Impact of Oestrogen Therapy on Diabetes and Vascular Risk

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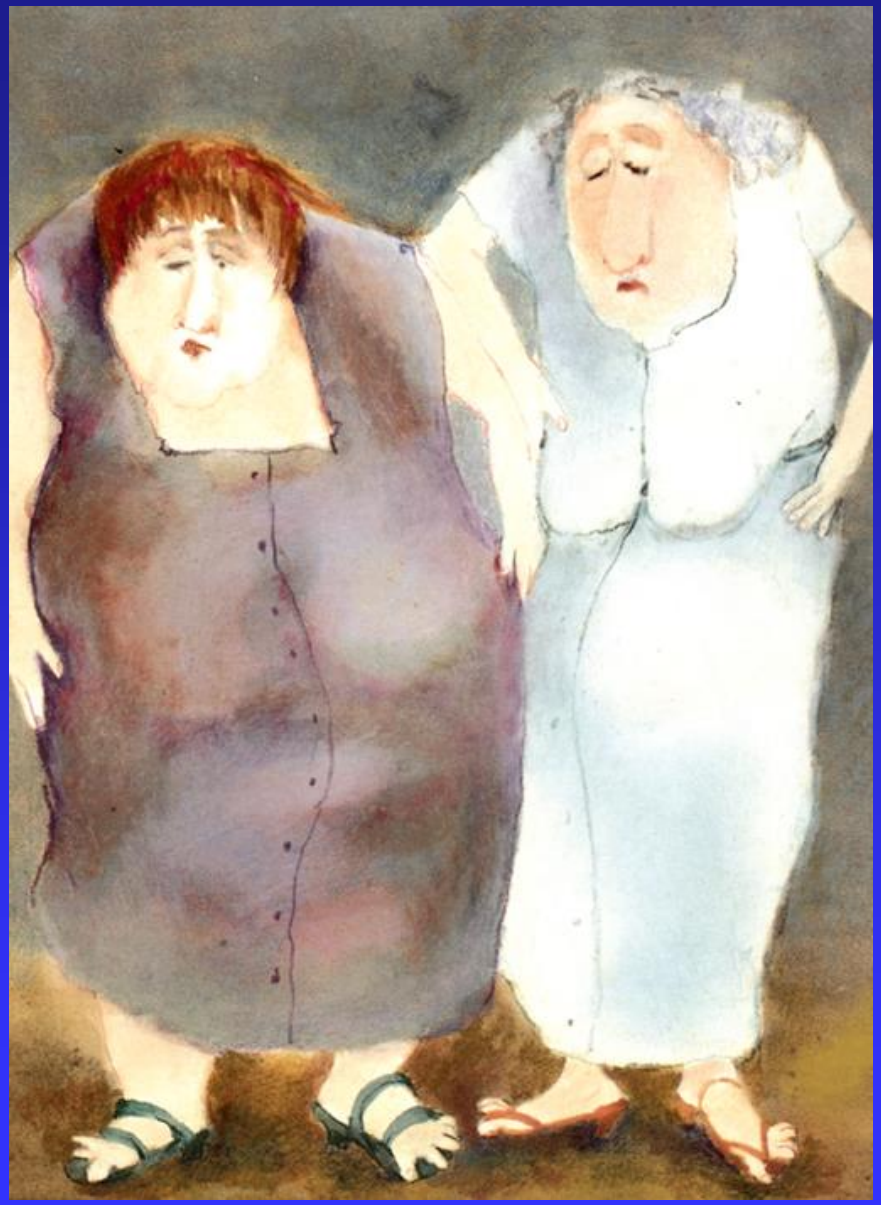
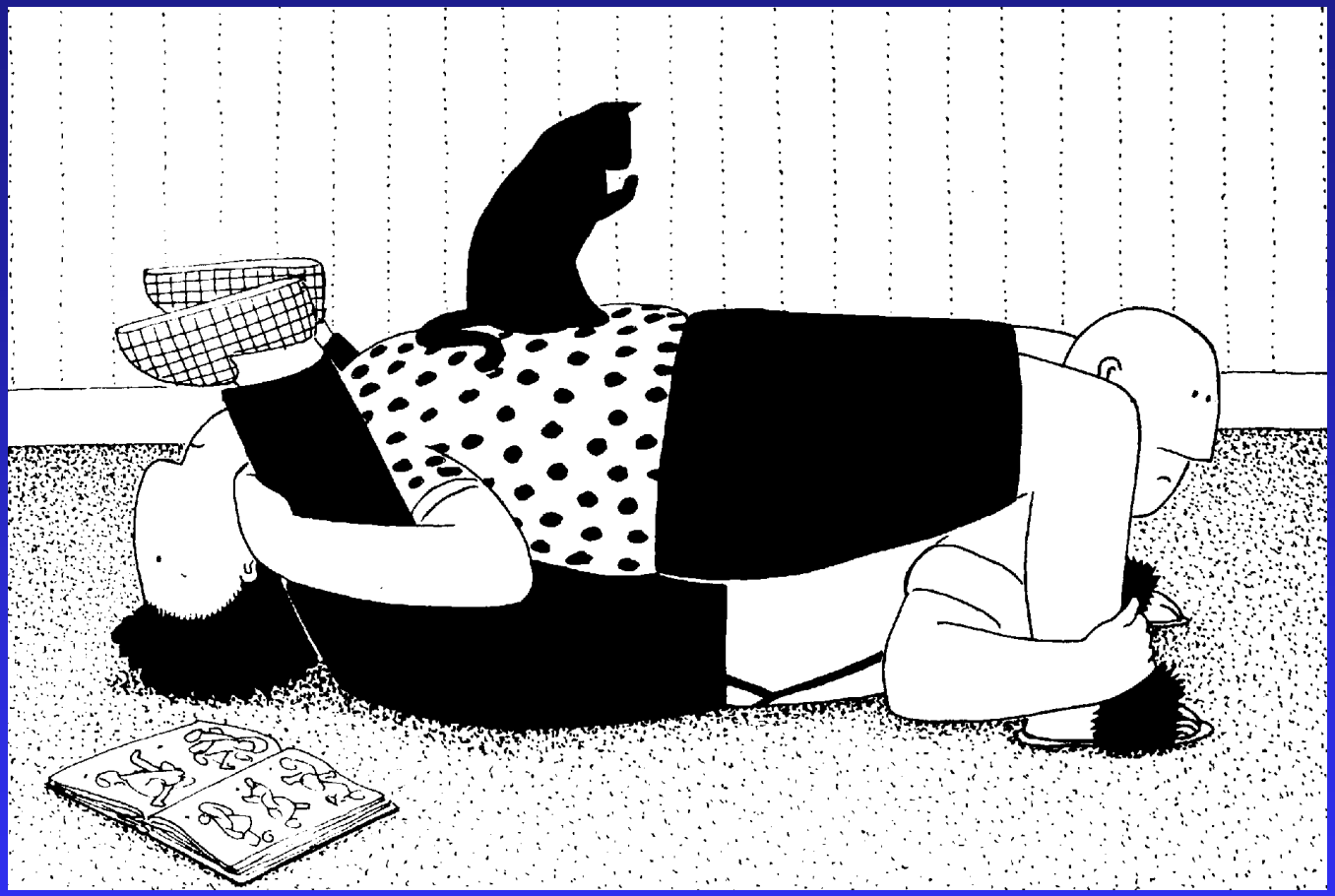
- Diabetes, menopause and HRT
- Diabetes and oral contraceptives

- Life expectancy has increased significantly
- Women spend 30 years (40% of active life) in the post menopausal state
- Diabetes most common chronic disease and is increasing
- 90% NIDDM, which is most common in obese individuals over 40 years

- **The menopause is a physiological process**
- **The consequence of ovarian failure can reduce quality of life**





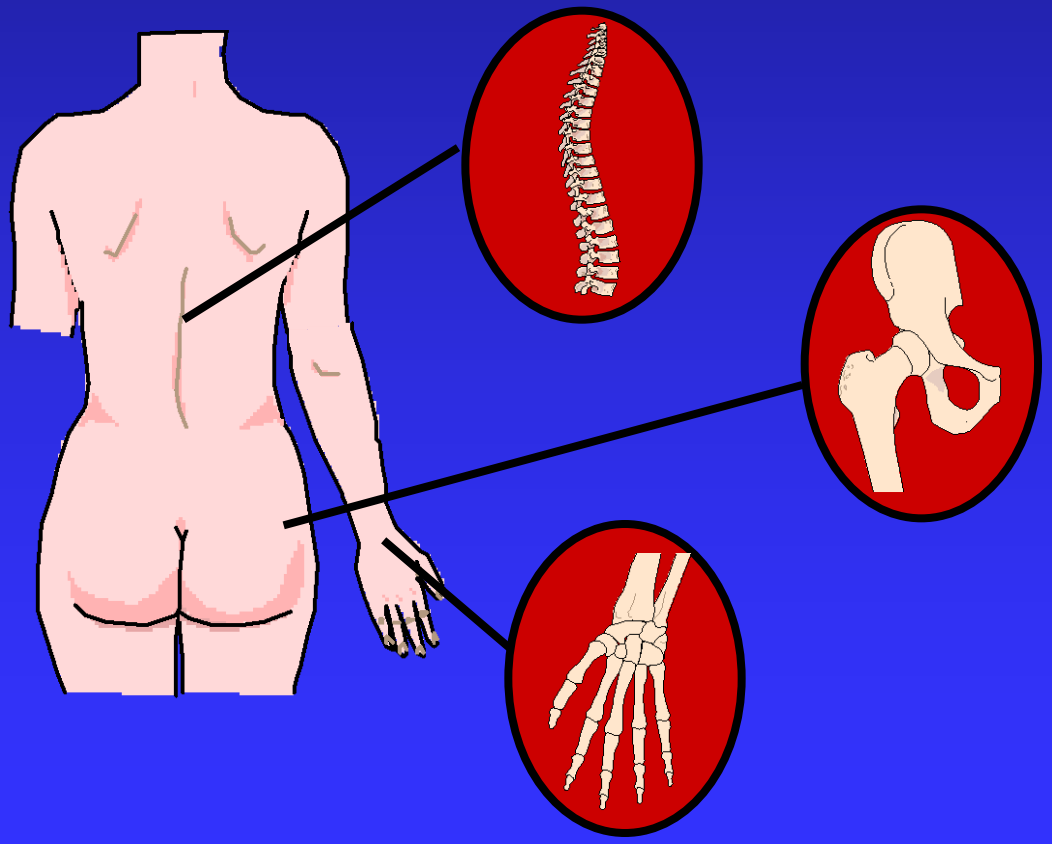
Sexual Dysfunction ?

Osteoporosis

Definition

'…… a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with consequent increase in bone fragility and susceptibility to fracture'

Common sites of fracture



- Menopause results in various metabolic changes that increase the CVD risk
- These include adverse changes in lipids and lipoproteins, and in glucose and insulin metabolism
- Diabetes major risk factor for CVD
- Women with diabetes are at a greater risk of CVD than men with diabetes
- Rate of CVD increase after menopause in women with diabetes

Gordon et al 1978
Pan et al 1986
Barrett-Connor et al 1991

Menopause & Metabolic Risk Factors for CVD

- Close association between menopause and chronological age
- Premature menopause results in the premature development of CVD
- Relative increase in androgenicity after menopause

Menopause & Lipids

- ↑ Cholesterol
- ↑ Triglycerides
- ↑ LDL
- ↓ HDL & HDL_2
- ↑ Lipoprotein (a)

Stevenson 2004

Menopause & Glucose & Insulin Metabolism

- Age related effects but changes in insulin metabolism at menopause
- ⇩ pancreatic insulin secretion and insulin elimination
- No immediate change in insulin resistance but an increase in IR with time
- No change in fasting blood glucose levels at menopause
- Post menopausal women become increasingly insulin resistant

Matthews et al 1989, Proudler et al 1992, Walton et al 1993, Toth et al 2000

Menopause, Body Fat & Haemostasis

- Overall ↑ in body fat and redistribution to male pattern
- ↑ in fibrinogen, factor VII and plasminogen activator inhibitor-1

Can HRT Reverse These Changes ?

HRT & Lipids

- Oestrogen lowers total cholesterol, largely due to a decrease in LDL
- Oral oestrogen increases HDL, particularly HDL_2
- Transdermal oestradiol has less effect on HDL but does increase HDL_2 and decrease HDL_3
- Type and route of administration of oestrogen determines its effect on triglycerides
- Progestogens have differing effects depending on androgenicity and dosage

PEPI Study - Fineberg 2000
HERS Study - Kanaya et al 2003
WHI Study - Rossouw 2004

HRT & Lipids

- WHI (combined arm) reported reductions in LDL of -12.7%, increase in HDL of 7.3% and triglyceride of 6.9%
- The oestrogen only arm reported reductions in LDL of -13.7%, increase in HDL of 15.1% and triglyceride of 25%

HRT, Lipids & Diabetes

- Triglyceride decreased by 22% by transdermal E2 and oral norethisterone compared to placebo in NIDDM *(Perera et al 2001)*
- Lipid profiles better overall in diabetic and non diabetic women on HRT than those who are not on HRT *(Crespo et al 2002)*
- No adverse effects on lipid profile in women with diabetes of transdermal E2

  (Araujo et al 2002, Fenkci et al 2003)

HRT, Glucose & Insulin

- Oral administration of 17ß-oestradiol brings changes in glucose concentrations suggestive of an improvement in insulin resistance *(Spencer et al 2000)*
- Transdermal E2 has neutral effects *(Spencer et al 2000)*
- Ethinyl oestradiol and CEE may raise insulin levels and impair glucose tolerance *(Spellacy et al 1972)*
- Progestogen effect varies

HRT, Glycaemic Control & Diabetes

- Cohort study of 15,435 women with NIDDM found that HRT users had a lower HbA_{1c} level

  (Ferrara et al 2001)

- Diabetic HRT users found to have better glycaemic control than non users *(Crespo et al 2002)*

- HRT found to reduce central adiposty, improve glycaemic control and physical functioning in women with diabetes *(Samaras et al 1999, Friday 2001)*

HRT & Vascular Function

- Oestrogen has many biological effects that are compatible with a beneficial effect on CVD risk.
  - Improved vascular reactivity and endothelial function
  - Vasodilation by stimulation of nitrous oxide in normal and diseased vessels
  - Atheroma formation decreased in monkeys

Does HRT Prevent or Cause CVD

- Observational studies suggest a 30-50% reduction in CVD amongst HRT users
- A meta-analysis of observational studies found a relative risk of CVD of 0.8 in women taking HRT compared with controls

(Beral et al 2002)

Does HRT Prevent or Cause CVD

HERS Study

- No benefit of CEE 0.625mg + MPA 2.5mg a day over placebo in women with established CVD
- 20% of patient in study had diabetes
- Initial risk of thrombotic events outweighed any potential benefits

Does HRT Prevent or Cause CVD

WHI Study

- ↑ risk of CVD seen in combined arm compared to placebo (HR 1.29, 1.02-1.63)
- Trend suggested elevated risk in early follow up period
- No increase in risk in oestrogen only arm
- Among those aged 50-59 years the HR for CVD was 0.56 (0.3-1.03)

Mortality & HRT

HRT did not effect the risk of CVD or cancer mortality but reduced mortality from other causes (OR 0.67, 0.51-0.88)

Salpeter et al 2004

HRT & Stroke

- Incidence of stroke increased in both combined HRT group (HR .131) and oestrogen only group (HR 1.39) of WHI Study
- Recent meta-analysis found ↑ risk of stroke, particularly ischaemic stroke with current HRT use (total stroke OR 1.29, 1.13-1.47) *(Bath & Gray 2005)*
- Do not forget risk of thromboembolism

HRT, Diabetes & CVD

- Despite the improved lipid profiles of diabetic women on HRT there is no definite evidence of cardiovascular protection
- In diabetic women with no history of MI, use of HRT was associated with a reduced risk of MI but was associated with an increase risk of further MI in women with a recent history *(Ferrara et al 2003)*
- HRT has been reported as worsening atherosclerosis in women with abnormal glucose tolerance *(Howard et al 2004)*
- Other studies have not shown any CVD protection

HRT & The Incidence of NIDDM

- HERS Study found incidence of diabetes to be less in HRT group than placebo (9.5 v 6.2%)
- WHI Study found absolute reduction of I5 incident causes of treated diabetes per 10,000 women per year of treatment
- Transdermal E2 also reduced incidence of NIDDM in healthy population *(Rossi et al 2004)*

Summary

- HRT is effective for treatment of vasomotor symptoms and should not be denied to women with diabetes with no history of CVD, stroke, VTE or breast cancer
- Alternative treatment should be considered for women with major risk factors
- Adjunct cardioprotective treatments could be used in women with CVD risk factors who want to take HRT

Summary

- Route of administration of oestrogen and type of progestogen used should be considered carefully
- Transdermal oestrogen must be used in women with raised triglycerides
- A non-androgenic progestogen or transdermal norethisterone is preferable
- HRT could be beneficial in younger post menopausal diabetic women

Summary

- HRT is effective for prevention of osteoporosis and patients with Type 1 diabetes are at risk of oesteoporosis
- Any abnormal bleeding while on HRT should be investigated as diabetics have a higher incidence of endometrial carcinoma
- Treatment of any particular woman with menopausal symptoms should be considered individually

Oral Contraceptives & Diabetes

- Meta-analysis of literature suggests that current use of low dose OCs increases risk of cardiovascular arterial disease *(Brillargeon et al 2005)*
- 2nd generation OCs ↑ 1.9 fold risk of MI and 2.5 fold risk of ischaemic stroke
- 3rd generation OCs doubled risk of IS but no effect on MI
- Care in women already at risk of such events due to diabetes, metabolic syndrome or PCOS
- Consideration of use of 3rd generation OCs