

# WEIGHT GAIN AFTER THE MENOPAUSE — IS IT INEVITABLE?

*Obesity was classified as a chronic disease by the WHO in 1997 and many women do gain weight as they age.*



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Health has been defined as a state of physical, psychological, emotional and social well-being, not merely the absence of disease or infirmity.<sup>1</sup> This paradigm can also be applied to obesity since it was classified as a chronic disease by the World Health Organization (WHO) in 1997.<sup>2</sup> It is likely that by refocusing emphasis on treatment to improve health rather than prevent complications alone, a more effective intervention strategy for managing the menopausal state will emerge.

## EPIDEMIOLOGY OF OBESITY

It is estimated that 500 million people worldwide are obese (body mass index (BMI) above 30 – weight/height<sup>2</sup>) and that more than 1 billion are overweight (BMI above 25).<sup>2</sup> In the UK alone, over 30 000 deaths a year are caused by obesity. The NHANES survey demonstrated a very definitive rise in the prevalence of obesity in the USA across all ethnic groups since 1976 (Fig. 1a). In addition, it also demonstrated an age-related increase in obesity between 45 and 65 years (Fig. 1b).<sup>3</sup> The South African Demographic and Health Survey of 1998 indicated that 31% of men and 53.8% of women are overweight or obese.<sup>4</sup> In this study population, 9.7% of men and 41.6% of women had a waist circumference above 102 cm and 85 cm, respectively. These circumference cut-offs are now used to identify an increase in visceral fat and accumulation of

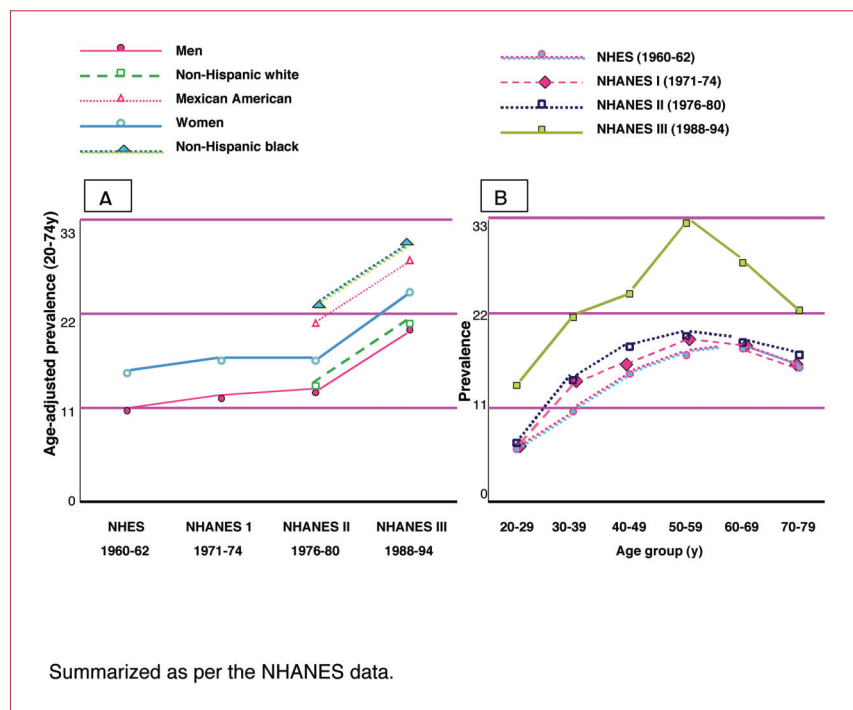


Fig. 1. The NHANES epidemiology survey.

abdominal obesity that is strongly linked to diseases of the metabolic syndrome.<sup>5</sup>

### OBESITY-RELATED CO-MORBID DISORDERS

These disorders include coronary heart disease or other atherosclerotic diseases, type 2 diabetes, sleep apnoea, gynaecological and reproductive abnormalities, osteoarthritis, gallbladder disease and cancer.<sup>6</sup> The metabolic syndrome is a multifaceted clinical disorder that is closely linked to obesity, and its diagnostic criteria are constantly being reassessed. Currently the ATP III classification of the National Cholesterol Education Programme is most frequently used<sup>7</sup> (Table I). The underlying pathogenesis and link between obesity and the multiple co-morbid diseases is complex and falls beyond the scope of this article.

Table I. **ATP III: Features of the metabolic syndrome**

#### Abdominal obesity

Waist circumference	
Men	> 102 cm
Women	> 88 cm
Elevated triglycerides	> 1.7 mmol
Low HDL cholesterol	
Men	< 0.9 mmol
Women	< 1.1 mmol
Raised blood pressure	> 130/ > 85 mmHg
Raised fasting glucose	> 6.1 mmol

### DETERMINANTS AND RISK FACTORS FOR OBESITY

The main determinants and risk factors for obesity include demographic, familial and personal factors, and have been summarised in Table II.

### IMPLICATIONS OF AGEING

The health implications of ageing are broad and will have an impact on physical, biological, hormonal and vascular factors. Frailty in the elderly

Table II. **Determinants of and risk factors for obesity**

#### Demographic factors

- Age
- Sex
- Race
- Socioeconomic circumstances
- Geography: Country of residence, urbanisation, industrialisation, migration

#### Personal factors

- Past or current overweight
- Age at onset of obesity
- Eating habits
- Physical inactivity/sedentary lifestyle
- Metabolic characteristics
- Cigarette smoking
- Psychological factors
- Pregnancy
- Concurrent illness or disability

#### Familial factors

- Heredity: Polygenes; single gene(s) with major effect
- Shared environments (cultural inheritance)
- Interaction between genetic susceptibility and environmental exposure

Epstein FH, Higgins M. In: Björntorp P, Brodoff BN, eds. *Obesity*. Philadelphia: Lippincott Company, 1992: 340.

has a strong physical correlation and as such there will be progressive muscle weakness, fatigue, inactivity, slow and unsteady gait and reduced endurance.<sup>8,9</sup> Apart from neurocognitive decline, biological factors are largely responsible for decreased physical conditioning (Table III). Of these, hormonal changes and changes in body composition are of specific relevance to the menopause.

The main decrease in energy expenditure in a patient aged 70 years compared with one of 25 years would be in the capacity for intense exercise, occupational energy expenditure, dietary-induced thermogenesis and a fall in basal metabolic rate. In addition, the cardiovascular capacity, even in a well-trained 60-year-old patient, will be diminished in relation to relative maximal aerobic power.<sup>10</sup> These changes, together with the above-mentioned physical and biological correlates, will have an impact on weight maintenance during the menopause.

### BODY MASS INDEX

Postmenopausal BMI will be strongly correlated to:<sup>11</sup>

- pre-menopausal BMI (a positive correlation)
- pre-menopausal level of physical activity (a negative correlation)
- ethnicity (Afro-American, Caucasian and Hispanic women appear more susceptible to postmenopausal weight gain, while Chinese and Japanese women appear to be relatively protected)
- surgical induction of the menopause (positive correlation)
- hormonal use (affords a relative protection with a 1 - 1.5 index less rise in BMI).

### SARCOPENIA

This translates from Greek as 'vanishing flesh'. Muscle is the greatest store of useable protein and will to a large degree determine the percentage basal metabolic rate and energy expenditure. From the age of 30

Table III. **Biological correlates****Elevations**

Blood levels of catabolic cytokines

- C-reactive protein
- Interleukin-6 (IL-6)

Hormones

- Cortisol production (especially postmenopausal women)

Markers of blood coagulation

- D-dimer
- Factor VIII

**Reductions**

Haemoglobin levels

- Normocytic subclinical anaemia

Hormones

- Growth hormone
  - Insulin-like growth factor-1 (IGF-1)
  - Testosterone (in men), oestrogen (in women)
  - Dihydroepiandrosterone (DHEA)
  - Oestradiol (E<sub>2</sub>)

Visceral proteins:

- Transferrin
- Retinol-binding protein
- Serum albumin

**Changes**

Body composition

- Sarcopenia
- Osteoporosis

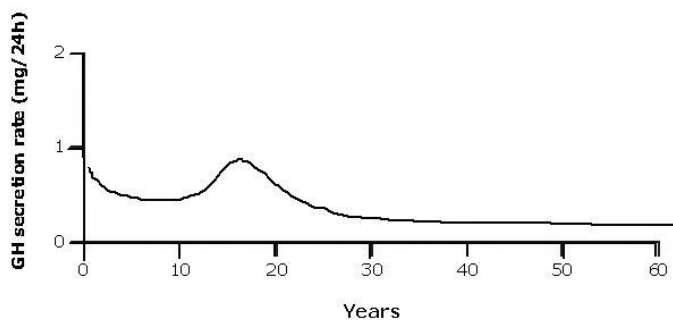
Van'tallie TB. *Metabolism* 2003; **52**: 22-26.<sup>8</sup>

- progressive resistance training (PRT) (muscle protein synthesis can be increased by 50% over 8 months with 3 half-hour sessions of PRT per week)
- growth hormone (GH) replacement
- oestrogen replacement with or without progesterone/norethisterone.<sup>15</sup>

With age, and in the absence of GH and hormone replacement therapy (HRT), muscle protein will be replaced by adipose tissue, leading to reduced physical ability and obesity, notably in the subcutaneous, abdominal and visceral areas.

**GROWTH HORMONE**

GH secretion is age dependent and peaks between 15 and 20 years, after which it decreases steadily (Fig. 2) GH increases the rate of protein synthesis, mobilises free fatty acid (FFA) from fat depots, decreases glucose uptake and oxidation, increases glyco-gen synthesis in muscle cells, increases bone turnover and causes sodium and water retention.<sup>16</sup> In 1998 the Growth Hormone Research Society defined GH deficiency (GHD) in adult life as a peak GH response of < 3 µg/l during an insulin tolerance test in patients with/without existing hypothalamic-pituitary disease. Serum insulin-like growth factor (IGF-1) values are a useful marker of adult GHD in patients with multiple pituitary hormone deficiencies.<sup>17</sup> Reduced lean body mass is an important feature of adult GHD and can typically be reduced by 7 - 8% compared with controls.<sup>18</sup> GHD will increase the percentage of body fat compared to muscle ratio and impair muscular performance. Physiological replacement of GH will reduce the percentage of body fat, decrease visceral adiposity, and improve lean and bone mass, exercise performance and cognitive function.<sup>19</sup> In addition it has a favourable effect on metabolism, with a reduced arterial intima media thickness, improved lipid profile and enhanced physiological activity.<sup>20</sup> A decrease in the percentage of body fat is particularly significant in the truncal (abdominal) area (Fig. 3).

**GH secretion is age-dependent**

Juul A, Jorgensen OL, eds. *Growth Hormone in Adults. Physiological and Clinical Aspects*. Cambridge: Cambridge University Press. 2001.<sup>16</sup>

Fig. 2. Growth hormone secretion is age-dependent.

years muscle mass will decrease at 3 - 6% per decade, leading to a considerable drop in energy expenditure.<sup>12,14</sup> At the time of the menopause, skeletal muscle loss increases 6-fold.<sup>13,14</sup> After a 60% decrease in muscle mass from baseline, additional functions, such as assistance in combating infection, will

cease to exist. Rapidly contracting muscle fibres will be lost first, leading to instability and slowing down of movement.<sup>13</sup> From the age of 60 years there will also be an element of nerve denervation and motor neuron death. Sarcopenia is largely reversible with:

- correct nutrition

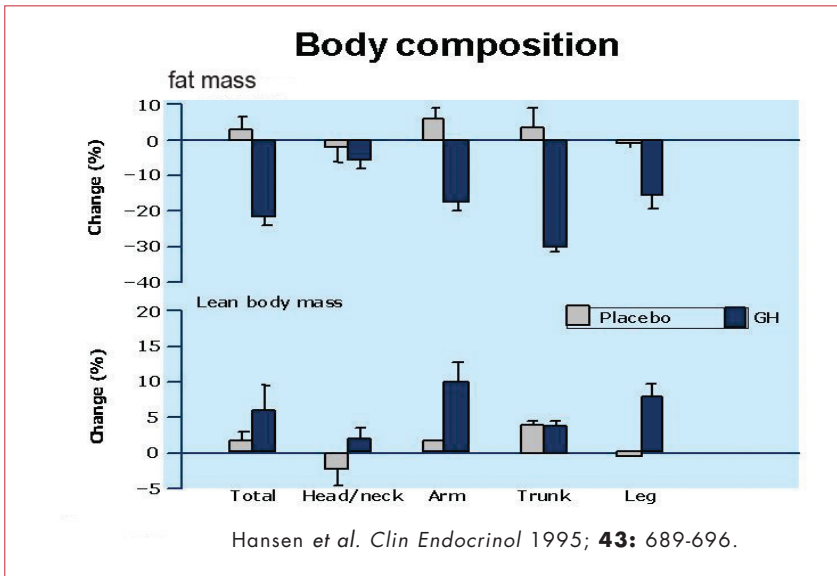


Fig. 3. Body composition.

**REPRODUCTIVE HORMONES AND HRT**

The changes in hormone secretion during the menopause are illustrated in Fig. 4.<sup>21</sup> There is loss of oestradiol and androstenedione production by the ovaries and a relative increase in ovarian secretion of testosterone (Table IV).<sup>21</sup> Adrenal secretion of

testosterone is decreased, and there is continuing adrenal secretion of androstenedione and an increased peripheral conversion of the latter steroid to oestrone. These changes will relate to an alteration in production rates between the pre- and post-menopausal state. Oestrogen replacement can reverse menopausal sarcopenia by increasing the release of GH

**EVIDENCE-BASED TRIALS**

A number of large trials have investigated the effect of HRT on weight, body composition and cardiovascular disease (CVD) risk status. The PEPI trial<sup>26</sup> concluded that the impact of HRT on weight was significant between 45 and 54 years, that the increase in waist-to-hip ratio associated with the menopause was reduced with HRT and that the overall CVD profile improved as a result of this. The difference of 3.5 kg in the first decade of HRT use, compared with controls, was mainly an oestrogen effect. The Danish Osteoporosis Prevention Study<sup>27</sup> investigated 2 000 women in a randomised trial for 5 years in early menopause. Weight gain in the HRT group was significantly less as a result of a lesser percentage fat increase and higher lean body mass. Weight gain in the control group was mainly due to a diminished capacity for physical activity and work.<sup>27</sup> The Postmenopausal Estrogen/Progestin Intervention Trial<sup>28</sup> prevented weight gain by 50% in the HRT group compared with the control group. Waist circumference and overall activity was superior in the HRT group. Smokers on oestrogen therapy lost a significant portion of the beneficial effects of HRT. A continuous 12-month oestrogen and progestin trial performed by Bolaji *et al.*<sup>29</sup> illustrated a protective effect in the gynoid to

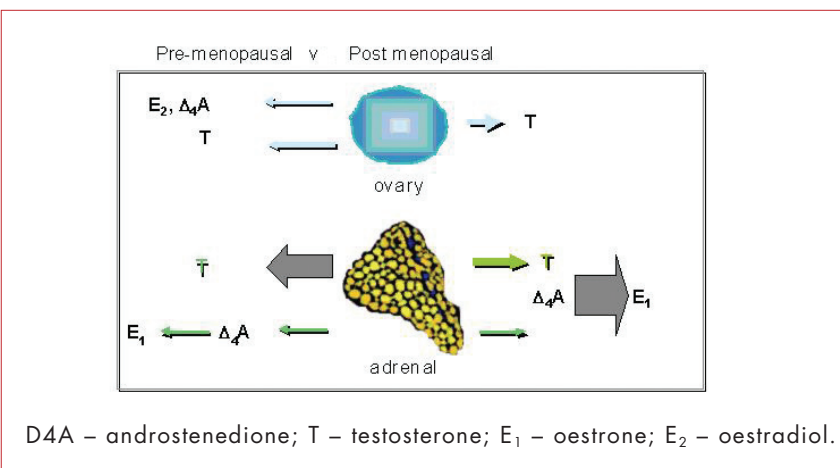


Fig. 4. Changes in hormone secretion at menopause.

Table IV. Representative reproductive hormone levels in women

Hormone	Pre-menopausal production rate	Postmenopausal production rate
Androstenedione	2.7 mg/d	16 mg/d
Testosterone	200 mg/d	150 mg/d
Oestrone	80 - 4 000 mg/d	55 mg/d
Oestradiol	50 - 500 mg/d	12 mg/d

*Oestrogen replacement can reverse menopausal sarcopenia by increasing the release of GH and IGF.*

*Weight gain in the menopause — is it likely? Physiologically the answer is yes. Is it inevitable? The answer is a clear no.*

*All women given HRT should be given a clear, non-sensationalist understanding of the risks and benefits of HRT.*

android fat distribution that occurs with the menopause.

To answer the question: Weight gain in the menopause — is it likely? Physiologically the answer is yes. Is it inevitable? The answer is a clear no, but each case must be judged individually, and HRT together with lifestyle modification will certainly benefit those at risk of weight gain, obesity and co-morbid diseases. As such, HRT should be viewed as an integral part of quality of life and maintenance of health as defined at the onset of this review.

### CONCLUSION

The risks and benefits of HRT have been extensively reviewed over the last 2 years.<sup>30-35</sup> Much has been said about the Women's Health Initiative

trial. No rational conclusions of overall metabolic risk can be based on this trial population as it was a high-risk population: the mean age was 67 and the mean BMI was 28.5 (overweight and 1.5 index points below frankly obese), 35% of the patients were on antihypertensive treatment, 4.4% were diabetic and 52.7% were previous or present smokers.<sup>36,37</sup> In 2004 the South African Menopause Society concluded that the overall risks of oestrogen and progestin therapy for the first 5 years after the menopause, and of oestrogen therapy alone for the first 10 years after the menopause, are very small.<sup>38</sup> All women given HRT should be given a clear, non-sensationalist understanding of the risks and benefits of HRT.

*References available on request.*

### IN A NUTSHELL

There is an age-related increase in obesity between the ages of 45 and 65 years.

The metabolic syndrome is a multifaceted clinical disorder that is closely linked to obesity and its diagnostic criteria are constantly being reassessed.

Hormonal changes and changes in body composition are of specific relevance to the menopause.

The main decrease in energy expenditure in a patient aged 70 years compared with a person aged 25 years would be in the capacity for intense exercise, occupational energy expenditure, dietary-induced thermogenesis and a drop in basal metabolic rate.

Postmenopausal BMI will be strongly related to:

- pre-menopausal BMI (a positive correlation)
- pre-menopausal level of physical activity (a negative correlation)

- ethnicity (Afro-American, Caucasian and Hispanic women appear more susceptible to postmenopausal weight gain, while Chinese and Japanese women appear relatively protected)
- surgical induction of menopause. (positive correlation)
- hormonal use (affords a relative protection with a 1 - 1.5 index less rise in BMI).

With age, and in the absence of GH and HRT, muscle protein will be replaced by adipose tissue leading to reduced physical ability and obesity, notably in the subcutaneous, abdominal and visceral areas.

In addition to having a favourable effect on lean body mass and bone mineral density, HRT with oestradiol with or without progesterone or norethisterone will also decrease percentage body fat with a favourable increase in the ratio of subcutaneous to visceral fat ratio in the abdominal ratio.

Weight gain is not inevitable in the menopause.

## SINGLE SUTURE

### PHYTO-OESTROGENS AND CARDIAC DISEASE

Dietary phyto-oestrogens (isoflavones and lignans – fruit, vegetables, nuts, and berries) are thought to lower the risk of cardiovascular disease, but a Dutch prospective study did not back this up. Researchers found no protective effect of higher intakes of low-dose phyto-oestrogens, although they suggested that smokers could put themselves in a better position with a higher intake of lignans. Stopping smoking would probably be far more effective.

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