243-53.

Cirillo DJ, Wallace RB, Rodabough RJ, Greenland P, LaCroix AZ, Limacher MC, Larson JC, Effect of estrogen therapy on gallbladder disease. JAMA. 2005;293(3):330-9.

Cleary MP, Grossman ME. Minireview: obesity and breast cancer. Breast Cancer Research. 2002;25(10):1675-80.

Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52705 women with breast cancer and 108411 women without breast cancer. Lancet. 1997;350:1047-59.

Craft S. The role of metabolic disorders in Alzheimer disease and vascular dementia: two roads converged. Arch Neurol. 2009;66(3):300-5.

Crespo CJ, Smit E, Snelling A, Sempois CT, Andersen RE. Hormone replacement therapy and its relationship to lipid and glucose metabolism in diabetic and nondiabetic postmenopausal women: results from the Third National Health and Nutrition Examination Survey (NHANES III). Diabetes Care. 2002;25(10):1675-80.

Cushman M, Kuller LH, Prentice R, Rodabough RJ, Psaty BM, Stafford RS, Sidney S, Rosendaal FR, Estrogen plus progesterin and risk of venous thrombosis. JAMA. 2004;292(13):1573-80.

Danielson KK, Elliott ME, LeCaire T, Binkley N, Palta M. Poor glycemic control is associated with low BMD detected in premenopausal women with type 1 diabetes. Osteoporos Int. 2009;20(6):923-33.

Derby CA, Crawford SL, Pasternak RC, Sowers MF, Sternfeld B, Matthews KA. Lipid changes during the menopause transition in relation to age and weight: the Study of Women's Health Across the Nation. Am J Epidemiol. 2009;169(11):1352-61.

Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393-403.

Ding EL, Song Y, Malik VS, Liu S. Differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2006;295(11):1288-99.

Ding EL, Song Y, Manson JE, Rifai N, Buring JE, Liu S. Plasma sex hormones and risk of developing type 2 diabetes in women: a prospective study. Diabetologia. 2007;50:2076-84.

Dorman JS, Steenkiste AR, Foley TP, Strotmeyer ES, Burke JP, Kuller LH, Kwoh CK. Menopause in type 1 diabetic women: is it premature? Diabetes. 2001;50(8):1857-62.

Dratva J, Real FG, Schindler C, Ackerman-Liebrich U, Gerbase MW, Probst-Hensch NM, Svanes C, Omenaas ER, Neukirch F, Wijst M, et al. Is age at menopause increasing across Europe? Results on age at menopause and determinants from two population-based studies. Menopause. 2009;16(2):385-94.

Dabuisson JT, Wagenknecht LE, D’Agostino RB, Haffner SM, Rewers M, Saad ME, Laws A, Herrington DM. Association of hormone replacement therapy and carotid wall thickness in women with and without diabetes. Diabetes Care. 1998;21(11):1790-6.

Eilassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. JAMA. 2006;296(2):193-201.

EMEA public statement on recent publications regarding hormone replacement therapy. Issued on 3 December 2003 (EMEA/33065/03). Access: http://www.emea.eu.int

Espeland MA, Hogan PE, Fineberg SE, Howard G, Schrott H, Waclawiw MA, Bush TL. Effect of postmenopausal hormone therapy on glucose and insulin concentrations. Diabetes Care. 1998;21(10):1589-95.

Espeland MA, Stefanick ML, Kritz-Silverstein D, Fineberg SE, Waclawiw MA, James MK, Greendale GA. Effect of postmenopausal hormone therapy on body weight and waist and hip girths. J Clin Endocrinol Metab. 1997;82(5):1549-56.

Fenkci S, Fenkci V, Yilmazer M, Serteser M, Koken T. Effects of short-term transdermal hormone replacement therapy on glycaemic control, lipid metabolism, C-reactive protein and proteinuria in postmenopausal women with type 2 diabetes and hypertension. Hum Reprod. 2003;18(4):866-70.

Ferrara A, Barrett-Conner E, Wingard DL, Edelstein SL. Sex differences in insulin levels in older adults and the effect of body size, estrogen replacement therapy, and glucose tolerance status: the Rancho Bernardo Study, 1984-1987. Diabetes Care. 1995;18(2):220-5.

Ferrara A, Quesenberry CP, Karter AJ, Njoroge CW, Jacobson AS, Selby JV. Current use of unopposed estrogen and estrogen plus progesterin and the risk of acute myocardial infarction among women with diabetes: the Northern California Kaiser Permanente Diabetes Registry, 1995-1998. Circulation. 2003;107(1):43-8.

Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O’Meara ES, Longstreth WT, Luchsinger JA. Midlife and late-life obesity and the risk of dementia: Cardiovascular Health Study. Arch Neurol. 2009;66(3):336-42.

Freedman RR, Krell W. Reduced thermoregulatory null zone in postmenopausal women and women with hot flashes. Am J Obstet Gynecol. 1999;181(11):1667-70.

Friberg E, Mantzoros CS, Wolk A. Diabetes and risk of endometrial cancer: a population-based prospective cohort study. Cancer Epidemiol Biomarkers Prev. 2007;16(2):276-80.

Friday KE, Dong C, Fontenot RU. Conjugated equine estrogen improves glycemic control and blood lipoproteins in postmenopausal women with type 2 diabetes. J Clin Endocrinol Metab. 2001;86(1):48-52.

Gold EB, Bromberger J, Crawford S, Samuels S, Greendale GA, Harlow SD, Skurnick J. Factors associated with age at natural menopause in a multiethnic sample of midlife women. Am J Obstet Gynecol. 1999;181(11):1667-70.

Gunter MJ, Hoover DR, Yu H, Wassertbeit-Smoller S, Rohan TE, Manson JE, Li J, Ho GY, Xue X, Anderson GL,
et al. Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. J Natl Cancer Inst. 2009;101(1): 48-60.

Hadjidi S, Gourdy P, Zaoui P, Guerci B, Roudaut N, Gautier JF, Chabin M, Maucou G, Ragot S. Effect of raloxifene – a selective oestrogen receptor modulator- on kidney function in post-menopausal women with Type 2 diabetes: results from a randomized, placebo-controlled trial. Diabetic Med. 2007; 24:906-10.

Hendrix SL, Cochrane BB, Nygaard IE, Handa VL, Barnabei VM, Iglesias C, Aragaki A, Naughton MJ, Wallace RB, McNeely SG. Effects of estrogen with and without progesterin on urinary incontinence. JAMA. 2005; 293(8):935-48.

Hjartåker A, Langseth H, Weiderpass E. Obesity and diabetes epidemics: cancer repercussions. Adv Exp Biol Med. 2008;630(7):72-93.

Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3): 266-81.

Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, Bassford T, Beresford SA, Black HR, Blanchette P, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354(7):69-83.

Janssen I, Powell LH, Crawford S, Lasley B, Sutton-Tyrrell K. Theeffect of alendronate on bone mineral density and biochemical markers of bone turnover in type 2 diabetic women: the Fracture Intervention Trial. Diabetes Care. 2004;27(7):1547-53.

Keegan TH, Schwartz AV, Baur DC, Sellmeyer DE, Kelsey JL. Analysis of factors affecting increase in bone mineral density at lumbar spine by bisphosphonate treatment in post-menopausal osteoporosis. J Bone Miner Metab. 2009;27(1): 76-82.

Lasserson J, Kollerup G, Quaade F, Sørensen OH. Bone mineral changes in obese women during a moderate weight loss with and without calcium supplementation. J Bone Miner Res. 2001; 16(1):141-7.

Kaji H, Hisa I, Inoue Y, Naito J, Sugimoto T, Kasuga M. Analysis of factors affecting increase in bone mineral density at lumbar spine by bisphosphonate treatment in post-menopausal osteoporosis. J Bone Miner Metab. 2009;27(1): 76-82.

Keegan TH, Schwartz AV, Baur DC, Sellmeyer DE, Kelsey JL. Effect of alendronate on bone mineral density and biochemical markers of bone turnover in type 2 diabetic women: the Fracture Intervention Trial. Diabetes Care. 2004;27(7):1547-53.

Kernohan AF, Sattar N, Hilditch T, Cleland SJ, Small M, Lumsden MA, Connell JM, Petrie JR. Effects of low-dose continuous combined hormone replacement therapy on glucose homeostasis and markers of cardiovascular risk in women with type 2 diabetes. Clin Endocrinol (Oxf). 2007; 66(1):27-34.

Khamaisa M, Regev N, Yarom N, Avni B, Leitersdorf E, Raz I, Eldad S. Possible association between diabetes and bisphosphonates-related jaw osteonecrosis. J Clin endocrinol Metab. 2007;92(5):1172-5.

Kloppenborg RP, van den Berg E, Kappelle LJ, Biessels GJ, Arky RA, Rosner B, Hennemehns CH, Speizer FE, Stampfer MJ. A prospective study of postmenopausal estrogen therapy and subsequent incidence of non-insulin-dependent diabetes mellitus. Ann Epidemiol. 1992;2(5):657-64.

Lee CG, Carr MC, Murdoch SJ, Mitchell E, Woods NF, Wener MH, Chandler WL, Boyko EJ, Brunzell JD. Adipokines, inflammation, and visceral adiposity across the metabolic transition: a prospective study. J Clin Endocrinol Metab. 2009;94(4):1104-10.

Løkkegaard E, Pedersen AT, Heitmann BL, Jovanovic Z, Keiding N, Hundtup YA, Obel EB, Ottesen B. Relation between hormone replacement therapy and ischaemic heart disease in women: prospective observational study. BMJ. 2003;326:426-30.

Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes. 2008;32:949-58.

Lucky e, Kagan R, Greenspan S, Bone H, Kiel RD, Simon J, Sackarowitz J, Palmisano J, Chen E, Petruschke RA, et al. Once-weekly alendronate 70 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis. Menopause. 2004;11(4):405-15.

Macedon MH, Mavroiedi A, Barr RJ, Fraser WD, Reid DM. Vitamin D status in postmenopausal women living at higher latitudes in the UK in relation to bone health, overweight, sunlight exposure and dietary vitamin D. Bone. 2008;42(5): 99-103.

Maddalozzo GF, Widrick JJ, Cardinal BJ, Winters-Stone KM, Hoffman MA, Snow CM. The effects of hormone replacement therapy and resistance training on spine bone mineral density in early postmenopausal women. Bone. 2007:40: 1244-51.

Maggio M, Lauratuni F, Ceda GP, Bandinelli S, Basaria S, Paoliolo G, Ble A, Egan JM, Metter EJ, Abbatocoma AL, et al. Association of hormonal dysregulation with metabolic syndrome in older women: data from the InCHIANTI study. J Am Physiol Endocrinol Metab. 2007;292(1):E353-8.

Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, Trevisan M, Black HR, Heckbert SR, Detrano R, et al. Estrogen plus progesterin and the risk of coronary heart disease. N Engl J Med. 2003;349(6):523-34.

Manson JE, Rimm EB, Colditz GA, Willett WC, Nathan DM, Arky RA, Rosner B, Hennekens CH, Speizer FE, Stampfer MJ. A prospective study of postmenopausal estrogen therapy and subsequent incidence of non-insulin-dependent diabetes mellitus. Ann Epidemiol. 1992;2(5):657-64.

Margolis KL, Bonds DE, Rodabough RJ, Tinker L, Phillips LS, Allen C, Bassford T, Burke G, Torrens J, Howard BV, et al. Effect of estrogen plus progesterin on the incidence of diabetes in postmenopausal women: results from the Women’s Health Initiative Hormone Trial. Diabetologia. 2004;47: 1175-87.

McKenzie J, Fisher BM, Jaap AJ, Stanley A, Paterson K, Sattar N. Effects of HRT on liver enzyme levels in women with type 2 diabetes: a randomized placebo-controlled trial. Clin Endocrinol (Oxf). 2006;65(1):40-4.

McKenzie J, Jaap AJ, Gallacher S, Kelly A, Crawford L, Greer IA, Rumlay A, Petrie JR, Lowe GD, Paterson K, et al. Metabolic, inflammatory and haemostatic effects of a low-dose continuous combined HRT in women with type 2 diabetes: potentially safer with respect to vascular risk? Clin Endocrinol (Oxf). 2003;59:682-9.

Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. Arch Intern Med. 2009;169(7):659-69.

Million Women Study Collaborators. Breast cancer and hormone replacement therapy in the Million Women Study. Lancet. 2003;362:419-27.

Nagamani M, Stuart CA. Specific binding and growth-promoting activity of insulin in endometrial cancer cells in culture. Am J Obstet Gynecol. 1998;179(1):6-12.

Napoli N, Thompson J, Civitelli R, Armamento-Villareal RC. Effects of dietary calcium compared with calcium supplements on estrogen metabolism and bone mineral density. Am J Clin Nutr. 2007;85(5):1428-33.

MENOPAUSE CARE FOR OBESE AND DIABETIC WOMEN — VERHAEGHE
Nilsson M, Johnson R, Ye W, Hveem K, Lagergren J. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. JAMA. 2003;290(1):66-72.

Patel A, Joshi R, de Galan B. Trials of cardiovascular risk factor management in type 2 diabetes. Curr Opinion Cardiol. 2009;24(in press)

Perera M, Sattar N, Petrie JR, Hillier C, Small M, Connell JM, Lowe GD, Lumsden M-A. The effects of transdermal estradiol in combination with oral norethisterone on lipoproteins, coagulation, and endothelial markers in post-menopausal women with type 2 diabetes: a randomized, placebo-controlled trial. J Clin Endocrinol Metab. 2001;86(3):1140-3.

Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, van der Schouw YT, Spencer E, Moons KG, Tjonneland A, et al. General and abdominal adiposity and risk of death in Europe. N Engl J Med. 2008;359(20):2105-20.

Prelecic GM, Beljic T, Balint-Peric L, Ginsburg J. Metabolic effects of tibolone in postmenopausal women with non-insulin dependent diabetes. Maturitas 1998;28:271-6.

Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009;373:1083-96.

Puuronen J, Piltonen T, Jaakola P, Ruokonen A, Morin-Papunen L, Tapanainen JS. Adrenal androgen production capacity remains high up to menopause in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2009;94(6):1973-8.

Rapp SR, Espeland MA, Shumaker SA, Henderson VW, Brunner RL, Manson JE, Gass ML, Stefanick ML, Lane DS, Hays J, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women. The Women's Health Initiative Memory Study: a randomized controlled trial. JAMA. 2003;289(20):2663-72.

Ravn P, Cizza G, Bjarnason NH, Thompson D, Daley M, Wasnich RD, McClung M, Hosking D, Yates AJ, Christiansen C. Low body mass index is an important risk factor for low bone mass and increased bone loss in early post-menopausal women. J Bone Miner Res. 1999;14(9):1622-7.

Riedt CS, Cifaiuotes M, Stahl T, Chowdhury HA, Schlussel y, Letine RL, V & V In OBGyn nilsson M, Johnson R, ye W, Hveem K, Lagergren J. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. JAMA. 2003;290(1):66-72.

Shapses SA, Riedt CS. Bone, body weight, and weight reduction: what are the concerns? J Nutr. 2006;136:1453-6.

Sowers MF, Zheng H, Tomey K, Karvonen-Gutierrez C, Jannausch M, Li X, Yosef M, Symons J. Changes in body composition in women over six years in midlife: ovarian and chronological aging. J Clin Endocrinol Metab. 2007;92(3):895-901.

Sprague BL, Trentham-Dietz A, Egan KM, Titus-Ernstoff L, Hampton JM, Newcomb PA. Proportion of invasive breast cancer attributable to risk factors modifiable after menopause. Am J Epidemiol. 2008;168(4):404-11.

Sternfeld B, Wang H, Quesenberry CP, Abrams B, Everson-Rose SA, Greendale GA, Matthews KA, Torrens JI, Sowers MF. Physical activity and changes in weight and waist circumference in midlife women: findings from the Study of Women's Health Across the Nation. Am J Epidemiol. 2004;160(9):912-22.

Stoney RM, Walker KZ, Best JD, Ireland PD, Giles GG, O’Dea K. Do postmenopausal women with NIDDM have a reduced acapacity to deposit and conserve lower-body fat? Diabetes Care. 1998;21(5):828-30.

Subak LL, Wing R, West DS, Franklin F, Vittinghoff E, Creasman JM, Richter HE, Myers D, Burgio KL, Gorin AA, et al. Weight loss to treat urinary incontinence in overweight and obese women. N Engl J Med. 2009;360(5):481-90.

The Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in post-menopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst. 2002;94(8):606-16.

The Look AHEAD research group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the Look AHEAD trial. Diabetes Care. 2007;30(6):1374-83.

Thurston RC, Sowers MF, Sutton-Tyrrell K, Everson-Rose SA, Lewis TT, Edmundowicz D, Matthews KA. Abdominal adiposity and hot flashes among midlife women. Menopause. 2008;15(3):429-34.

Verhaeghe J, Bouillon R. Effects of diabetes and insulin on bone physiology. In: Principles of Bone Biology (ed. Bilezikian J.), 3rd Edition, 2008, pp 983-99. Academic Press, San Diego, CA, USA.

Visekruna M, Wilson D, McKierman FE. Severely suppressed bone turnover and atypical skeletal fragility. J Clin Endocrinol Metab. 2008;93(8):2948-52.

Wadden TA, West DS, Neiberg RH, Wing RR, Ryan DH, Johnson KC, Foreyt JP, Hill JO, Trence DL, Vitolins MZ. One-year weight losses in the Look AHEAD trial. Diabetes Care. 2007;30(6):1374-83.

Wassertheil-Smoller S, Hendrix SL, Limacher M, Heiss G, Johnson KC, Foreyt JP, Hill JO, Trence DL, Vitolins MZ. One-year weight losses in the Look AHEAD Study: factors associated with success. Obesity. 2009;17(4):713-21.

Wassertheil-Smoller S, Hendrix SL, Limacher M, Heiss G, Kooperberg C, Baird A, Kotchen J, Curb JD, Black H, Rossouw JE, et al. Effect of estrogen plus progestin on stroke in postmenopausal women. The Women’s Health Initiative: a randomized trial. JAMA. 2003;289(20):2673-84.