

# The effects of diet on circulating sex hormone levels in men

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There is considerable epidemiological evidence that a Western-style diet may increase the risk of certain hormone-dependent conditions in men via its effects on hormone metabolism. Experimental evidence also suggests that dietary factors may exert subtle effects on hormone metabolism. Here we review the clinical and epidemiological evidence that diet is associated with circulating sex hormone levels in men. In comparison with factors such as age and BMI, nutrients do not appear to be strong determinants of sex hormone levels. Dietary intervention studies have not shown that a change in dietary fat and/or dietary fibre intake is associated with changes in circulating sex hormone concentrations over the short term. The data on the effects of dietary phyto-oestrogens on sex hormone levels in men are too limited for conclusions to be drawn. Observational studies between men from different dietary groups have shown that a vegan diet is associated with small but significant increases in sex-hormone-binding globulin and testosterone concentrations in comparison with meat-eaters. However, these studies have not demonstrated that variations in dietary composition have any long-term important effects on circulating bioavailable sex hormone levels in men. This lack of effect may be partly explained by the body's negative feedback mechanism, which balances out small changes in androgen metabolism in order to maintain a constant level of circulating bioavailable androgens. It appears, therefore, that future studies should look for dietary effects on the feedback mechanism itself, or on the metabolism of androgens within the target tissues.

## Diet: Sex hormones: Men

### Introduction

The effects of diet on circulating sex hormone levels are potentially of great importance for the prevention of hormone-related disease. Sex hormones influence the development of prostate cancer, now the commonest cancer in men in some Western countries (Parkin *et al.* 1992). Sex hormones also influence a variety of other conditions in men, such as infertility (Kaiser *et al.*

**Abbreviations:** A-diol-g, androstanediol glucuronide; DHT, dihydrotestosterone; FT, free testosterone; LH, leuteinising hormone; SHBG, sex-hormone-binding globulin.

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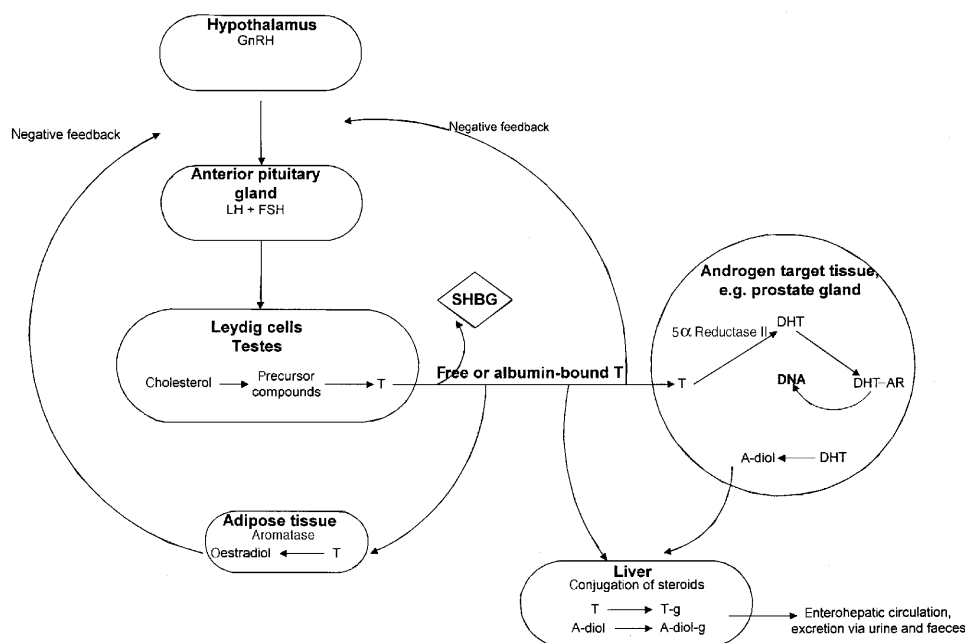
1988), low sperm count (Lee *et al.* 1998; Liu *et al.* 1999), and benign prostatic hyperplasia (Denis *et al.* 1999). Diet-related changes in hormone metabolism may also be of interest to elite athletes, who may benefit from maximising anabolic steroid production to enhance physical performance (Brotherhood, 1984; Miller & Wolfe, 1999). Dietary habits are changing rapidly across the world, with many developing countries increasing their *per capita* consumption of animal fat and protein in line with a more Western diet. Conversely, large numbers of Westerners are adopting a semi-vegetarian or vegetarian diet, and the number of vegans (who eat no animal products at all) is increasing (Ball, 1997; Vegetarian Society UK, 2000). It is therefore of great importance to understand the effects of such large-scale changes in diet on sex hormone metabolism.

The present review evaluates the epidemiological evidence for diet-related changes in circulating concentrations of sex hormones in men. Much of the research has focused on the hypothesis that a low-fat high-fibre diet is associated with lower androgen concentrations. An outline of the biology of sex hormones in men is given first, and the proposed biological mechanisms through which dietary factors may influence sex hormone production and/or metabolism are reviewed. The clinical and epidemiological studies that have examined the relationship between diet and sex hormone levels in men are then reviewed and their findings discussed.

### **The biology of sex hormones in men**

Sex steroid hormones are mitogens and promote growth of cells in many target organs. In men, androgens stimulate male sexual differentiation and development, pubertal masculinisation, initiation of spermatogenesis and maintenance of sexual function. An overview of the relationships between hormone secretion, target tissues and androgen metabolism is given in Fig. 1. Testosterone is synthesised from cholesterol in Leydig cells within the testes, with production being stimulated by secretion of luteinising hormone (LH) from the anterior pituitary gland. In turn, the pulsatile secretion of gonadotrophin-releasing hormone from the hypothalamus regulates LH secretion. Once testosterone enters the general circulation, a large percentage (approximately 50%) is tightly bound to sex-hormone-binding globulin (SHBG) and is considered unavailable for biological action (Coffey & Isaacs, 1981). Testosterone is also bound to albumin (approximately 48%), but with much lower affinity than for SHBG, and this albumin-bound testosterone probably serves as a buffer to protect testosterone from rapid metabolism (Manni *et al.* 1985). The remaining testosterone (approximately 2%) is unbound or free testosterone (FT). Only testosterone that is not bound to SHBG (i.e. FT and albumin-bound testosterone) can enter target tissue cells by passive diffusion. For the purpose of the present review we will generally restrict discussion of the bioavailable fraction of testosterone to measurements of FT. The amount of testosterone that is freely available to enter cells is largely determined by the circulating concentration of SHBG. A relatively small increase in plasma SHBG concentration will produce a large reduction in the amount of circulating FT (Dunn *et al.* 1981).

Testosterone production is regulated by negative feedback of circulating testosterone on LH secretion, so that high levels of circulating testosterone lead to a reduction in the frequency and amount of pulsatile LH release. This process can occur both directly and after testosterone is aromatized to oestradiol, as oestrogens also exert a negative feedback on LH secretion (Marynick *et al.* 1979; Kletter *et al.* 1997). Cross-sectional studies of samples of normal men invariably show a positive correlation between serum concentrations of testosterone and



**Fig. 1.** Main pathways of androgen action and metabolism. A-diol, androstenediol; A-diol-g, androstenediol glucuronide; AR, androgen receptor; DNA, deoxyribonucleic acid; DHT, dihydrotestosterone; FSH, follicle-stimulating hormone; GnRH, gonadotrophin-releasing hormone; LH, luteinising hormone; SHBG, sex-hormone-binding globulin; T, testosterone; T-g, testosterone glucuronide.

SHBG, because high concentrations of SHBG reduce the proportion of testosterone that is bioavailable, therefore the total concentration of testosterone increases to produce adequate levels of bioavailable testosterone.

Androgenic action is mediated once non-SHBG-bound testosterone enters the target cells, such as the epithelial cells of the prostate and seminal vesicles. Most of the testosterone is then irreversibly reduced into its more active form, dihydrotestosterone (DHT), by  $5\alpha$ -reductase type II (Bruchovsky *et al.* 1988). Some of the DHT re-enters the blood, and circulating DHT is almost entirely derived from this peripheral conversion of testosterone. Although the circulating concentration of testosterone is approximately ten times higher than that of DHT, organs such as the prostate gland contain much greater levels of DHT than testosterone (Coffey & Isaacs, 1981). DHT is the principal growth-regulating androgen because it has a much higher affinity to bind to the androgen receptor than testosterone. Once bound to the androgen receptor, the resultant complex is transported to the nucleus to transactivate target genes involved in cell growth and other androgen-dependent activities (Wilding, 1995).

The serum concentration of DHT has limited value as a marker of peripheral androgen metabolism. Most DHT formed in the prostate does not enter the circulation, but is metabolised within the prostate to androstenediol, which is mostly conjugated to its glucuronide form (A-diol-g) in the liver before excretion (Rittmaster *et al.* 1993). The serum concentration of A-diol-g is thought to be a reasonably specific marker of intra-prostatic DHT and  $5\alpha$ -reductase activity (Rittmaster *et al.* 1993; Thigpen *et al.* 1993).

Approximately 75–90% of circulating oestrogens in men are derived from extraglandular aromatization of testosterone and androstenedione (largely derived from the adrenal glands), to oestradiol and oestrone respectively, in adipose tissue (Farnsworth, 1996). Oestrogens have a stimulatory effect on cell growth (Ehrlichman *et al.* 1981), especially in the prostate gland as they exist at much higher levels in this organ than in plasma or in skeletal muscle (Belis, 1980).

Steroids are conjugated with glucuronic acid and H<sub>2</sub>SO<sub>4</sub> in the liver, secreted in bile, and enter the enterohepatic circulation. Here they are either hydrolysed and reabsorbed into the bloodstream and are ultimately excreted via the kidneys, or are excreted via the faecal route (see p. 164).

### Non-dietary determinants of sex hormone levels in men

#### *Age*

It is now well documented that circulating androgen levels in men decline with age. Total testosterone falls by about 18–25% between the ages of 20 and 70 years (Gray *et al.* 1991; Simon *et al.* 1992; Wu *et al.* 1995; Morley *et al.* 1997). Accompanying this decline in plasma testosterone concentration is a larger age-associated increase in the plasma SHBG concentration of 30–50% between the ages of 20 and 70 years (Field *et al.* 1994; Wu *et al.* 1995; Lecomte *et al.* 1998). This causes a more pronounced decline in FT concentration of 40–50% (Dai *et al.* 1981; Korenman *et al.* 1990; Nahoul & Roger, 1990; Gray *et al.* 1991), which is accompanied by a small increase in the LH concentration (Morley *et al.* 1997). The total oestradiol concentration might be expected to fall with age due to the decline in testosterone concentrations. However, the usual increase in body fat with age increases the conversion of testosterone to oestradiol, and therefore is likely to offset this reduction. A failure to account for variations in BMI may have contributed to the inconsistencies of this association in the data (Gray *et al.* 1991; Ferrini & Barrett-Connor, 1998). The level of oestradiol that is biologically available falls with age because of the corresponding rise in SHBG concentration (Ferrini & Barrett-Connor, 1998).

The fall in testosterone production with increasing age is largely caused by a reduction in Leydig cell mass and function (Gooren, 1996). It has also been suggested that both the frequency and amplitude of LH pulsatile secretion are reduced with age (Kaufman *et al.* 1990). This process leads to a gradual failure of LH to respond sufficiently to the decline in testosterone levels, resulting in an eventual increase in circulating LH concentration in an attempt to stimulate testosterone production (Zwart *et al.* 1996). The reduced testosterone production is then unable to compensate for the fall in FT caused by the rise in SHBG concentration (Winters & Atkinson, 1997). The reasons why SHBG concentration increases with age remain to be clarified, but may relate to the age-associated decline in levels of growth hormone and/or insulin-like growth factor-I levels (Vermeulen *et al.* 1996; Lecomte *et al.* 1998).

#### *BMI*

Another well-established determinant of hormone levels is BMI (kg/m<sup>2</sup>). There is a 20–30% reduction in testosterone concentration between clinically-obese men (BMI  $\geq$  30 kg/m<sup>2</sup>) compared with lean men (BMI < 20 kg/m<sup>2</sup>) (Field *et al.* 1994; Wu *et al.* 1995; Vermeulen *et al.* 1996; Ferrini & Barrett-Connor, 1998) and up to a 40% reduction in SHBG concentration between lean and clinically-obese men (Field *et al.* 1994; Wu *et al.* 1995; Vermeulen *et al.* 1996). Most studies have reported either a small decline or no association between BMI and FT concentration (Glass *et al.* 1977; Wu *et al.* 1995; Vermeulen *et al.* 1996; Ferrini & Barrett-

Connor, 1998) and this finding is consistent with the observation that A-diol-g concentration is not significantly associated with BMI (Vermeulen *et al.* 1993; Pasquali *et al.* 1997). Increasing BMI is associated with an increase in circulating oestrogens (Kley *et al.* 1980a ; Zumoff *et al.* 1981), probably caused by the peripheral conversion of androgens to oestrogens in adipose tissue (Schneider *et al.* 1979; Kley *et al.* 1980b).

The mechanisms underlying the hormonal changes that occur with an increasing BMI are not fully understood, but the primary effect of obesity may be to cause a decrease in SHBG concentration, perhaps due to an inhibitory effect of hyperinsulinaemia on SHBG production (Pasquali *et al.* 1995). The reduction in SHBG then leads to an increase in the proportion of FT and a corresponding fall in testosterone production via the negative feedback mechanism to maintain FT concentration at a constant level. In severely-obese men (BMI > 40 kg/m<sup>2</sup>), low LH and testosterone concentrations have been reported, indicating impairment of the feedback regulation of testosterone levels (Vermeulen *et al.* 1993).

### *Ethnicity*

There is some evidence to suggest that young African-American men (under 40 years of age) have higher circulating levels of testosterone than Caucasian men (Ross *et al.* 1986; Ellis & Nyborg, 1992). However, such differences have not been observed in studies in older men (Hill *et al.* 1980; Kubricht *et al.* 1999), indicating that increasing age may attenuate racial differences in testosterone concentration (Ellis & Nyborg, 1992). The evidence that Asian men of any age have lower levels of testosterone compared with Caucasian men is more inconsistent, with both associations (De Jong *et al.* 1991; Santer *et al.* 1998) and no associations being found (Lookingbill *et al.* 1991; Ellis & Nyborg, 1992; Ross *et al.* 1992; Jin *et al.* 1999). Nevertheless, Caucasian and African-American men have been found to have 25–45% higher A-diol-g concentrations compared with Asian men at young ages (Lookingbill *et al.* 1991; Ross *et al.* 1992). Furthermore, plasma ratios of DHT:testosterone (an indirect measure of tissue metabolism of testosterone to DHT and a marker of 5 $\alpha$ -reductase activity) have also been reported to be higher among elderly Caucasian men compared with men of Chinese or Japanese origin (Wu *et al.* 1995; Jin *et al.* 1999).

### *Other factors*

Little is known about the relationship between other lifestyle factors and sex hormone levels. The evidence that acute alcohol intake suppresses testosterone concentration is inconsistent (Gordon *et al.* 1976; Ylikahri *et al.* 1978), although differences in dose and duration of alcohol consumption may have accounted for some of the discrepant findings (Ellingboe, 1987). Cross-sectional analyses have also reported conflicting results on the association between habitual moderate alcohol intake and testosterone concentration (Dai *et al.* 1981; Stefanick *et al.* 1987; Key *et al.* 1990a; Field *et al.* 1994; Wu *et al.* 1995; Ferrini & Barrett-Connor, 1998). However, long-term heavy alcohol consumption and its associated liver cirrhosis, as well as general liver failure, has been consistently associated with low testosterone concentrations (Distiller *et al.* 1976; Valimaki *et al.* 1982) and a high SHBG concentration (Bahnsen *et al.* 1981).

Epidemiological evidence that cigarette smoking affects circulating levels of testosterone is inconsistent (Barrett-Connor & Khaw, 1987; Dai *et al.* 1988; Field *et al.* 1994; Wu *et al.* 1995; Hsieh *et al.* 1998). Furthermore, the mechanisms through which smoking might influence sex hormone levels remain to be elucidated (Matzkin & Soloway, 1993). Physical and psy-

chological stresses have been associated with a lower testosterone concentration (Krenz *et al.* 1972; Theorell *et al.* 1990; Nilsson *et al.* 1995). Circulating SHBG concentration is known to be affected by thyroid hormone, exogenous oestrogens, stress and hyperprolactinaemia (Rosner, 1990). Several medical conditions and/or medications used to treat conditions such as epilepsy (Duncan *et al.* 1999), cardiovascular disease (Sapin *et al.* 1992) and hypertension (Suzuki *et al.* 1988) have also been associated with changes in circulating sex hormone levels. However, many of these relationships have not been well established, largely due to the small number of subjects studied and the limited ability of many studies to control for possible confounding factors.

### **Dietary effects on sex hormone levels: possible mechanisms**

The fact that severe dietary restriction has a large effect on hormone metabolism suggests that hormone levels are, to some extent, nutritionally regulated. It has therefore been suggested that less extreme changes in diet may also have physiologically significant effects on circulating sex hormone levels. Several mechanisms have been proposed through which changes in the nutritional composition of the diet might affect hormone metabolism.

#### *The effects of severe undernutrition on circulating sex hormone levels*

It is well known that in circumstances of chronic undernutrition such as anorexia nervosa hormone metabolism is severely affected. This situation is most evident among young women, with a reduction in circulating gonadotropin and oestrogen concentrations and disruption of the menstrual cycle (Foppiani *et al.* 1997; Warren *et al.* 1999). Severe undernutrition in men also results in severe hypogonadotrophic hypogonadism, with very low concentrations of testosterone and LH (Lado-Abeal *et al.* 1999; Tomova & Kumano, 1999).

#### *The effects of a low-fat high-fibre diet on the enterohepatic circulation of steroids*

Less extreme changes in diet may also affect circulating hormone levels through effects on the enterohepatic circulation of steroids, which plays an important role in the metabolism of sex hormones in man. Within the liver, steroids are metabolised and conjugated with H<sub>2</sub>SO<sub>4</sub> and/or glucuronic acid. Approximately 20–50% of conjugated steroids are secreted into the bile and enter the small intestine; the remaining steroids are excreted in the urine. Most of the biliary conjugates (approximately 90%) are hydrolysed by intestinal bacteria, which host hydrolytic enzymes, of which the  $\beta$ -glucuronidases and the sulfatases are the most important. Once steroids are hydrolysed in the intestine, approximately 80% are reabsorbed into the bloodstream and partly re-conjugated in the intestinal mucosa. The conjugates that escape hydrolysis (approximately 10%) are excreted via the faecal route. The reabsorbed steroids are passed via the portal system to the liver, where they are mostly re-conjugated and re-enter the bile to repeat the enterohepatic cycle. The physiological significance of the enterohepatic circulation is not well understood, but the overall effect is a delay in the excretion of steroids, and hence an increase in plasma and urinary levels (Adlercreutz & Martin, 1980; Adlercreutz *et al.* 1987; Groh *et al.* 1993). Dietary factors that affect gastrointestinal function, especially bacterial metabolism and the intestinal absorptive capacity, could therefore influence hormonal status.

A low-fat high-fibre diet, characterised by a low intake of animal products and a high intake of plant foods, could in theory influence the enterohepatic circulation and reduce circulating hormone concentrations via three main mechanisms. Some types of dietary fibre (NSP) have been shown to trap or bind steroids excreted in the bile (Kay & Strasberg, 1978; Adlercreutz *et al.* 1987), thereby increasing their faecal excretion and reducing enterohepatic circulation. Indeed, fibre intake in women has been found to increase faecal excretion (Goldin *et al.* 1982) and reduce urinary excretion of steroids (Armstrong *et al.* 1981; Goldin *et al.* 1982). However, the evidence that this results in a concomitant reduction in circulating plasma oestrogen levels is inconsistent (Barbosa *et al.* 1990; Rose *et al.* 1991; Goldin *et al.* 1994; Stark *et al.* 1998). There is some evidence that this mechanism may also affect androgen metabolism in men, because *in vitro* studies have found fibre (particularly water-insoluble fibre such as lignin) to bind to testosterone and DHT (Shultz & Howie, 1986). Vegan men who have a high intake of dietary lignins have been shown to have a substantially higher faecal excretion of conjugated steroids than meat-eaters (Ross *et al.* 1990; Pusateri *et al.* 1990).

A second mechanism through which dietary fibre and resistant starch (i.e. starch that escapes hydrolysis) may interrupt hormone metabolism is via a faecal bulking effect (Shetty & Kurpad, 1986; Birkett *et al.* 1997). An increase in faecal weight and moisture will decrease the transit time through the intestine and colon (Birkett *et al.* 1997), resulting in a greater proportion of steroids being excreted via the faecal route, rather than being reabsorbed into the enterohepatic circulation (Lewis *et al.* 1997).

Finally, a low-fat high-fibre diet may alter the composition of faecal bacterial flora, decreasing  $\beta$ -glucuronidase activity in the intestine. This process will result in reduced reabsorption of unconjugated steroid hormones into the bloodstream (Goldin & Gorbach, 1976; Järvenpää *et al.* 1980; Reddy *et al.* 1980). However, other experimental studies have not found diet to influence faecal bacterial activity (Cummings *et al.* 1978; Goldin *et al.* 1980) and the variation in type and dose of fibre, as well as experimental design, makes interpretation of these studies difficult.

#### *The effects of a low-fat high-fibre diet on circulating insulin levels*

Alternatively, it has been hypothesised that a low-fat high-fibre diet might indirectly increase serum androgen levels, by preventing the development of insulin resistance (Smith, 1994), which is associated with reduced levels of SHBG (Haffner *et al.* 1994; Pasquali *et al.* 1995). High amounts of dietary fibre (particularly pectin) and resistant starch reduce the rate of glucose absorption in the intestine, thereby increasing net glucagon concentration, reducing insulin levels and enhancing insulin sensitivity (Jenkins *et al.* 1978). Indeed, reductions in glucose and insulin levels have been observed following a diet high in dietary fibre (Anderson *et al.* 1995; Thorsdottir *et al.* 1998). Lower insulin levels might lead to an increase in SHBG production, as insulin has been demonstrated to directly inhibit SHBG secretion *in vitro* (Plymate *et al.* 1988). Insulin is also inversely correlated with SHBG concentrations among both normal-weight and obese men (Strain *et al.* 1994; Pasquali *et al.* 1995; Vermeulen *et al.* 1996). Indeed, the inhibitory effect of hyperinsulinaemia on SHBG concentration appears to occur irrespective of an individual's BMI (Lazarus *et al.* 1998). In accordance with this finding, cross-sectional data from normal-weight and obese men show that insulin levels are also negatively correlated with testosterone concentrations (Haffner, 1996; Tchernof *et al.* 1997). As such, lower insulin levels may be associated with higher testosterone levels due to an increase in SHBG production.

*The effects of fat on circulating sex hormone levels*

It has been widely suggested that animal fat, which is rich in saturated fatty acids, may increase concentrations of circulating sex hormones by directly influencing androgen production and/or metabolism. However, there is no compelling biological mechanism for such an effect. In fact, the hypothesis that fat may increase androgen levels has been largely derived from broad ecological observations that fat consumption appears to parallel rates of prostate cancer incidence (Rose *et al.* 1986; Yu *et al.* 1991), together with the theory that high androgen levels increase the risk for prostate cancer (Gann *et al.* 1996).

Some experimental evidence suggested that high concentrations of polyunsaturated fatty acids might influence circulating levels of bioavailable steroids by reducing the binding of testosterone (Martin *et al.* 1986; Reed *et al.* 1986) and oestradiol to SHBG (Bruning & Bonfrer, 1986; Reed *et al.* 1986). However, such an effect has not been observed at physiological concentrations (Diver, 1993) and an *in vivo* study did not find a strong relationship between free fatty acid concentration and the percentage free hormone concentration in women (Key *et al.* 1990b).

*The effects of dietary phyto-oestrogens on circulating sex hormone levels*

Isoflavones and lignans are two groups of diphenolic compounds (generically named phyto-oestrogens) that are widely distributed in plants. They have structural similarities with oestradiol and have been implicated in altering sex hormone metabolism via several mechanisms. Soyabean products are the primary food source of the isoflavone glycosides genistin and daidzin, which are metabolised by colonic microflora to the biologically-active aglycones, genistein and daidzein. Daidzein can be further metabolised to equol and *O*-desmethylangolensin (Setchell, 1998), all of which have oestrogenic activity. Flaxseed and fibre-rich foods such as bran, whole cereals and legumes are the most abundant source of the mammalian lignan precursors, matairesinol and secoisolariciresinol (Thompson *et al.* 1991). These compounds are metabolised by bacteria in the intestinal tract to enterolactone and enterodiol respectively (Lampe *et al.* 1994).

The majority of the phyto-oestrogen precursor compounds are hydrolysed by intestinal bacteria, and the aglycones and their metabolites are absorbed into the bloodstream to undergo enterohepatic circulation in a similar fashion to endogenous steroid hormones (Adlercreutz *et al.* 1987). A daily intake of 25–100 mg isoflavones, which is typical of that consumed in Asian countries (Barnes *et al.* 1995) or in some vegetarian and vegan diets (Adlercreutz *et al.* 1993) is thought to be high enough to elicit a physiological response (Adlercreutz & Mazur, 1997). However, there is considerable inter-individual variation in isoflavone excretion following consumption of soyabean foods (Hutchins *et al.* 1995). The conversion of daidzein to equol by intestinal microbes only occurs in approximately 30% of the population (Hutchins *et al.* 1995), although a high-carbohydrate low-fat diet (Bowey *et al.* 1988) and chronic soyabean ingestion may increase this conversion rate (Lu *et al.* 1995). Such dietary differences in the intestinal bacterial environment may be of importance, as these compounds vary greatly in their potency, ranging from 1/500 to 1/1000 of the activity of oestradiol, with equol being much more potent than *O*-desmethylangolensin (Markiewicz *et al.* 1993; Sathyamoorthy *et al.* 1994).

Isoflavones and lignans were originally believed to influence hormone metabolism due to their ability to bind to the oestrogen receptor in cells, to block the action of the more potent oestrogens, and hence exert anti-oestrogenic and anti-gonadotrophic effects (Adlercreutz *et al.* 1992; Markiewicz *et al.* 1993). However, these compounds may also affect steroid metabolism



via other mechanisms. *In vitro* studies suggest phyto-oestrogens can directly increase hepatic SHBG synthesis (Adlercreutz *et al.* 1992; Mousavi & Adlercreutz, 1993; Loukovaara *et al.* 1995), thereby potentially reducing the availability of testosterone to enter target cells and elicit a biological response. Phyto-oestrogens may also have enzyme-inhibitory effects; of particular interest is the ability of the isoflavone genistein to inhibit  $17\beta$ -hydroxysteroid dehydrogenase,  $5\alpha$ -reductase and aromatase (Adlercreutz *et al.* 1992; Evans *et al.* 1995; Pelissero *et al.* 1996). Reduced activity of these enzymes could hypothetically lead to lower levels of plasma androgens and oestrogens, and lower levels of DHT in androgen target cells, but the relevance of these effects at physiological concentrations in human subjects has not been established.

## Studies of diet and hormone levels in men

### *Intervention studies*

Several studies have investigated the effects of different dietary regimens on endogenous hormone levels in men. For the present review, we identified studies through a search of the Medline<sup>®</sup> database for literature on sex hormones and dietary intervention studies, written in the English language. Such studies have generally focused on differences in total dietary fat and/or dietary fibre intake on circulating hormone levels. The investigation of the hormonal effects of phyto-oestrogens in men is still in its infancy, although a few small studies have been published (mostly in abstract form).

*Changes in dietary fat and/or dietary fibre intake* Table 1 summarises the dietary intervention studies that have focused on the effect of changes in dietary fat and/or dietary fibre consumption on endogenous hormone levels. Typically, study subjects who ate a Western diet (approximately 40% energy from fat) were given a low-fat diet (less than 25% energy from fat) or *vice versa* over a period of a few weeks in a controlled setting. Individualised meals or menus were prepared to maintain body weight throughout the intervention period (unless on a weight-reducing diet; Rosenthal *et al.* 1985). In most studies there was no control group, and baseline hormone levels were compared with measurements obtained after the period of dietary intervention.

Despite the relatively short study periods, these dietary regimens may be sufficient to elicit physiological changes as they involve large changes in fat intake of > 15% of total energy. The first dietary intervention study was conducted using twenty-four North American white and black men given a low-fat diet, and twenty black South African men given a high-fat 'Western' diet, for 3 weeks. A large reduction in total fat (from 40 to 25% energy intake) was associated with a significant fall in plasma cholesterol concentration among the black Americans, and significant reductions in plasma testosterone concentration in both the black and white Americans (Hill *et al.* 1980). Although the change to a Western diet was associated with a significant increase in cholesterol concentration in the black South African men, it was also associated with a significant fall in testosterone concentration (Hill *et al.* 1980), an observation that was repeated in a later study (Hill *et al.* 1982). Neither study found oestradiol concentration to be significantly affected by diet, although oestrone concentration was substantially higher following the high-fat regimen (Hill *et al.* 1982).

A study conducted in thirty white Finnish men found a low-fat diet (resulting in a change from 40 to 25% energy intake from fat) to be associated with significantly ( $P < 0.01$ ) reduced testosterone and FT concentrations after 6 weeks (Hämäläinen *et al.* 1984). DHT, SHBG and oestradiol concentrations also declined, but these changes were not statistically significant.

**Table 1.** Dietary intervention studies of changes in fat and/or dietary fibre intake and percentage change in hormone concentrations in men

Reference	Study population	n	Dietary intervention	Fat and/or fibre change	Diet period (weeks)	Age (years; mean or range)
Hill <i>et al.</i> (1980)	USA, white USA, black SA, black	11 13 20	W to LFV W to LFV LFV to W	40 to 25 % E from fat 40 to 25 % E from fat 25 to 40 % E from fat	3 3 3	49 45 43
Hill <i>et al.</i> (1982)	SA, black	13	LFV to W	25 to 40 % E from fat	3	66
Hämäläinen <i>et al.</i> (1984)	Finland, white	30	W to LF	40 to 25 % E from fat	6	40-49
Rosenthal <i>et al.</i> (1985)	USA, white	21	W to LF, Hfib	<10 % E from fat, 9.5 g fibre/MJ	3	50-60
Reed <i>et al.</i> (1987)	UK, white	6	HF to LF	>100 g to <20 g fat	2	21-47
Raben <i>et al.</i> (1992)	Denmark, white	8	Normal to V	5.7 g fibre/MJ	6	21-28
Dorgan <i>et al.</i> (1996)	USA, race not stated	43	Normal to M HF to LF, Hfib	2.7 g fibre/MJ 40 % E from fat, 2 g fibre/MJ to <20 % E from fat, 5 g fibre/MJ	6 10	21-28 19-56

**Table 1.** Continued

Reference	Wt (kg)	Cholesterol (%)	Mean change from baseline to intervention							LH (%)
			T (%)	FT (%)	DHT (%)	SHBG (%)	Oestrone (%)	Oestradiol (%)		
Hill <i>et al.</i> (1980)	-1.6 -0.4	2 -10*	-32*	na na	na na	na na	na na	na na	-12 -2	na na
Hill <i>et al.</i> (1982)	0.8	7*	-18*	na	na	na	na	na	19	na
Hämäläinen <i>et al.</i> (1984)	0.7	na	-22*	na	na	na	na	41*	-15	-10*
Rosenthal <i>et al.</i> (1985)	-1	na	-15*	-13*	-10	-9	0	0	-15	2
Reed <i>et al.</i> (1987)	-5.2	-21*	0	na	na	na	na	na	-50*	na
Raben <i>et al.</i> (1992)	Not given	-22*	2	-21*	na	21*	3	na	0	na
Dorgan <i>et al.</i> (1996)	Not given	na	-35*	-23	-29	-6	-4	-6	-31	-23
	-0.6	na	-20	-15	-4	-4	-4	8	-4	-14
		na	-11	+6	-8	-4	-4	-4	9	na

T, testosterone; FT, free testosterone; DHT, dihydrotestosterone; SHBG, sex-hormone-binding globulin; LH, luteinising hormone; SA, South Africa; W, Western diet; LFV, low-fat vegetarian diet; LF, low-fat diet; Hfib, high-fibre diet; HF, high-fat diet; V, vegetarian diet; M, omnivorous diet; E, total energy intake; na, not applicable. Difference in hormone concentration between normal and intervention period was significant. \* $P < 0.05$ .

A diet extremely low in fat and high in dietary fibre given to obese men in hospital was associated with a significant reduction in plasma cholesterol concentration ( $P < 0.01$ ), no change in testosterone concentration, and a 50% reduction in oestradiol concentration (Rosenthal *et al.* 1985). However, because the weight of the subjects was significantly reduced ( $P < 0.01$ ) by an average of 5 kg during the 3-week intervention period, changes in hormone levels in this study must be interpreted with caution. In particular, a loss of fat may have contributed to the rapid reduction in oestradiol concentration. Furthermore, many of these hospitalised subjects had medical conditions and/or were receiving medications that are known to influence steroid hormones (such as anti-hypertensive drugs and insulin for diabetes). These subjects were also enrolled in an exercise programme during the intervention period, making it impossible to attribute the hormonal changes observed to the dietary change.

Reed *et al.* (1987) examined the effects of a low-fat diet by comparing the differences in sex hormone levels after changing from a high-fat diet (more than 100 g fat/d) to a very low-fat diet (less than 20 g fat/d) in six men. As predicted, there was a significant reduction ( $P < 0.01$ ) in cholesterol concentration when on the low-fat diet, even after an intervention period of only 2 weeks. SHBG concentration was also significantly elevated ( $P < 0.001$ ), and FT concentration declined correspondingly. There were no reported differences in testosterone or oestradiol concentrations. However, due to the small number of study subjects, these results should be interpreted with caution.

One study investigated the effects of a change from a high-meat diet to a lacto-ovo-vegetarian diet, whilst maintaining the same energy and overall fat intake, on sex hormone levels in eight men (Raben *et al.* 1992). This study incorporated a cross-over design, whereby participants were separated into two groups at the start of each diet. After 6 weeks on one diet, subjects were given a 4-week wash-out period on their habitual diet and then switched over to the other diet. Mean testosterone concentration declined significantly ( $P < 0.001$ ) by 35% after 6 weeks on the vegetarian diet compared with baseline values, and although testosterone also declined on the meat diet, it was not significantly different from initial values. FT, DHT, oestradiol and LH concentrations were also not significantly different on either diet. The subjects were young elite endurance athletes whose hormonal profile may well be different from that of the predominantly middle-aged men recruited in the other studies.

One study implemented a randomised cross-over design whereby subjects were matched by age, BMI and smoking status and randomly assigned either to the low-fat high-fibre diet or the high-fat low-fibre diet, before crossing over to the other diet (Dorgan *et al.* 1996). The dietary effect was assessed by comparing the differences in hormone levels between the two dietary regimens. This study had more power than the other studies to discern small effects due to a larger number of study subjects ( $n = 43$ ). There were no substantial differences in the circulating concentrations of testosterone, FT, DHT, SHBG, oestrogens or LH in men when transferred from a high-fat low-fibre diet to a low-fat high-fibre diet for 10 weeks (Dorgan *et al.* 1996).

These dietary intervention studies have not established the effects, if any, of dietary fat and/or fibre intake on circulating sex hormone concentrations. In general, they have shown that, as expected, cholesterol concentration was elevated following a high-fat low-fibre diet, and reduced on a low-fat high-fibre diet, but the reported changes in sex hormone levels following dietary intervention were inconsistent. Testosterone concentration was found to be reduced following change to both a high-fat low-fibre diet and a low-fat high-fibre diet, and most of the studies have failed to observe any association between a low-fat high-fibre diet and concentrations of other sex hormones or SHBG. The high inter-correlation of nutrient intakes, the short intervention periods and the small numbers of subjects in all these studies, coupled with

**Table 2.** Dietary intervention studies of phyto-oestrogen supplements and percentage change in sex hormone concentrations in men

Reference	Study population	n	Dietary intervention	Phyto-oestrogen equivalent	Diet period (weeks)	Age range (years)
Shultz <i>et al.</i> (1991)	USA, white	6	13.5 g/d flaxseed flour	9.1 mg secoisolariciresinol/d‡	6	25–72
Lu <i>et al.</i> (1998)	USA, race not stated	Not given	355 ml soya milk	100 mg genistein/d, 100 mg daidzein/d	4	Not given
Cassidy <i>et al.</i> (1998)†	UK, race not stated	6	40 g/d linseed	27 mg secoisolariciresinol/d	4	60–63
		6	60 g/d TVP	45 mg isoflavones/d	4	60–63

**Table 2.** *Continued*

Reference	Mean change from baseline to intervention (%)							
	Weight	Cholesterol	T	DHT	A-diol-g	SHBG	LH	FSH
Shultz <i>et al.</i> (1991)	0	na	2	1	na	-5	na	na
Lu <i>et al.</i> (1998)	Not given	na	0	na	-13	na	na	na
Cassidy <i>et al.</i> (1998)†	Not given	-7	na	na	na	na	-10	-15*
	Not given	0	na	na	na	na	-13	0

T, testosterone; DHT, dihydrotestosterone; A-diol-g, androstane diol glucuronide; SHBG, sex-hormone-binding globulin; LH, luteinising hormone; FSH, follicle-stimulating hormone; TVP, textured vegetable protein; na, not applicable.

Mean change between normal and intervention period was significant: \* $P < 0.05$ .

†Results from Hughes *et al.* (1994) are also presented (an earlier publication of the study).

‡Intake estimated from data in Cassidy *et al.* (1998).

the lack of control groups in most studies, reduced the ability to detect differences in hormone levels that could be attributable to dietary change.

*Changes in phyto-oestrogen intake* There are very few data regarding the effects of phyto-oestrogens on circulating sex hormone levels in men, and the studies to date have included very small numbers of subjects with limited information on hormonal change following phyto-oestrogen consumption (Table 2). Lignan supplementation, in the form of six slices of flaxseed bread per d for 6 weeks, was found to have no effect on circulating testosterone, FT or SHBG concentrations in six men (Shultz *et al.* 1991). Soyabean consumption in the form of 355 ml soya milk supplementation for 4 weeks also had no effect on serum testosterone concentration, although there was a non-significant 13% decrease in A-diol-g concentration compared with pre-soyabean diet values (Lu *et al.* 1998). A similar study investigated the effects of foods containing both isoflavones and lignans on gonadotrophin levels in six elderly men (Cassidy *et al.* 1998): 40 g linseed/d was associated with a 10% reduction in LH concentration and a significant ( $P < 0.05$ ) 15% reduction in follicle-stimulating hormone concentration; 60 g textured vegetable protein/d was also associated with a 13% reduction in LH, but the change in follicle-stimulating hormone concentration was negligible (Cassidy *et al.* 1998).

The current data on dietary intervention studies of phyto-oestrogens and sex hormone levels in men are too scanty to interpret with confidence. Although much more research has been done in women due to the potential anti-oestrogenic effects of phyto-oestrogens, the evidence for an effect on sex hormones and/or SHBG concentrations still remains weak and inconsistent (Phipps *et al.* 1993; Baird *et al.* 1995; Lu *et al.* 1996; Brzezinski *et al.* 1997). As with the dietary fat intervention studies, interpretation is hampered by the small numbers of study subjects and lack of control groups. Confounding may also be a problem due to the parallel ingestion of dietary fibre and soyabean protein, which could have independent effects on hormone levels. The short intervention periods and the probable inclusion of individuals with varying habitual diets makes interpretation of the effects of phyto-oestrogens on sex hormone levels very difficult. This situation is a result of gut-flora composition, which has an important role in the metabolism of phyto-oestrogens, and is largely a result of long-term dietary habits.

## Observational studies

### *Associations between nutrient intake and circulating hormone levels: correlational analyses*

A small number of cross-sectional studies have investigated the relationship between dietary intake and circulating sex hormones in men. Although nutrients have been observed to be more weakly associated with hormone levels than factors such as age and BMI, several statistically significant associations have been reported. Bishop *et al.* (1988) examined the association of diet with circulating hormone levels while controlling for genetic factors by analysing the differences in hormone levels according to the variation in dietary intake between 155 monozygotic twin pairs. As expected, weight and BMI were the strongest determinants of hormone levels, although fat intake was significantly positively associated with A-diol-g concentration (Spearman correlation coefficient,  $r$  0.26), Zn and protein were negatively associated with FT concentration ( $r$  -0.22 and -0.25 respectively) and crude fibre was positively associated with SHBG concentration ( $r$  0.26). These associations were not adjusted for BMI.

The relationships between lifestyle factors and dietary intake and sex hormone levels were also investigated in a random sample of 1241 middle-aged US men (Field *et al.* 1994). After adjustment for multiple potential confounders, A-diol-g concentration was found to be significantly negatively correlated with protein and crude fibre intake (Pearson's partial correlation coefficients,  $r = 0.10$  and  $-0.06$  respectively) and positively correlated with alcohol intake ( $r = 0.08$ ). SHBG concentration was positively correlated with crude and dietary fibre ( $r = 0.08$ ), and negatively correlated with animal fat ( $r = 0.06$ ). No nutrients were associated with testosterone or FT concentrations. A study among forty male meat-eaters and vegans also found that no nutrients were correlated with testosterone or FT concentrations after multiple adjustment for age, BMI and diet group (Key *et al.* 1990a). However, SHBG concentration was significantly positively correlated with total fat, saturated and polyunsaturated fatty acids (Pearson's partial correlation coefficients,  $r > 0.35$ ), but not with dietary fibre (Key *et al.* 1990a). In contrast, a cross-sectional analysis of 1563 middle-aged US men found no association between fat intake and SHBG concentration, but found protein intake to be negatively correlated with SHBG and dietary fibre intake to be positively correlated with SHBG after multiple adjustment for lifestyle factors and other hormones (Longcope *et al.* 2000).

The reasons for the inconsistencies between these studies may partly be due to confounding factors that were not accounted for in some of the analyses. The lack of variability in nutrient intake in most of these studies is also likely to limit their power to detect small associations. Finally, some of these associations are likely to be a result of chance due to the large number of significance tests performed.

#### *Differences in serum hormone levels between meat-eaters, vegetarians and vegans*

To date, six studies have compared circulating hormone levels between long-standing meat-eaters, vegetarians and/or vegans, in another approach to identifying the effects of diet on hormone metabolism at a population level. These studies have some advantages over intervention trials in that they can more easily include large numbers, and the period of dietary exposure is usually much longer. However, dietary intakes are usually not as extreme as those provided in the intervention studies. Any physiological effects of diet on circulating hormone levels might be expected to be more pronounced between meat-eaters and vegans, rather than between meat-eaters and lacto-ovo-vegetarians.

Differences in macronutrient intake between meat-eaters, vegetarians and vegans in these six studies are shown in Table 3. In order to make nutrient intakes more easily comparable between dietary groups, nutrient densities (intake as a percentage of energy or per MJ) are presented along with absolute intakes. Vegetarian diets can vary quite widely, but are usually lower in saturated fatty acids, contributing between 5 and 10% total energy, compared with a predominantly meat-eating diet (10–15% energy). Conversely, intake of polyunsaturated fatty acids is higher among vegetarians, and in particular among vegans, contributing 8–10% energy, compared with meat-eaters (4–7% energy; Key *et al.* 1990a; Allen *et al.* 2000). Nevertheless, total fat intake as a percentage of energy is generally similar between meat-eaters and non meat-eaters (contributing 30–40% energy in all dietary groups). As such, the main hypothesis addressed by the intervention studies, that total fat intake is related to hormone levels, cannot be adequately addressed. Both lacto-ovo-vegetarian and vegan diets are lower in protein and cholesterol, and higher in carbohydrate and dietary fibre than a diet including regular meat consumption. Furthermore, the protein bioavailability is reduced by approximately 10% on a vegetarian fibre-rich diet (World Health Organization, 1985). Non-meat-

**Table 3.** Study characteristics and dietary intake among meat-eaters, vegetarians and vegans

Reference	Study population	Dietary group	n	Age (years)	BMI (kg/m <sup>2</sup> )	Energy (MJ/d)
Deslypere & Vermeulen (1984)	Belgium, white	Meat	34	26	23	
		Macrobiotic	12	33	21	
		Meat, monks	15	73	24	
Howie & Shultz (1985)	USA, white	Veg, monks	23	69	25	11.0
		Meat	8	56	26	9.6
		Meat, SDA	10	55	28	11.2
		Veg, SDA	12	57	26	11.0
Bélanger <i>et al.</i> (1989)	Canada, white	Meat	14	27	23	11.3
		Veg	15	29	21	10.9
Key <i>et al.</i> (1990a)*	UK, white	Meat	57	40	23	10.8
Pusateri <i>et al.</i> (1990)	USA, white	Vegan	51	41	22	8.6
		Meat, SDA	18	21-36	na	10.4
		Veg, SDA	20	21-36	na	12.2
Allen <i>et al.</i> (2000)	UK, white	Vegan, SDA	15	21-36	na	10.3
		Meat	226	53	26	8.9
		Veg	237	46	23	8.1
		Vegan	233	43	23	

**Table 3.** Continued

Reference	Carbohydrate		Protein		Total fat		SFA		PUFA		Cholesterol		Dietary fibre	
	g/d	% E	g/d	% E	g/d	% E	g/d	% E	g/d	% E	mg/d	g/MJ	g/d	g/MJ
Deslypere & Vermeulen (1984)	253	39	83	15	116	40	32	11	57 <sup>†</sup>	20	438	39.8	20	1.82
	260	40	105	13	96	38	32	13	43	17	309	32.2	23	2.40
Howie & Shultz (1985)	360	51	94	11	101	34	31	10	51	17	197	17.6	37	3.30
	317	48	109	17	107	37	43	15	12	4.0	524	47.6	14	1.27
Bélanger <i>et al.</i> (1989)	394	58	85	13	89	30	27	9.0	19	6.0	296	0.80	38	3.36
	299	43	92	14	111	38	38	13	22	7.0	na	na	35	3.21
Key <i>et al.</i> (1990a)*	371	54	73	11	95	33	18	6.0	30	10	na	na	57	5.28
	266	48	76	16	80	35	23	10	27 <sup>†</sup>	12	195	22.6	16	1.85
Pusateri <i>et al.</i> (1990)	351	53	79	13	92	33	23	8.0	31	11	184	17.7	34	3.27
	475	61	78	10	99	30	15	5.0	56	17	3.00	0.25	50	4.10
Allen <i>et al.</i> (2000)	278	44	99	17	93	34	32	12	14	5.4	327	31.7	25	2.40
	284	52	68	13	73	31	20	8.7	14	6.1	112	12.6	32	3.65
	267	54	60	13	63	30	10	4.9	17	8.2	21.0	2.60	37	3.47

E, total energy intake; Veg, vegetarian diet; SDA, Seventh Day Adventist; SFA, saturated fatty acid; PUFA, polyunsaturated fatty acid; na, not applicable.

\*Dietary composition based on twenty-two meat-eaters and eighteen vegans.

†Total unsaturated fatty acids measured as the sum of linoleic and oleic acids in Howie & Shultz (1985) and Pusateri *et al.* (1990).

eaters will also tend to have a higher intake of dietary phyto-oestrogens than meat-eaters due to higher consumption of soyabean, other legumes and unrefined plant foods (Adlercreutz *et al.* 1993). However, accurate data on intakes of phyto-oestrogens are limited.

Differences in serum hormone concentrations between meat-eaters, vegetarians and vegans in these studies are shown in Table 4. Vegans have been observed to have a significantly higher mean SHBG concentration than meat-eaters; this difference is partly due to differences in BMI between the groups, but even after adjusting for this, vegans are found to have 11–19% higher SHBG concentrations than meat-eaters ( $P < 0.05$ ; Key *et al.* 1990a; Allen *et al.* 2000). SHBG concentration has also been reported to be significantly higher in vegetarians compared with meat-eaters ( $P < 0.05$ ; Bélanger *et al.* 1989), although the substantially lower BMI among these vegetarians may have accounted for these findings. A larger study, which accounted for the differences in BMI between diet groups, found no difference in mean SHBG between vegetarians and meat-eaters (Allen *et al.* 2000).

Concomitant with an increase in SHBG concentration among vegans compared with meat-eaters is the small increase in testosterone concentration (Key *et al.* 1990a; Pusateri *et al.* 1990; Allen *et al.* 2000), although Allen *et al.* (2000) was the only study large enough to detect significant differences ( $P < 0.05$ ). One small study reported no differences in testosterone concentration between dietary groups (Deslypere & Vermeulen, 1984), and another found Seventh Day Adventist (SDA) vegetarians to have a lower mean testosterone concentration than non-Seventh Day Adventist meat-eaters ( $P < 0.05$ ); the fact that they were not significantly different to SDA meat-eaters, however, suggests that factors relating to other lifestyle characteristics may account for this difference (Howie & Shultz, 1985).

There is generally consistent evidence to suggest that circulating concentrations of FT, DHT and A-diol-g are similar between dietary groups (Deslypere & Vermeulen, 1984; Howie & Shultz, 1985; Key *et al.* 1990a; Allen *et al.* 2000). The only exception to these findings is the significantly lower A-diol-g concentration among vegetarians compared with meat-eaters ( $P < 0.05$ ) in the small study of Bélanger *et al.* (1989). As mentioned previously, these results should be interpreted with caution due to the potential confounding effect of BMI.

One early study reported a significantly lower oestradiol concentration in vegetarians compared with meat-eaters ( $P < 0.05$ ; Howie & Shultz, 1985). Other studies, however, have not substantiated this finding (Deslypere & Vermeulen, 1984; Bélanger *et al.* 1989; Key *et al.* 1990a; Pusateri *et al.* 1990). Similarly, no differences in LH concentration have been reported between meat-eaters, vegetarians and vegans (Deslypere & Vermeulen, 1984; Howie & Shultz, 1985; Allen *et al.* 2000).

There is evidence that circulating SHBG concentration is higher in vegans than meat-eaters, even after accounting for the differences in BMI between dietary groups. Identification of the nutritional characteristics of a vegan diet that may increase SHBG concentration is difficult; the effects of diet on SHBG could involve several inter-related underlying mechanisms, aside from the diet-related change in body composition. As mentioned previously, these mechanisms may involve the effects of decreased fat and increased fibre, phyto-oestrogens and/or greater insulin sensitivity. Dietary fibre has been most consistently positively correlated with SHBG in correlational analyses (Bishop *et al.* 1988; Field *et al.* 1994; Longcope *et al.* 2000), although Key *et al.* (1990a) reported no association. However, the fibre intake was high even among the meat-eaters in this latter study (Table 3) which might mask a correlation over a broader range of fibre intakes. The relationship between fat intake and SHBG concentration has been more inconsistent, with negative (Field *et al.* 1994), positive (Key *et al.* 1990a) and no associations being reported (Bishop *et al.* 1988; Longcope *et al.* 2000). There are, as yet, no cross-sectional data which have examined the association between phyto-oestrogen con-



Table 4. Serum hormone concentrations among meat-eaters, vegetarians and vegans

Reference	Dietary group	n	Age (years; mean or range)	BMI (kg/m <sup>2</sup> )	Matched or adjusted for BMI	T (nmol/l)	FT* (nmol/l)	DHT (nmol/l)	A-diol-g (nmol/l)	SHBG (nmol/l)	Oestradiol (pmol/l)	LH (IU/l)
Deslypere & Vermeulen (1984)	Meat	34	26	23	No	20.5	0.33	na	na	na	115	1.5†
	Macrobiotic	12	33	21		20.7	0.29	na	na	na	87.7	1.4
	Meat, monks	15	73	24		17.2	0.20	na	na	na	112	2.5
Howie & Shultz (1985)	Veg, monks	23	69	25		16.9	0.20	na	na	na	108	1.9
	Meat	8	56	26	Yes	23.1 <sup>a</sup>	na	1.80	na	na	73.8 <sup>a</sup>	14
	Meat, SDA	10	55	28		18.7	na	1.60	na	na	83.3	8.5
Bélanger <i>et al.</i> (1989)	Veg, SDA	12	57	26		16.9 <sup>a</sup>	na	1.90	na	na	47.4 <sup>a</sup>	9.8
	Meat	14	27	23	No	19.4	0.79 <sup>a</sup>	1.61	17.7 <sup>a</sup>	24.8 <sup>a</sup>	139	na
	Veg	15	29	21		22.9	0.61 <sup>a</sup>	1.48	11.1 <sup>a</sup>	34.5 <sup>a</sup>	147	na
Key <i>et al.</i> (1990a)	Meat	57	40	23	Yes	14.3	0.36	na	na	na	100	na
	Vegan	51	41	22		15.3	0.36	na	na	39.5 <sup>b</sup>	90	na
	Meat, SDA	18	21–36	na	Yes	24.8	na	na	na	na	62.2	na
Pusateri <i>et al.</i> (1990)	Veg, SDA	20	21–36	na		23.2	na	na	na	na	55.6	na
	Vegan, SDA	15	21–36	na		25.1	na	na	na	na	62.1	na
	Meat	226	53	26	Yes	20.3 <sup>b</sup>	0.42	na	8.72	45.7 <sup>b</sup>	na	5.43
Allen <i>et al.</i> (2000)	Veg	237	46	23		20.1 <sup>c</sup>	0.43	na	8.49	43.6 <sup>c</sup>	na	5.23
	Vegan	233	43	23		21.7 <sup>b,c</sup>	0.44	na	8.80	48.7 <sup>b,c</sup>	na	5.20

<sup>a, b, c</sup> Values with the same superscript letter within individual studies were significantly different ( $P < 0.05$ ).

Veg, vegetarian diet; SDA, Seventh Day Adventist; T, testosterone; FT, free testosterone; DHT, dihydrotestosterone; A-diol-g, androstenediol glucuronide; SHBG, sex-hormone-binding globulin; LH, luteinising hormone; na, not applicable.

\*FT calculated as the free androgen index in Deslypere & Vermeulen (1984), by dialysis in Bélanger *et al.* (1989), from empirical formula in Key *et al.* (1990a), and from the law of mass action in Allen *et al.* (2000).

†LH values are expressed as ng/l.

sumption and SHBG concentration in men. The only study in women found no association with soyabean intake (Nagata *et al.* 1997).

A plausible explanation for the higher testosterone concentration observed in vegans is that an increase in SHBG causes an increase in testosterone in order to maintain a constant FT concentration (Dunn *et al.* 1981). This interpretation is substantiated by the similar concentrations of bioavailable androgens, as measured by FT, DHT and A-diol-g concentrations, observed among meat-eaters, vegetarians and vegans.

### General discussion

There is considerable epidemiological evidence that a Western-style diet may increase the risk of certain hormone-dependent diseases via its effects on hormone metabolism (Giles & Ireland, 1997; Denis *et al.* 1999). However, the mechanisms through which diet may influence circulating hormone concentrations in men are not well understood. In comparison with factors such as age and BMI, nutrients do not appear to be strong determinants of hormone levels. However, there is experimental evidence to suggest that dietary factors may exert subtle effects on hormone metabolism which, although difficult to detect in small epidemiological studies, may be sufficient to exert physiological effects.

There is little evidence from intervention studies that diet is related to serum androgen levels, with changes to both low-fat and high-fat diets having been reported to reduce testosterone, FT and DHT concentrations over the short-term. Data from observational studies do not support the hypothesis that a diet low in saturated fatty acids is associated with lower androgen concentrations. Indeed, there is a tendency for testosterone levels to be slightly higher among vegans than meat-eaters, most probably as a direct response to an elevated SHBG concentration. A vegetarian and/or low-fat diet also has not been shown to influence LH levels, further implying that effects on androgens are insufficient to provoke a gonadotrophic response. Given the absence of clear effects of diet on androgens, the lack of dietary effect on oestrogens would be expected because circulating oestrone and oestradiol in men are largely derived from peripheral conversion of androgens. One explanation as to why diet does not appear to elicit substantial differences in circulating androgen levels is due to the body's natural feedback mechanism to maintain the internal environment. Indeed, the small increase in testosterone concentration observed among vegan men is almost certainly caused by the increase in SHBG, in order to maintain a constant level of FT.

Little work has been done on the effects of phyto-oestrogens in men. The increase in SHBG concentration observed in vegans compared with meat-eaters could to some extent be due to their consumption of phyto-oestrogens. However, larger studies are needed to have sufficient power to determine whether phyto-oestrogens modulate SHBG levels *in vivo*. The 13% reduction in A-diol-g observed following dietary supplementation of isoflavones (Lu *et al.* 1998) is consistent with the experimental evidence that phyto-oestrogens may inhibit 5 $\alpha$ -reductase activity (Evans *et al.* 1995). However, in a much larger study, vegetarian and vegan men who were known to consume soyabean regularly were not found to have lower A-diol-g levels than meat-eaters (Allen *et al.* 2000). It may be that soyabean consumption among Western vegetarians is not sufficient to exert physiological effects.

### Methodological issues

Measuring diet based on self-recall and food-frequency questionnaires will almost certainly contain some degree of measurement error. Such random misclassification of dietary exposure

will reduce the ability to detect small associations between diet and circulating hormone levels. Although this factor is not likely to affect short-term intervention studies and observational data between dietary groups, it could be of importance when investigating the association between nutrient intakes and hormone levels in correlation studies.

Most epidemiological studies on hormones have taken blood measurements from a single sample for each individual, because the collection and storage of multiple blood samples is both difficult and expensive. Due to the known circadian variation of adrenal and gonadal steroid concentrations within individuals (Goldman *et al.* 1985; Cooke *et al.* 1993), the majority of studies have ensured that all blood samples were taken at the same time of day. A single measurement of circulating serum testosterone and DHT concentrations has been shown to reflect mean annual androgen concentrations in middle-aged men reliably, with a Pearson's correlation coefficient of 0.85 between the first sample and the mean of seven subsequent samples taken over a 1-year period (Vermeulen & Verdonck, 1992). The within-subject variation of testosterone and SHBG measurements taken from men over a 12-month period have been reported to be substantially less than the between-subject variability (Valero-Politi & Fuentes-Arderiu, 1993). Little is known about the long-term reliability of a single serum measurement for other hormones.

Most research has been based on the assumption that the critical exposure period for evaluating the effect of diet on hormone levels is current dietary intake. Indeed, dietary intervention studies measure hormone concentrations a few weeks after dietary change. However, dietary intake during early childhood or adolescence, when the influence of hormones may be particularly important in male sexual development, may be a more important determinant of adult circulating hormone levels. Suggestions have also been made that exposure to high concentrations of androgens *in utero* among the black African-American population might predispose male offspring to an increased steroid hormone secretion and/or to an increased sensitivity to the effects of testosterone in adulthood (Henderson *et al.* 1988). However, to our knowledge, there has been no research into the effect of early nutritional experiences in relation to adult circulating hormones in man.

## Conclusion

Circulating sex hormone levels in men are strongly related to age and BMI. Increasing age is associated with a small decline in testosterone concentration, a substantial increase in SHBG concentration, and a large decline in FT concentration. An increase in BMI is associated with a substantial fall in the concentrations of testosterone and SHBG, but FT remains constant, except in severe obesity.

In comparison with these factors, the effects of diet on circulating sex hormone levels appear to be small. There is little evidence from dietary intervention studies to support the hypothesis that a change from a high-fat low-fibre diet to a low-fat high-fibre diet is associated with lower androgen levels and a higher SHBG concentration. The data on phyto-oestrogen supplements and their effects on endogenous hormone levels are, to date, too sparse for conclusions to be drawn. The findings from cross-sectional analyses of dietary intake and hormone levels have been inconsistent, although there is a suggestion that dietary fibre may be associated with higher SHBG levels. Observational studies between different dietary groups have shown that a vegan diet is associated with a small but significant increase in SHBG concentration. This increase is associated with a corresponding small increase in testosterone concentration, resulting in no alteration in the level of biologically-available testosterone.

In conclusion, the data available have not demonstrated that variations in dietary composition have any long-term important effects on circulating sex hormone levels in men. This lack of effect may be partly explained by the efficient homeostatic control of bioavailable testosterone by negative feedback, which can readily adjust testosterone production to compensate for changes in binding by SHBG or clearance through the liver. It therefore appears that future studies should look for dietary effects on the feedback mechanism itself, perhaps by phyto-oestrogens, or on the metabolism of androgens within the target tissue.

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