Review article

The optimal diet for women with polycystic ovary syndrome?

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An optimal diet is one that not only prevents nutrient deficiencies by providing sufficient nutrients and energy for human growth and reproduction, but that also promotes health and longevity and reduces the risk of diet-related chronic diseases. The composition of the optimal diet for women with polycystic ovary syndrome (PCOS) is not yet known, but such a diet must not only assist short term with weight management, symptoms and fertility, but also specifically target the long-term risks of type 2 diabetes, CVD and certain cancers. With insulin resistance and compensatory hyperinsulinaemia now recognised as a key factor in the pathogenesis of PCOS, it has become clear that reducing insulin levels and improving insulin sensitivity are an essential part of management. Diet plays a significant role in the regulation of blood glucose and insulin levels, yet research into the dietary management of PCOS is lacking and most studies have focused on energy restriction rather than dietary composition *per se*. On the balance of evidence to date, a diet low in saturated fat and high in fibre from predominantly low-glycaemic-index-carbohydrate foods is recommended. Because PCOS carries significant metabolic risks, more research is clearly needed.

Polycystic ovary syndrome: Insulin resistance: Glycaemic index

Sabate (2003) defines an optimal diet as one that not only prevents nutrient deficiencies by providing sufficient nutrients and energy for human growth and reproduction, but that also promotes health and longevity and reduces the risk of diet-related chronic diseases. The composition of the optimal diet for women with polycystic ovary syndrome (PCOS) is not yet known. Research findings allow us, however, to speculate on the type of eating pattern that could best address the health concerns that women with this condition face.

In the short term, the dietary management of PCOS needs to focus on weight loss, the amelioration of symptoms such as acne and hirsutism, and improved fertility in those who wish to fall pregnant. In the long term, dietary management must address the increased risk of type 2 diabetes, CVD and certain cancers, which are associated with this condition.

Polycystic ovary syndrome: pathophysiology and associated health risks

PCOS is the most common endocrine disorder in women, affecting an estimated 5–10 % of women of reproductive age (Franks, 1995; Knockenhauer *et al.* 1998; Asuncion *et al.* 2000). Once thought of as a fertility problem, it is now known that PCOS is a metabolic disorder with serious health consequences. Classic features of the syndrome include oligomenorrhoea or amenorrhoea, anovulation, infertility, hirsutism, acne and accelerated scalp hair loss. Diagnosis requires the presence of two out of three of the following: (1) oligo- or anovulation; (2) clinical and/or biochemical signs of hyperandrogenism; (3) polycystic ovaries, with the exclusion of other aetiologies such as congenital adrenal hyperplasia, androgen-secreting tumours and Cushing's syndrome (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004).

Insulin resistance, with compensatory hyperinsulinaemia, has been identified as a key component in the pathophysiology of PCOS in both lean and obese women, putting them at risk of developing type 2 diabetes and CVD (Chang *et al.* 1983; Dunaif *et al.* 1989; Dunaif, 1997). It is estimated that 50–70 % of women with PCOS have insulin resistance.

Studies have shown an increased prevalence of impaired glucose tolerance (IGT) and type 2 diabetes in both normal-weight and obese women with PCOS (Dunaif *et al.* 1987; Dahlgren *et al.* 1992*b*; Ehrmann *et al.* 1999; Legro *et al.* 1999; Wild *et al.* 2000; Elting *et al.* 2001; Norman *et al.* 2001; Weerakiet *et al.* 2001). The rate of conversion from normoglycaemia to IGT and type 2 diabetes is also increased (Ehrmann *et al.* 1999; Norman *et al.* 2001).

In addition, gestational diabetes appears to be more common in women with PCOS (Lanzone *et al.* 1995; Lesser & Garcia, 1997; Holte *et al.* 1998; Paradisi *et al.* 1998; Radon *et al.* 1999; Bjercke *et al.* 2002) and there is an increased risk of miscarriage in these women (Glueck *et al.* 1999).

A number of studies have also found a higher incidence of risk factors for CVD in women with PCOS. Risk factors include dyslipidaemia (predominantly high triacylglycerols and low HDL) and hypertension, with hyperinsulinaemia a strong predictor of CVD risk (Conway *et al.* 1992; Dahlgren *et al.* 1992*a*; Wild *et al.* 1992; Talbott *et al.* 1995; Wild, 1995; Robinson *et al.* 1996; Talbott *et al.* 1998; Mather *et al.* 2000; Elting *et al.* 2001; Legro *et al.* 2001; Pirwany *et al.* 2001; Strowitzki *et al.* 2002; Fenkci *et al.* 2003). Smaller LDL particle size (Sampson *et al.* 1996; Dejager *et al.* 2001; Pirwany *et al.* 2001), elevated plasminogen activator inhibitor-1 levels (Dahlgren *et al.* 1994; Talbott *et al.* 2000), elevated serum C-reactive protein (Fenkci *et al.* 2003) and raised plasma homocysteine levels (Wijeyarante *et al.* 2004) have also been demonstrated in women with PCOS. Finally, studies have demonstrated increased oxidative stress and decreased antioxidant levels in these women (Sabuncu *et al.* 2001; Fenkci *et al.* 2003). Despite these risk factors, however, evidence of an increased mortality from CVD in PCOS is lacking and further studies are needed (Pierpoint *et al.* 1998; Wild *et al.* 2000; Legro, 2003).

Evidence of an increased incidence of endometrial cancer in women with PCOS is limited despite concerns of a higher risk due to chronic anovulation with consequent unopposed oestrogen secretion (Hardiman *et al.* 2003). There is some evidence that the risk is higher in those who are overweight or obese (Coulam *et al.* 1983; Furberg & Thune, 2003). One study has shown a positive association between PCOS and family history of breast cancer (Atimo *et al.* 2003), but while PCOS does carry some risks for breast cancer including hyperinsulinaemia and obesity, no links have yet been established.

Dietary management of polycystic ovary syndrome

Research into the dietary management of PCOS is lacking, despite the fact that lifestyle modifications including diet, exercise and weight loss have been shown to be beneficial. A reduction in weight of as little as 5 % of total body weight has been shown to reduce insulin levels, improve menstrual function, reduce testosterone levels and improve symptoms of hirsutism and acne (Pasquali *et al.* 1989; Kiddy *et al.* 1992; Guzick *et al.* 1994; Andersen *et al.* 1995; Clark *et al.* 1995; Crave *et al.* 1995; Holte *et al.* 1995; Jakubowicz & Nestler, 1997; Clark *et al.* 1998; Huber-Buchholz *et al.* 1999; Wahrenberg *et al.* 1999; Pasquali *et al.* 2000; van Dam *et al.* 2002; Crosignani *et al.* 2003; Moran *et al.* 2003; Gambineri *et al.* 2004; Moran *et al.* 2004; Stamets *et al.* 2004). These findings are summarised in Table 1.

Approximately 50 % of women with PCOS are obese and this obesity is associated with a greater degree of insulin resistance, hyperinsulinaemia, lipid abnormalities, hyperandrogenism, hirsutism and menstrual irregularities (Pasquali & Casimirri, 1993; Pasquali *et al.* 1993, 1994; Andersen *et al.* 1995; Ciaraldi *et al.* 1997; Gambineri *et al.* 2002). Furthermore, there is a higher prevalence of abdominal body fat distribution in women with PCOS, even those of a normal body weight, and this increase in visceral fat has been shown to be associated with glucose intolerance and dyslipidaemia (Kirchengast & Huber, 2001; Yildirim *et al.* 2003).

Women with PCOS often report difficulties losing weight, although some studies have not shown this to be the case (Jakubowitz & Nestler, 1997; Pasquali *et al.* 2000). Clark *et al.* (1995), however, found that obese, infertile women presenting to

a weight-loss programme aimed at improving fertility outcomes had experienced an average weight gain ten times that of the normal population before starting the programme. In addition, Holte *et al.* (1995) found that while insulin resistance in obese women with PCOS was reduced by weight loss to similar levels as BMI-matched controls, there was a persistent increased early insulin response to glucose, which could provide a stimulus to weight gain.

Most of the studies of dietary intervention in women with PCOS have focused on energy restriction rather than dietary composition *per se*, yet the weight loss seen in most of these studies has been small in comparison with the outcomes achieved. And while the incidence of insulin resistance is higher in women with PCOS who are obese, and weight loss clearly improves outcomes for these women, not all women with PCOS who have insulin resistance are overweight or obese. Studies have demonstrated a higher incidence of insulin resistance, IGT and type 2 diabetes in women with PCOS of normal weight (Chang *et al.* 1983; Jialal *et al.* 1987; Dunaif *et al.* 1989; Fenkci *et al.* 2003), suggesting that dietary management of this condition must go beyond weight loss.

In most of the dietary studies in women with PCOS, improvements in metabolic and reproductive outcomes have been closely related to improvements in insulin sensitivity, suggesting that dietary modification designed to improve insulin resistance may produce benefits greater than those achieved by energy restriction alone.

With the high incidence of insulin resistance and IGT and the increased risk of type 2 diabetes in women with PCOS, research into the effects of diet and exercise on diabetes prevention is highly relevant to this group. The Diabetes Prevention Program achieved a 58 % reduction in risk of progression from IGT to type 2 diabetes with lifestyle modification, with the average weight loss a modest 5·6 kg (Diabetes Prevention Program Research Group, 2002). These results were similar to the Finnish Diabetes Prevention Study, which also achieved a 58 % reduction in risk of diabetes with lifestyle changes including diet and exercise (Tuomilehto *et al.* 2001). In this study average weight loss in the intervention group was 4·2 kg. While the Diabetes Prevention Program and Diabetes Prevention Study included only overweight and obese subjects, the Da Qing Study in China achieved a reduction in the incidence of diabetes with diet and exercise that was equally successful in normal-weight and obese subjects, suggesting that the benefits of diet and exercise were not related only to weight loss (Pan *et al.* 1997).

With insulin resistance and compensatory hyperinsulinaemia now recognised as key factors in the pathogenesis of PCOS, it has become clear that reducing insulin levels and improving insulin sensitivity are an essential part of the management of this condition. While much of the recent research has focused on the insulin-sensitising agent, metformin, diet also plays a significant role in the regulation of blood glucose and insulin levels. In fact the Diabetes Prevention Program showed that lifestyle modification (diet and exercise) in individuals with IGT produced a greater reduction in risk of developing type 2 diabetes than metformin (Diabetes Prevention Program Group, 2002). In addition, a recent meta-analysis of the effects of metformin use in PCOS found that while metformin does improve ovulation rate, both alone and in combination with clomiphene, equal or better ovulation rates have been achieved using lifestyle modification (Lord *et al.* 2003).

Table 1. Summary of studies of dietary intervention in polycystic ovary syndrome

Reference	Subjects (n)	Duration	Dietary intervention	Mean baseline BMI (kg/m^2)	Weight loss achieved	WC and WHR	FBG	Fasting insulin	Blood fats	MC	Hirsutism	Free testosterone	SHBG
Kiddy et al. (1992)	24	6–7 months	4200 kJ/d	34	7·5 %	N/A	N/A	↓	N/A	↑*	↓*	↓*	↑*
Crave et al. (1995)	24	4 months	Low fat (20 g/d) 6300 kJ/d	33	5·8 %	↓	NS	↓	NS	N/A	NS	NS	↑
Holte et al. (1995)	13	14·9 months	Low fat (30 %) 5040 kJ/d	32	14 %	↓	NS	↓	N/A	↑	NS	↓	↑
Jakubowicz & Nestler (1997)	12	8 weeks	Composition not specified 4200–5040 kJ/d About 44 % carbohydrate, 34 % fat, 22 % protein	32	7·5 %	NS	NS	↓	N/A	N/A	N/A	↓	↑
Huber-Buchholz et al. (1999)	18	6 months	Diet and exercise programme Composition not specified	35 RO 38 NO	2–5 %	↓†	N/A	↓†	N/A	↑†	N/A	N/A	NS
Wahrenberg et al. (1999)	9	3 months	VLCD	38	14·8 %	NS	↓	↓	N/A	N/A	N/A	↓	↑
Pasquali et al. (2000)	20	7 months	5040–5880 kJ/d (50 % carbohydrate, 30 % fat, 20 % protein)	40	4·9 %	↓	NS	↓	N/A	↑	NS	NS	NS
van Dam et al. (2002)	15	7 d	VLCD (4200 kJ/d) liquid diet	39	2·6 %	NS	↓	↓	N/A	N/A	N/A	↓	NS
Crosignani et al. (2003)	33	10–39 weeks (to achieve 10 % weight loss)	5040 kJ/d (20 % protein, 55 % carbohydrate, 25 % fat)	32	76 % lost >5 %	↓*	N/A	N/A	N/A	↑*	N/A	N/A	N/A
Moran et al. (2003)‡	28	16 weeks (12 weeks energy restriction, 4 weeks maintenance)	6000 kJ/d HP (30 % protein, 40 % carbohydrate, 30 % fat) v. HC (15 % protein, 55 % carbohydrate, 30 % fat)	38	33 % lost >10 % 7·5 %	N/A	NS	↓	↓ TC ↓ Triacylglycerols ↓ LDL	↑	NS	↑	↑
Gamberini et al. (2004)	40	7 months	5040–5880 kJ/d (50 % carbohydrate, 30 % fat, 20 % protein)	38	5·9 %	N/A	NS	↓	NS	NS	NS	NS	NS

Table 1. *Continued*

Reference	Subjects (n)	Duration	Dietary intervention	Mean baseline BMI (kg/m²)	Weight loss achieved	WC and WHR	FBG	Fasting insulin	Blood fats	MC	Hirsutism	Free testosterone	SHBG
Moran *et al.* (2004)‡	20	16 weeks (12 weeks energy restriction, 4 weeks maintenance)	6000 kJ/d HP (30 % protein, 40 % carbohydrate, 30 % fat) v. HC (15 % protein, 55 % carbohydrate, 30 % fat)	37 HC 36 HP	7·5 %	N/A	NS	↓	N/A	N/A	N/A	N/A	N/A
Stamets *et al.* (2004)‡	26	4 weeks	4200 kJ/d deficit HP (40 % carbohydrate, 30 % fat, 30 % protein) v. HC (55 % carbohydrate, 30 % fat, 15 % protein)	38	3·6 %HP 4·2 %HC	↓	N/A	↓	↓ TC ↓ LDL	N/A	N/A	↓	N/A

WC, waist circumference; WHR, waist:hip ratio; FBG, fasting blood glucose; MC, menstrual cyclicity; SHBG, sex hormone-binding globulin; RO, regular ovulation; NO, anovulatory; N/A, not available or measured; VLCD, very-low-energy diet; TC, total cholesterol; HP, high protein; HC, high carbohydrate.

* In those who lost at least 5 % of body weight.

† In 'responders' only – those who regained ovulation during study.

‡ Effect of hypoenergetic diet for both groups combined – no significant difference between groups.

Only a few studies have compared the use of metformin with diet and exercise in women with PCOS and the findings have been conflicting. A recent study found that while the addition of metformin to a hypoenergetic diet improved menstrual function, there was no improvement in insulin sensitivity and hyperinsulinaemia (Gambineri *et al.* 2004). Similarly, Hoeger *et al.* (2004) found no benefits on insulin sensitivity or glucose metabolism with the addition of metformin to lifestyle changes, although the combination did result in a greater weight loss and reduction in androgen levels compared with lifestyle changes or metformin alone.

Dietary management of insulin resistance

Weight loss and exercise are known to improve insulin sensitivity and reduce the risk of conversion from IGT to diabetes. Altering the composition of the diet, however, independent of weight loss, may also influence insulin sensitivity. Reducing glycaemic load (GL) can reduce postprandial glucose levels and the resulting hyperinsulinaemia that characterises this condition. What is not clear is the best way to achieve a reduction in GL – reducing glycaemic index (GI) or reducing carbohydrate intake. While both types of dietary change will reduce insulin levels, resulting in short-term benefits, the long-term impact of these changes is likely to be quite different. If carbohydrate intake is reduced, it must be replaced by either fat or protein – both of these strategies have potential problems for women with PCOS (see Table 2). Furthermore, while low-carbohydrate diets result in an immediate lowering of blood glucose levels, long-term ingestion of such diets results in an increase in hepatic glucose production and a reduction in peripheral glucose utilisation, a state of insulin resistance (Colagiuri & Brand Miller, 2002).

Dietary fat

While animal studies demonstrate that a diet high in fat, particularly saturated fat, may lead to insulin resistance, human intervention studies investigating changes in dietary fat intake have been inconclusive, possibly due to their short duration and inadequate sample size (Riccadi & Rivellese, 2000). A review by Vessby (2000) found no significant changes in insulin sensitivity with any of the randomised controlled trials conducted in patients with type 2 diabetes or non-diabetic subjects.

Epidemiological studies, however, do suggest an association between a high fat, particularly saturated fat, intake and reduced insulin sensitivity (Feskens & Kromhout, 1990; Lovejoy & DiGirolamo, 1992; Mayer *et al.* 1993; Parker *et al.* 1993; Marshall *et al.* 1997; Mayer-Davis *et al.* 1997). An increased risk of developing type 2 diabetes has also been associated with the consumption of higher-fat diets (Marshall *et al.* 1991; Tsunehara *et al.* 1991; Colditz *et al.* 1992; Marshall *et al.* 1994). Furthermore, subjects with insulin resistance and type 2 diabetes have been found to have changes in the fatty acid pattern in serum cholesteryl esters (a marker of dietary fat intake) with a higher proportion of saturated fatty acids and lower proportions of linoleic acid (Salomaa *et al.* 1990; Vessby *et al.* 1994*a,b*; Öhrvall *et al.* 1996; Wang *et al.* 2003).

Some studies also indicate that a high-fat diet is more deleterious in those who are inactive, supporting the importance of the role of exercise in managing insulin resistance (Marshall *et al.* 1991; Mayer *et al.* 1993; Mayer-Davis *et al.* 1997).

Table 2. Interventions to lower glycaemic load (GL) − benefits and risks

Dietary intervention…	Reduce carbohydrate − replace with MUFA	Reduce carbohydrate − replace with protein	Reduce GI of diet
Effect on GL	Reducing carbohydrate from 55 to 40 % and replacing with MUFA will reduce GL by about 40 units	Reducing carbohydrate from 55 to 45 % and increasing protein from 12 to 25 % will reduce GL by about 35 units	Maintaining a higher-carbohydrate diet but reducing average GI from 70 to 50 will reduce GL by about 50 units
Possible benefits	Increased HDL	Reduced triacylglycerols*	Increased satiety
	Reduced triacylglycerols	Increased weight loss*	Increased HDL
	Traditional Mediterranean diets have been associated with a reduced risk of CVD and some cancers	Increased satiety	Reduced triacylglycerols
			Improved insulin sensitivity
			Increased fat loss
			Reduced NEFA
			Reduced PAI-1 levels
			Reduced risk of type 2 diabetes mellitus
			Reduced risk of CVD
			Reduced risk of some cancers
Possible risks	Possibility of weight gain or reduced weight loss with higher fat intake, especially in a Western diet context	Higher risk of type 2 diabetes associated with higher red meat intake	Nil demonstrated
	Increased NEFA	Effects on kidney function and bone mineral density remain unclear	
		Increased risk of some cancers with higher intake of animal protein and reduced intake of whole grains, fruit and vegetables	

GI, glycaemic index; PAI, plasminogen activator inhibitor.
* Not maintained at 12 months.

While studies comparing high-monounsaturated fat with high-carbohydrate diets have found a high-monounsaturated-fat diet results in reduced triacylglycerols and increased HDL-cholesterol, there is little evidence of the benefits of such diets for improving insulin resistance (Garg, 1998). However, one study of 162 healthy individuals, randomised to a high-saturated-fat or high-MUFA diet for 3 months, found that a high-MUFA diet significantly improved insulin sensitivity (Vessby, for the Kanwu Study Group, 1999). Interestingly, the beneficial effect disappeared when total fat intake exceeded 38 %, possibly explaining why other studies have not found the same benefits of a high-MUFA diet. A recent study in which carbohydrates were exchanged for monounsaturated fats in an energy-restricted diet in thirty-two overweight subjects found a significant reduction in fasting insulin levels along with weight loss that was independent of dietary composition (Colette *et al.* 2003). Total fat contributed 39 % and monounsaturated fat 23 % of energy in this study.

Despite the possible benefits of a higher-fat diet for those with insulin resistance, a major concern with these diets is the possibility of weight gain resulting from the higher energy density (kJ/g food). High-fat diets have been shown to contribute to obesity while *ad libitum* low-fat diets have been shown to prevent weight gain in normal-weight subjects and cause weight loss in overweight subjects (Bray & Popkin, 1998; Astrup *et al.* 2000; Hays *et al.* 2004). Nevertheless, most of the studies to date have been isoenergetic and short-term; thus *ad libitum* long-term studies are needed to clarify the issue. In one such study, the *ad libitum* low-fat high-carbohydrate diet induced weight loss in individuals over a 6-week period while the high-monounsaturated-fat diet did not (Gerhard *et al.* 2004). There was no significant difference in blood fats or blood glucose control between the two diets.

Another concern for those with insulin resistance is the effects of a high-fat diet on thrombogenesis. The optimal anti-thrombogenic diet is one that is low in fat and high in complex carbohydrate and dietary fibre, with fatty acid composition being of minor importance (Marckmann, 2000). Other studies, however, have found a low-fat diet to be associated with potentially adverse effects on haemostatic factors, while replacing saturated fats with MUFA resulted in positive changes (Kris-Etherton *et al.* 2002). PUFA-rich diets may not be as helpful as MUFA-rich diets. One study in women with PCOS found that an increased intake of PUFA resulted in a significant increase in fasting glucose levels and a reduction in plasma NEFA but no change in insulin levels, blood lipids, testosterone or sex hormone-binding globulin levels (Kasim-Karakas *et al.* 2004).

High-protein diets

Recent times have seen a renewed interest in high-protein diets for weight loss, diabetes management and for women with PCOS. To date, however, there is little evidence to suggest benefits of high-protein diets on insulin resistance and some evidence that this type of diet may worsen insulin resistance and impair glucose metabolism (Rossetti *et al.* 1989; Lariviere *et al.* 1994; Linn *et al.* 1996, 2000; Krebs *et al.* 2002).

A number of studies in women with PCOS, overweight and obese subjects, as well as those with hyperinsulinaemia and type 2 diabetes have failed to show significant long-term benefits of a high-protein diet on weight loss or insulin sensitivity (Parker *et al.* 2002; Farnsworth *et al.* 2003; Foster *et al.* 2003; Moran *et al.* 2003; Stamets *et al.* 2004; Stern *et al.* 2004).

Two studies in women with PCOS have shown that while a hypoenergetic diet results in significant weight loss and

consequent improvement in metabolic and reproductive abnormalities, a high-protein diet is no more effective than a high-carbohydrate diet (Moran *et al.* 2004; Stamets *et al.* 2004).

Only one study, of seventy-nine obese subjects with a high prevalence of type 2 diabetes or the metabolic syndrome, found a greater weight loss and a relative improvement in insulin sensitivity and triacylglycerol levels independent of weight loss following 6 months on a low-carbohydrate, higher-protein diet (37 % carbohydrate, 22 % protein) (Samaha *et al.* 2003). At 12 months follow-up, however, differences in weight loss and insulin levels were not significant (Stern *et al.* 2004). Previously, Baba *et al.* (1999) failed to show a significant difference in fasting insulin levels between a high-protein and high-carbohydrate diet in thirteen obese hyperinsulinaemic males despite a greater weight loss on the high-protein diet. Fat loss was not significantly different between the two diets.

Skov *et al.* (1999) studied the effect of replacement of carbohydrate by protein in *ad libitum* fat-reduced diets in sixty-five overweight and obese subjects and found that those following the high-protein diet achieved a greater loss of weight and body fat over the 6-month study period. No differences between total cholesterol and HDL-cholesterol were seen between the groups and while a greater reduction in plasma triacylglycerols was seen after 3 months in the high protein group, there were no significant differences at 6 months. Insulin levels were not measured. Farnsworth *et al.* (2003) also found a greater reduction in fasting triacylglycerols with a higher-protein diet in a study of fifty-seven overweight men and women over 16 weeks, although weight loss was similar to the standard-protein diet. Whether these differences would be sustained over a longer time period is questionable, considering the results from longer-term studies (Skov *et al.* 1999; Foster *et al.* 2003).

Finally, a short 6 d study, comparing a low-GI, low-fat, high-protein diet with the conventional American Heart Association phase 1 diet (high carbohydrate, moderate protein) in abdominally obese men found the low-GI, high-protein diet resulted in favourable changes in the metabolic risk profile, which were significantly different from changes with the American Heart Association diet (Dumesnil *et al.* 2001). The low-GI, high-protein diet, consumed *ad libitum*, resulted in a 25 % reduction in energy intake with no increase in hunger, and a significant decrease in triacylglycerols (35 %) and plasma insulin levels and a significant increase in LDL peak particle size. Whether the benefits achieved with this diet were a result of the lower carbohydrate and higher protein intake, the low GI of the carbohydrate foods consumed, or the combination of these, however, was unclear.

While not increasing blood glucose levels to the same extent as carbohydrate foods, protein foods do elicit an insulin response and the impact of this in those with insulin resistance is not clear. There are also concerns about the safety of high-protein, low-carbohydrate diets including the effects on kidney function, bone mineral density and the reduction in intake of protective foods such as fruit, vegetables and whole grains. Three recent studies have also shown a positive association between dietary haem-Fe intake in women (Lee *et al.* 2004; Song *et al.* 2004) and haem-Fe from red meat in men (Jiang *et al.* 2004) and the risk of type 2 diabetes, while a positive association between intake of red meat, processed meats and animal protein and incidence of type 2 diabetes in women has also been found (Schulze *et al.* 2003; Song *et al.* 2004). While the findings of these studies need to be confirmed, they provide further evidence that diets high in animal protein may be detrimental to those with insulin resistance.

Finally, with a high intake of fruits, vegetables and whole grains shown to protect against CVD, diabetes and cancer, and some studies showing a high intake of animal protein may increase cancer risk (World Cancer Research Fund, 1997), the role of dietary protein needs further investigation for management of this condition. Risk of endometrial cancer, in particular, has been shown to be inversely associated with a higher intake of plant foods, whole grains and soya products and positively associated with a higher intake of energy, fat and animal foods (Zheng *et al.* 1995; Goodman *et al.* 1997; McCann *et al.* 2000; Littman *et al.* 2001; Petridou *et al.* 2002).

Carbohydrates, dietary fibre and glycaemic index

Unlike diets high in fat or protein, there is now a significant body of evidence demonstrating the benefits of low-GI diets. While many of the features of insulin resistance, including postprandial glycaemia and insulinaemia, hypertriacylglycerolaemia, low HDL levels and fibrinolysis may be worsened by a high-carbohydrate diet, there is increasing evidence that the type of carbohydrate in the diet is important. In particular, many studies show that low- and high-GI foods have significantly different effects on metabolism (Jenkins *et al.* 2002).

The concept of GI was first introduced in the early 1980s as a method for classifying carbohydrate foods according to their effect on postprandial glycaemia (Jenkins *et al.* 1981). Early research was concentrated on diabetes and a recent meta-analysis confirmed the benefits of a low-GI diet for individuals with diabetes (Brand-Miller *et al.* 2003).

Since this time, there have been a number of studies showing that a low-GI diet can improve insulin resistance as well as many of its metabolic consequences including increasing HDL and plasminogen activator inhibitor-1 levels (Jenkins *et al.* 1985, 1987; Wolever, 1992; Wolever *et al.* 1992; Frost *et al.* 1999; Jarvi *et al.* 1999). A high-GI diet, in contrast, has been shown to worsen postprandial insulin resistance (Brynes *et al.* 2003).

Several epidemiological studies have also associated a low-GI diet with reduced risk of CVD and type 2 diabetes (Salmeron *et al.* 1997a,b; Liu *et al.* 2000). Of interest, Salmeron *et al.* (1997a,b) found that in both men and women, the association between high dietary GL and an increased risk of type 2 diabetes was related to GI and not the amount of dietary carbohydrate, challenging the idea that a high carbohydrate intake is detrimental to those with insulin resistance. Similarly, McKeown *et al.* (2004) found a positive association between GI and both insulin resistance and prevalence of the metabolic syndrome but no association with total carbohydrate intake.

Both the San Luis Valley study and the Iowa Women's Health Study failed to show a relationship between the amount of carbohydrate and either hyperinsulinaemia or the onset of diabetes (Marshall *et al.* 1994; Meyer *et al.* 2000). A more recent prospective study found that a low-fat high-carbohydrate diet (54 % carbohydrate) was associated with improved glucose tolerance and a reduced progression to diabetes in subjects with IGT (Swinburn *et al.* 2001).

Saldana *et al.* (2004) examined the relationship between macronutrient intake in early pregnancy and the development of glucose intolerance in nearly 1700 women. They found that both the

substitution of carbohydrate for fat and the addition of carbohydrate, without controlling for total energy, significantly reduced the risk of IGT and gestational diabetes mellitus. Predicted probabilities of IGT and gestational diabetes mellitus were reduced by one half with a 10 % decrease in dietary fat and a 10 % increase in dietary carbohydrate.

Wolever & Mehling (2002) found that reducing the GI of the diet without altering total carbohydrate intake reduced postprandial glucose by the same amount as lowering total carbohydrate intake, but only the low-GI diet resulted in significant reduction of NEFA. Lowering NEFA is desirable because high levels are linked with dyslipidaemia (Byrne *et al.* 1994), hypertension (Fagot-Campagna *et al.* 1998) and an increased risk of type 2 diabetes (Paolisso *et al.* 1995) and CVD (Carlsson *et al.* 2000).

The Dietary Approaches to Stop Hypertension (DASH) study also highlighted the benefits of a high-carbohydrate diet (Appel *et al.* 1997). The DASH study showed a significant improvement in lipids and blood pressure with dietary modification, despite a relatively high (57 %)-carbohydrate diet. While not specifically looking at insulin resistance or dietary GI, the intervention diet was high in fruit, vegetables, whole grains and low-fat dairy products and was therefore likely to have been a relatively low-GI diet. The effects of this dietary pattern on insulin sensitivity have since been tested in the PREMIER Interventions on Insulin Sensitivity study, in which a comprehensive behavioural intervention for hypertension (weight loss, reduced Na intake, increased physical activity and moderate alcohol intake) was trialled with and without the DASH dietary pattern. A greater improvement in insulin sensitivity was found with the DASH diet than the comprehensive behavioural intervention alone, supporting the benefits of a high-carbohydrate, high-fibre dietary pattern (Ard *et al.* 2004).

The third National Health and Nutrition Examination Survey found that carbohydrate intakes were not associated with HbA1c, plasma glucose, or serum insulin concentrations but were inversely associated with the risk of elevated serum C-peptide, again supporting the benefits of a higher carbohydrate intake (Yang *et al.* 2003).

Several studies have shown fibre consumption to be associated with a reduced risk of type 2 diabetes (Marshall *et al.* 1997; Boeing *et al.* 2000; Meyer *et al.* 2000). In the Health Professionals Follow-up Study and the Nurses' Health Study there was an independent inverse association between both cereal fibre intake and a low-GI diet and the risk of type 2 diabetes (Salmeron *et al.* 1997*a,b*).

A higher intake of whole grains has also been shown to be associated with a reduced risk of type 2 diabetes (Liu *et al.* 2000; Meyer *et al.* 2000; Montonen *et al.* 2003). Supporting this, Pereira *et al.* (2002) demonstrated improved insulin sensitivity in overweight subjects, independent of body weight, when refined grains were replaced with whole grains over a 6-week period and Liese *et al.* (2003) found a higher intake of whole grains to be associated with increased insulin sensitivity in a study of 978 subjects with normal glucose tolerance or IGT. Intake of high-fibre whole-grain foods has also been shown to be inversely associated with weight gain in middle-aged women (Liu *et al.* 2003).

Considering their increased risk of IGT and type 2 diabetes, these studies are of particular relevance to women with PCOS.

While more research is still needed, studies to date suggest that a moderately high-carbohydrate, lower-GI diet may assist in weight management by influencing appetite and fuel partitioning. Short-term feeding studies have generally found low-GI foods to increase satiety, reduce hunger or lower subsequent voluntary food intake while high-GI foods are associated with increased appetite and higher energy intake (Ludwig *et al.* 1999*a,b*; Ludwig, 2000; Roberts, 2000). High-GI foods have also been shown to be associated with a greater oxidation of carbohydrate and a lower oxidation of fat (Febbraio *et al.* 2000; Pawlak *et al.* 2000). A recent study looking at the effects of high-carbohydrate meals with different GI on substrate utilisation during subsequent exercise found that the low-GI meal resulted in a higher rate of fat oxidation during exercise compared with the higher-GI meal (Wu *et al.* 2003). While some of these studies are underpowered, differences consistently favour a low-GI diet.

In human subjects, a hypoenergetic high-GI diet has been shown to reduce resting energy expenditure to a greater extent than a hypoenergetic low-GI diet, despite similar weight loss over 1 week (Agus *et al.* 2000). A low-GI diet in overweight men resulted in greater fat loss compared with a high-GI diet of similar nutrient content (Bouche *et al.* 2002). A limited number of studies in both adults and children have also shown that weight loss and body-fat loss may be superior on a diet modified to lower GI (Slabber *et al.* 1994; Spieth *et al.* 2000; Dumesnil *et al.* 2001; Brynes *et al.* 2003; Ebbeling *et al.* 2003). In pregnant women, low-GI diets have been shown to reduce weight gain compared with high-GI diets despite similar energy and macronutrient contents (Clapp, 1997). Animal studies provide further evidence of long-term effects on body weight. A recent study in rats found that the high-GI diet resulted in significantly more body fat and less lean body mass than the macronutrient-matched low-GI diet over 18 weeks (Pawlak *et al.* 2004). Despite similar body weights, the high GI group showed impairments in glucose tolerance and fat metabolism and evidence of β-cell destruction.

Low-GI diets have also been associated with a reduced risk of endometrial cancer (Augustin *et al.* 2003), breast cancer (Augustin *et al.* 2001), colon cancer (Franceschi *et al.* 2001) and ovarian cancer (Jenkins *et al.* 2003), all of which may be linked with high insulin levels.

Finally, with little research into dietary composition in PCOS, two studies investigating the effects of diet on modifying hormonal profiles in women are of interest. The first study, in postmenopausal women with high testosterone levels, found that a comprehensive dietary change designed to reduce insulin resistance resulted in a significant increase in sex hormone-binding globulin and a significant decrease in testosterone, body weight, waist:hip ratio, total cholesterol, fasting blood glucose and insulin (Berrino *et al.* 2001). The diet focused on lowering intake of animal fats and increasing intake of fibre, low-GI carbohydrates, monounsaturated and *n*-3 polyunsaturated fats and phyto-oestrogens. The second study found that a diet designed to evoke a low insulin response (with a focus on low-GI carbohydrates) reduced insulin concentrations and weight in obese hyperinsulinaemic females significantly more than a conventional diet with the same energy and macronutrient content (Slabber *et al.* 1994). These studies support the hypothesis that a low-GI diet may provide the greatest benefits for women with PCOS and insulin resistance. Carbohydrate intake in these studies was relatively high (51 and 50 % of energy, respectively).

Diet, weight loss and fertility

Studies using lifestyle modification have demonstrated improvements in ovulation and fertility with modest weight losses of 5–10 % of initial body weight (Kiddy *et al.* 1992; Holte *et al.* 1995; Huber-Buchholz *et al.* 1999; Pasquali *et al.* 2000; Crosignani *et al.* 2003; Moran *et al.* 2003). Energy restriction alone, independent of weight loss, has also been shown to improve reproductive parameters (Moran *et al.* 2003). To date, studies of the effect of dietary composition *per se* on fertility in women with PCOS are limited. One study found no difference in menstrual cyclicity between a high-protein and low-protein diet (Moran *et al.* 2003). Another found that a PUFA-rich diet significantly increased urinary pregnanediol 3-glucuronide in women with PCOS, although only two of the seventeen subjects showed signs of ovulation. Luteinising hormone, follicle-stimulating hormone, sex hormone-binding globulin, dehydroepiandrosterone sulfate and testosterone levels did not change (Kasim-Karakas *et al.* 2004).

Conclusion

The recognition of the link between PCOS and insulin resistance offers an excellent opportunity for the early intervention to prevent or delay the onset of type 2 diabetes and CVD in women with PCOS. While the dietary management of PCOS should focus on weight reduction for those who are overweight, consideration also needs to be given to the role of varying dietary composition in increasing insulin sensitivity. On the balance of evidence, a diet low in saturated fat and high in fibre with predominantly low-GI-carbohydrate foods would appear to be the most logical choice. Such a diet may help short term in improving the symptoms of this condition, as well as long term, in reducing the risk of diseases linked with insulin resistance.

References

Agus MS, Swain JF, Larson CL, Eckert EA & Ludwig DS (2000) Dietary composition and physiologic adaptations to energy restriction. *Am J Clin Nutr* **71**, 901–907.

Andersen P, Seljeflot I, Abdelnoor M, Arnesen H, Dale PO, Lovik A & Birkeland K (1995) Increased insulin sensitivity and fibrinolytic capacity after dietary intervention in obese women with polycystic ovary syndrome. *Metabolism* **44**, 611–616.

Appel LJ, Moore TJ, Obarzanek E, *et al.* (1997) for the DASH Collaborative Research Group A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* **336**, 1117–1124.

Ard JD, Grambow SC, Liu D, Slentz CA, Kraus WE & Svetkey LP (2004) The effect of the PREMIER interventions on insulin sensitivity. *Diabetes Care* **27**, 340–347.

Astrup A, Ryan L, Grunwald GK, Storgaard M, Saris W, Melanson E & Hill JO (2000) The role of dietary fat in body fatness: evidence from a preliminary meta-analysis of *ad libitum* low-fat dietary intervention studies. *Br J Nutr* **83**, Suppl. 1, S25–S32.

Asuncion M, Calvo RM, San Millan JL, Sancho J, Avila S & Escobar-Morreale HF (2000) A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. *J Clin Endocrinol Metab* **85**, 2434–2438.

Atimo WU, El-Mahdi E & Hardiman P (2003) Familial associations in women with polycystic ovary syndrome. *Fertil Steril* **80**, 143–145.

Augustin LS, Dal Maso L, La Vecchia C, Parpinel M, Negri E, Vaccarella S, Kendall CW, Jenkins DJ & Francesch S (2001) Dietary glycemic index and glycemic load, and breast cancer risk: a case-control study. *Annals of Oncology* **12**, 1533–1538.

Augustin LS, Gallus S, Bosetti C, Levi F, Negri E, Franceschi S, Dal Maso L, Jenkins DJ, Kendall CW & La Vecchia C (2003) Glycemic index and glycemic load in endometrial cancer. *Int J Cancer* **105**, 404–407.

Baba NH, Sawaya S, Torbay N, Habbal Z, Azar S & Hashim SA (1999) High protein vs high carbohydrate hypoenergetic diet for the treatment of obese hyperinsulinemic subjects. *Int J Obes* **23**, 1202–1206.

Berrino F, Bellati C, Secreto G, Camerini E, Pala V, Panico S, Allegro G & Kaaks R (2001) Reducing bioavailable sex hormones through a comprehensive change in diet: the diet and androgens (DIANA) randomised trial. *Cancer Epidemiol Biomark Prev* **10**, 25–33.

Bjercke S, Dale PO, Tanbo T, Storeng R, Ertzeid G & Abyholm T (2002) Impact of insulin resistance on pregnancy complications and outcome in women with polycystic ovary syndrome. *Gynecol Obstet Invest* **54**, 94–98.

Boeing H, Weisgerber UM, Jeckel A, Rose HJ & Kroke A (2000) Association between glycated hemoglobin and diet and other lifestyle factors in a nondiabetic population: cross-sectional evaluation of data from the Potsdam cohort of the European Prospective Investigation into Cancer and Nutrition Study. *Am J Clin Nutr* **71**, 1115–1122.

Bouche C, Rizkalla SW, Luo J, Vidal H, Veronese A, Pacher N, Fouquet C, Lang V & Slama G (2002) Five week, low-glycemic index diet decreases total fat mass and improves plasma lipid profile in moderately overweight nondiabetic men. *Diabetes Care* **25**, 822–828.

Brand-Miller J, Hayne S, Petocz P & Colagiuri S (2003) Low-glycemic index diets in the management of diabetes: a meta-analysis of randomised controlled trials. *Diabetes Care* **26**, 2261–2267.

Bray G & Popkin B (1998) Dietary fat intake does affect obesity! *Am J Clin Nutr* **68**, 1157–1173.

Brynes AE, Edwards MC, Ghatei MA, Dornhorst A, Morgan LM, Bloom SR & Frost GS (2003) A randomised four-intervention crossover study investigating the effect of carbohydrates on daytime profiles of insulin, glucose, non-esterified fatty acids and triacylglycerols in middle-aged men. *Br J Nutr* **89**, 207–218.

Byrne CD, Wareham NJ, Brown DC, Clark PM, Cox LJ, Day NE, Palmer CR, Wang TW, Williams DR & Hales CN (1994) Hypertriglyceridaemia in subjects with normal and abnormal glucose tolerance: relative contributions of insulin secretion, insulin resistance and suppression of plasma non-esterified fatty acids. *Diabetologia* **37**, 889–896.

Carlsson M, Westman Y, Almgren P & Groop L (2000) High levels of nonesterified fatty acids are associated with increased familial risk of cardiovascular disease. *Aterioscler Thromb Vasc Biol* **20**, 1588–1594.

Chang RJ, Nakamura RM, Judd HL & Kaplan SA (1983) Insulin resistance in nonobese patients with polycystic ovarian disease. *J Clin Endocrinol Metab* **57**, 356–359.

Ciaraldi TP, Morales AJ, Hickman MG, Odom-Ford R, Olefsky JM & Yen SS (1997) Cellular insulin resistance in adipocytes from obese polycystic ovary syndrome subjects involves adenosine modulation of insulin sensitivity. *J Clin Endocrinol Metab* **82**, 1421–1425.

Clapp JL (1997) Diet, exercise and feto-placental growth. *Arch Gynecol Obstet* **261**, 101–107.

Clark AM, Ledger W, Galletly C, Tomlinson L, Blaney F, Wang X & Norman RJ (1995) Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. *Hum Reprod* **10**, 2705–2712.

Clark AM, Thornley B, Tomlinson L, Galletley C & Norman RJ (1998) Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. *Hum Reprod* **13**, 1502–1505.

Colagiuri S & Brand Miller J (2002) The 'carnivore connection' – evolutionary aspects of insulin resistance. *Eur J Clin Nutr* **56**, Suppl. 1, S30–S35.

Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC & Seizer FE (1992) Diet and risk of clinical diabetes in women. *Am J Clin Nutr* **55**, 1018–1023.

Collette C, Percheron C, Pares-Herbute N, Michel F, Pham T-C, Brillant L, Descomps B & Monnier L (2003) Exchanging carbohydrate for monounsaturated fats in energy-restricted diets: effects on metabolic profile and other cardiovascular risk factors. *Int J Obes* **27**, 648–656.

Conway GS, Agrawal R, Betteridge DJ & Jacobs HS (1992) Risk factors for coronary artery disease in lean and obese women with the polycystic ovary syndrome. *Clin Endocrinol* **37**, 119–125.

Coulam CB, Annegers JF & Kranz JS (1983) Chronic anovulation syndrome and associated neoplasia. *Obstet Gynecol* **71**, 253–256.

Crave JC, Fimbel S, Lejeune H, Cugnardey N, Dechaud H & Pugeat M (1995) Effects of diet and metformin administration on sex hormone-binding globulin, androgens and insulin in hirsute and obese women. *J Clin Endocrinol Metab* **80**, 2057–2062.

Crosignani PG, Colombo M, Vegetti W, Somigliana E, Gessati A & Ragni G (2003) Overweight and obese anovulatory patients with polycystic ovaries: parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet. *Hum Reprod* **18**, 1928–1932.

Dahlgren E, Janson PO, Johansson S, Lapidus L, Lindstedt G & Tengborn L (1994) Hemostatic and metabolic variables in women with polycystic ovary syndrome. *Fertil Steril* **61**, 455–460.

Dahlgren E, Janson PO, Johansson S, Lapidus L & Oden A (1992*a*) Polycystic ovary syndrome and risk for myocardial infarction: evaluated from a risk factor model based on a prospective population study of women. *Acta Obstet Gynecol Scand* **71**, 599–604.

Dahlgren E, Johansson S, Lindstedt G, Knutsson F, Oden A, Janson PO, Mattson LA, Crona N & Lundberg PA (1992*b*) Women with polycystic ovary syndrome wedge resected in 1956 to 1965, a long-term follow-up focusing on natural history and circulating hormones. *Fertil Steril* **57**, 505–513.

Dejager S, Pichard C, Giral P, Bruckert E, Federspield MC, Beucler I & Turpin G (2001) Smaller LDL particle size in women with polycystic ovary syndrome compared to controls. *Clin Endocrinol* **54**, 455–462.

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

Dumesnil JG, Turgeon J, Tremblay A, *et al.* (2001) Effect of a low-glycaemic index-low-fat-high protein diet on the atherogenic metabolic risk profile of abdominally obese men. *Br J Nutr* **86**, 557–568.

Dunaif A, Graf M, Mandeli J, Laumas V & Dobrjansky A (1987) Characterization of groups of hyperandrogenic women with acanthosis nigricans, impaired glucose tolerance and/or hyperinsulinemia. *J Clin Endocrinol Metab* **65**, 499–507.

Dunaif A, Segal KR, Futterweit W & Dobrjansky A (1989) Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes* **38**, 1165–1174.

Ebbeling CB, Leidig MM, Sinclair KB, Hangen JP & Ludwig DS (2003) A reduced-glycemic load diet in the treatment of adolescent obesity. *Arch Pediatr Adolesc Med* **157**, 773–779.

Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK & Imperial J (1999) Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. *Diabetes Care* **22**, 141–146.

Etling MW, Korsen TJ, Bezemer PD & Schoemaker J (2001) Prevalence of diabetes mellitus, hypertension and cardiac complaints in a follow-up study of a Dutch PCOS population. *Hum Reprod* **16**, 556–560.

Fagot-Campagna A, Balkau B, Simon D, Warnet JM, Claude JR, Ducimetiere P & Eschwege E (1998) High free fatty acid concentration: an independent risk factor for hypertension in the Paris Prospective Study. *Int J Epidemiol* **27**, 809–813.

Farnsworth E, Luscombe ND, Noakes M, Wittert G, Argyiou E & Clifton PM (2003) Effect of a high-protein, energy-restricted diet on body composition, glycemic control, and lipid concentrations in overweight and obese hyperinsuilinemic men and women. *Am J Clin Nutr* **78**, 31–39.

Febbraio MA, Keenan J, Angus DJ, Campbell SE & Garnham AP (2000) Preexercise carbohydrate ingestion, glucose kinetics, and muscle glycogen use: effect of the glycaemic index. *J Appl Physiol* **89**, 1845–1851.

Fenkci V, Fenkci S, Yilmazer M & Serteser M (2003) Decreased total antioxidant status and increased oxidative stress in women with polycystic ovary syndrome may contribute to the risk of cardiovascular disease. *Fetil Steril* **80**, 123–127.

Feskens EJ & Kromhout D (1990) Habitual dietary intake and glucose tolerance in euglycemic men: the Zutphen study. *Int J Epidemiol* **19**, 953–959.

Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, Mohammed BS, Szapary PO, Rader DJ, Edman JS & Klein S (2003) A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* **348**, 2082–2090.

Franceschi S, Dal Maso L, Augustin L, Negri E, Parpinel M, Boyle P, Jenkins DJ & La Vecchia C (2001) Dietary glycemic load and colorectal cancer risk. *Ann Oncol* **12**, 173–178.

Franks S (1995) Polycystic ovary syndrome. *N Engl J Med* **333**, 853–861.

Frost G, Leeds AA, Dore CJ, Madeiros S, Brading S & Dornhurst A (1999) Glycemic index as a determinant of serum HDL-cholesterol concentration. *Lancet* **353**, 1045–1048.

Furberg A & Thune I (2003) Metabolic abnormalities (hypertension, hyperglycaemia and overweight), lifestyle (high energy intake and physical inactivity) and endometrial cancer risk in a Norwegian cohort. *Int J Cancer* **104**, 669–676.

Gambineri A, Pelusi C & Genghini S (2004) Effect of flutamide and metformin administered alone or in combination in dieting obese women polycystic ovary syndrome. *Clin Endocrinol* **60**, 241–249.

Gambineri A, Pelusi C, Vicennati V, Pagotto U & Pasquali R (2002) Obesity and the polycystic ovary syndrome. *Int J Obesity* **26**, 883–896.

Garg A (1998) High monounsaturated fat diets for patients with diabetes mellitus: a meta-analysis. *Am J Clin Nutr* **67**, Suppl. 577S–582S.

Gerhard GT, Ahmann A, Meeuws K, McMurry MP, Duell PB & Connor WE (2004) Effects of a low-fat diet compared with those of a high-monounsaturated fat diet on body weight, plasma lipids and lipoproteins, and glycemic control in type 2 diabetes. *Am J Clin Nutr* **80**, 668–673.

Glueck CJ, Wang P, Fontaine RN, Sieve-Smith L, Tracy T & Moore SK (1999) Plasminogen activator inhibitor activity: an independent risk factor for the high miscarriage rate during pregnancy in women with polycystic ovary syndrome. *Metabolism* **48**, 1589–1595.

Goodman MT, Wilkens LR, Hankin JN & Kolonel LN (1997) The association of dietary phytoestrogens with the risk for endometrial cancer. *Am J Epidemiol* **146**, 294–306.

Guzick DS, Wing R, Smith D, Berga SL & Winters SJ (1994) Endocrine consequences of weight loss in obese, hyperandrogenic, anovulatory women. *Fertil Steril* **61**, 598–604.

Hardiman P, Pillay OS & Atiomo W (2003) Polycystic ovary syndrome and endometrial carcinoma. *Lancet* **361**, 1810–1812.

Hays NP, Starling RD, Liu X, Sullivan DH, Trappe TA, Fluckey JD & Evans WJ (2004) Effects of an *ad libitum* low-fat, high carbohydrate diet in body fat distribution in older men and women. *Arch Int Med* **164**, 210–217.

Hoeger KM, Kochman L, Wixom N, Craig K, Miller RK & Guzick DS (2004) A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study. *Fertil Steril* **82**, 421–429.

Holte J, Bergh T, Berne C, Wide L & Lithell H (1995) Restored insulin sensitivity but persistantly increased early insulin secretion after weight loss in obese women with PCOS. *J Clin Endocrinol Metab* **80**, 2586–2593.

Holte J, Gennarelli G, Wide L, Lithell H & Berne C (1998) High prevalence of polycystic ovaries and associated clinical, endocrine and metabolic features in women with previous gestational diabetes mellitus. *J Clin Endocrinol Metab* **83**, 1143–1150.

Huber-Buchholz MM, Carey DGP & Norman RJ (1999) Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. *J Clin Endocrinol Metab* **84**, 1470–1474.

Jakubowicz DJ & Nestler JE (1997) 17α-Hydroxyprogesterone responses to leuprolide and serum androgens in obese women with and without polycystic ovary syndrome after dietary weight loss. *J Clin Endocrinol Metab* **82**, 556–560.

Jarvi AE, Karlstrom BE, Granfeldt YE, Bjorck IE, Asp NG & Vessby BO (1999) Improved glycemic control and lipid profile and normalized fibrinolytic activity on a low-glycemic index diet in type 2 diabetic patients. *Diabetes Care* **22**, 10–18.

Jenkins DJ, Augustin LS, Dal Maso L, *et al.* (2003) Dietary glycemic index, glycemic load and ovarian cancer risk: a case-control study in Italy. *Ann Oncol* **14**, 78–87.

Jenkins DJ, Kendall CW, Augustin LS, Franceschi S, Hamidi M, Marchie A, Jenkins AL & Axelsen M (2002) Glycemic index: overview of implications in health and disease. *Am J Clin Nutr* **76**, 266S–273S.

Jenkins DJ, Wolever TM, Kalmusky J, Giudici S, Giordano C, Patten R, Wong GS, Bird JN, Hall M & Buckley G (1987) Low glycemic index diet in hyperlipidemia: use of traditional starchy foods. *Am J Clin Nutr* **46**, 66–71.

Jenkins DJ, Wolever TM, Kalmusky J, Giudici S, Giordano C, Wong GS, Bird JN, Patten R, Hall M & Buckley G (1985) Low glycemic index carbohydrate foods in the management of hyperlipidemia. *Am J Clin Nutr* **42**, 604–617.

Jenkins DJ, Wolever TM, Taylor RH, Barker H, Fielden H, Baldwin JM, Bowling AC, Newman HC, Jenkins AL & Goff DV (1981) Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr* **34**, 362–366.

Jialal I, Naiker P, Reddi K, Moddley J & Joubert SM (1987) Evidence for insulin resistance in non-obese patients with polycystic ovarian disease. *J Clin Endocrinol Metab* **64**, 1066–1072.

Jiang R, Ma J, Ascherio A, Stampfer MJ, Willett WC & Hu FB (2004) Dietary iron intake and blood donations in relation to risk of type 2 diabetes in men: a prospective cohort study. *Am J Clin Nutr* **79**, 70–75.

Kasim-Karakas SE, Almario RU, Gregory L, Wong R, Todd H & Lasley BL (2004) Metabolic and endocrine effects of a polyunsaturated fatty acid-rich diet in polycystic ovary syndrome. *J Clin Endocrinol Metab* **89**, 615–620.

Kiddy DS, Hamilton-Fairley D, Bush A, Short F, Anyaoku V, Reed MJ & Franks S (1992) Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. *Clin Endocrinol* **36**, 105–111.

Kirchengast S & Huber J (2001) Body composition characteristics and body fat distribution in lean women with polycystic ovary syndrome. *Hum Reprod* **16**, 1225–1260.

Knockenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR & Azziz R (1998) Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinol Metab* **83**, 3078–3082.

Krebs M, Krssak M, Bernroider E, Anderwald C, Brehm A, Meyerspeer M, Nowotny P, Roth E, Waldhausl W & Roden M (2002) Mechanism of amino acid-induced skeletal muscle insulin resistance in humans. *Diabetes* **51**, 599–605.

Kris-Etherton PM, Binkoski AE, Zhao G, Coval SM, Clemmer KF, Hecker KD, Jacques H & Etherton TD (2002) Dietary fat: assessing the evidence in support of a moderate-fat diet; the benchmark based on lipoprotein metabolism. *Proc Nutr Soc* **61**, 287–298.

Lanzone A, Caruso A, Di Simone N, De Carolis S, Fulghesu AM & Mancuso S (1995) Polycystic ovary disease. A risk factor for gestational diabetes. *J Reprod Med* **40**, 312–316.

Lariviere F, Chiasson J, Taverroff A & Hoffer L (1994) Effects of dietary protein restriction on glucose and insulin metabolism in normal and diabetic humans. *Metabolism* **43**, 462–467.

Lee DH, Folsom AR & Jacobs DR Jr (2004) Dietary iron intake and type 2 diabetes incidence in postmenopausal women: the Iowa Women's Health Study. *Diabetologia* **47**, 185–194.

Legro RS (2003) Polycystic ovary syndrome and cardiovascular disease: a premature association? *Endocrine Rev* **24**, 302–312.

Legro RS, Kunselman AR, Dodson WC & Dunaif A (1999) Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J Endocrinol Metab* **84**, 165–169.

Legro RS, Kunselman AR & Dunaif A (2001) Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. *Am J Med* **111**, 607–613.

Lesser KB & Garcia FA (1997) Association between polycystic ovary syndrome and glucose intolerance during pregnancy. *J Matern Fetal Med* **6**, 303–307.

Liese AD, Roach AK, Sparks KC, Marquart L, D'Agostino RB Jr & Mayer-Davis EJ (2003) Whole-grain intake and insulin sensitivity: the Insulin Resistance Atherosclerosis Study. *Am J Clin Nutr* **78**, 965–971.

Linn T, Geyer R, Prassek S & Laube H (1996) Effect of dietary protein intake on insulin secretion and glucose metabolism in insulin-dependant diabetes mellitus. *J Clin Endocrinol Metab* **81**, 3938–3943.

Linn T, Grönemeyer D, Aygen S, Scholz N, Busch M & Bretzel R (2000) Effect of long-term dietary protein intake on glucose metabolism in humans. *Diabetologia* **43**, 1257–1265.

Littman AJ, Beresford SA & White E (2001) The association of dietary fat and plant foods with endometrial cancer (United States). *Cancer Causes Control* **12**, 691–702.

Liu S, Willett WC, Mason JE, Hu FB, Rosner B & Colditz G (2003) Relation between changes in intake of dietary fiber and grain products and changes in weight and development of obesity among middle-aged women. *Am J Clin Nutr* **78**, 920–927.

Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, Hennekens CH & Manson JE (2000) A prospective study of dietary glycemic load, carbohydrate intake and risk of coronary heart disease in US women. *Am J Clin Nutr* **71**, 1455–1461.

Lord JM, Flight IHK & Norman RJ (2003) Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *Br Med J* **327**, 951–966.

Lovejoy J & DiGirolamo M (1992) Habitual dietary intake and insulin sensitivity in lean and obese adults. *Am J Clin Nutr* **55**, 1174–1179.

Ludwig DS (2000) Dietary glycemic index and obesity. *J Nutr* **130**, 280S–283S.

Ludwig DS, Majzoub JA, AI-Zahrani A, Dallal GE, Blanco I & Roberts SB (1999*a*) High glycemic index foods, overeating, and obesity. *Pediatrics* **103**, E261–E266.

Ludwig DS, Pereira MA, Kroenke CH, Hilner JE, Van Horn L, Slattery ML & Jacobs DR Jr (1999*b*) Dietary fibre, weight gain and cardiovascular risk factors in young adults. *J Am Med Assoc* **282**, 1539–1546.

McCann SE, Freudenheim JL, Marshall JR & Brasure JR (2000) Diet in the epidemiology of endometrial cancer in Western New York (United States). *Cancer Causes Control* **11**, 965–974.

McKeown NM, Meigs JB, Liu S, Saltzman E, Wilson PWF & Jacques PF (2004) Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort. *Diabetes Care* **27**, 538–546.

Marckmann P (2000) Dietary treatment of thrombogenic disorders related to the metabolic syndrome. *Br J Nutr* **83**, Suppl. 1, S121–S126.

Marshall JA, Bessesen SH & Hamman RF (1997) High saturated fat and low starch and fibre are associated with hyperinsulinemia in a non-diabetic population – the San Luis Valley Diabetes Study. *Diabetologia* **40**, 430–438.

Marshall JA, Hamman RF & Baxter J (1991) High-fat, low carbohydrate diet and the etiology of non-insulin dependent diabetes mellitus. The San Luis Diabetes Study. *Am J Epidemiol* **134**, 590–603.

Marshall JA, Hoag S, Shetterley S & Hamman RF (1994) Dietary fat predicts conversion from impaired glucose tolerance to NIDDM – The San Luis Valley Diabetes Study. *Diabetes Care* **17**, 50–56.

Mather KJ, Kwan F & Corenblum B (2000) Hyperinsulinemia in polycystic ovary syndrome correlates with increased cardiovascular risk independent of obesity. *Fertil Steril* **73**, 150–156.

Mayer EJ, Newman B, Quesenberry CP Jr & Selby JV (1993) Usual dietary fat intake and insulin concentrations in women twins. *Diabetes Care* **16**, 1459–1469.

Mayer-Davis EJ, Monaco JH, Hoen HM, Carmichael S, Vitolins MZ, Rewers MJ, Haffner SM, Ayad MF, Bergman RN & Karter AJ (1997) Dietary fat and insulin sensitivity in a triethnic population. The role of obesitas. The Insulin Resistance Atherosclerosis Study (IRAS). *Am J Clin Nutr* **65**, 79–87.

Meyer KA, Kushi LH, Jacobs DR, Slavin J, Sellers TA & Folsom AR (2000) Carbohydrates, dietary fibre and incident type 2 diabetes in older women. *Am J Clin Nutr* **71**, 921–930.

Montonen R, Knekt, Jarvinen R, Aromaa A & Reunanen A (2003) Wholegrain and fiber intake and the incidence of type 2 diabetes. *Am J Clin Nutr* **77**, 622–629.

Moran LJ, Noakes M, Clifton PM, Tomlinson L & Norman RJ (2003) Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. *J Clin Endocrinol Metab* **88**, 812.

Moran LJ, Noakes M, Clifton PM, Wittert GA, Tomlinson L, Galletly C, Luscombe ND & Norman RJ (2004) Ghrelin and measures of satiety are altered in polycystic ovary syndrome but not differentially affected by diet composition. *J Clin Endocrinol Metab* **89**, 3337–3344.

Norman RJ, Masters L, Milner CR, Wang JX & Davies MJ (2001) Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome. *Hum Reprod* **16**, 1995–1998.

Öhrvall M, Berglund L, Salminen I, Lithell H, Aro A & Vessby B (1996) The serum cholesterol ester fatty acid composition but not the serum concentration of alpha tocopherol predicts the development of myocardial infarction in 50-year-old men, 19 years follow up. *Atherosclerosis* **127**, 65–71.

Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, *et al.* (1997) Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* **20**, 537–544.

Paolisso G, Tataranni PA, Foley FE, Bogardus C, Howard BV & Ravussin E (1995) A high concentration of fasting plasma non-esterified fatty acids is a risk factor for the development of NIDDM. *Diabetologia* **38**, 1213–1217.

Paradisi G, Fulghesu AM, Ferrazzani S, Moretti S, Proto C, Soranna L, Caruso A & Lanzone A (1998) Endocrino-metabolic features in women with polycystic ovary syndrome during pregnancy. *Hum Reprod* **13**, 542–546.

Parker B, Noakes M, Luscombe N & Clifton P (2002) Effect of a high-protein, high-monounsaturated fat weight loss diet on glycemic control and lipid levels in type 2 diabetes. *Diabetes Care* **25**, 425–430.

Parker DR, Weiss ST, Troisi R, Cassano PA, Vokones PS & Landsberg L (1993) Relationship of dietary saturated fatty acids and body habitus to serum insulin concentrations, the normative aging study. *Am J Clin Nutr* **58**, 129–136.

Pasquali R, Antenucci D, Casimirri F, Venturoli S, Paradisi R, Fabbri R, Balestra V, Melchionda N & Barbara L (1989) Clinical and hormonal characteristics of obese amenorrheic hyperandrogenic women before and after weight loss. *J Clin Endocrinol Metab* **68**, 173–179.

Pasquali R & Casimirri F (1993) The impact of obesity on hyperandrogensim and polycystic ovary syndrome in premenopausal women. *Clin Endocrinol* **39**, 1–16.

Pasquali R, Casimirri F, Cantobelli S, Labate AM, Venturoli S, Paradisi R & Zannarini L (1993) Insulin and androgen relationships with abdominal body fat distribution in women with and without hyperandrogensim. *Horm Res* **39**, 179–187.

Pasquali R, Casimirri F, Venturoli S, Antonio M, Morselli L, Reho S, Pezzoli A & Paradisi R (1994) Body fat distribution has weight-independent effects on clinical, hormonal and metabolic features of women with polycystic ovary syndrome. *Metabolism* **43**, 706–713.

Pasquali R, Gambineri A, Biscotti D, Vicennati V, Gagliardi L, Colitta D, Fiorini S, Cognigni GE, Filicori M & Morselli-Labate AM (2000) Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. *J Clin Endocrinol Metab* **85**, 2767–2774.

Pawlak D, Kushner J & Ludwig D (2004) Effects of dietary glycaemic index on adiposity, glucose homoeostasis, and plasma lipids in animals. *Lancet* **364**, 778–785.

Pawlak DB, Denyer GS & Brand-Miller JC (2000) Low post-prandial fat oxidation after a high glycemic index meal leads to increased body fat in chronically fed rats. *Obes Res* **8**, 128S Abstr.

Pereira MA, Jacobs DR Jr, Pins JJ, Raatz SK, Gross MD, Slavin JL & Seaquist ER (2002) Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. *Am J Clin Nutr* **75**, 848–855.

Petridou E, Kedikoglou S, Koukoulomatis P, Dessypris N & Tricholpoulous D (2002) Diet in relation to endometrial cancer risk: a case-control study in Greece. *Nutr Cancer* **44**, 16–22.

Pierpoint T, McKeigue PM, Isaacs AJ, Wild SH & Jacobs HS (1998) Mortality of women with polycystic ovaries at long-term follow-up. *J Clin Epidemiol* **51**, 581–586.

Pirwany IR, Fleming R, Greer IA, Packard CJ & Sattar N (2001) Lipids and lipoprotein subfractions in women with PCOS: relationship to metabolic and endocrine parameters. *Clin Endocrinol* **54**, 447–453.

Radon PA, McMahon MJ & Meyer WR (1999) Impaired glucose tolerance in pregnant women with polysystic ovary syndrome. *Obstet Gynecol* **94**, 194–197.

Riccardi G & Rivellese AA (2000) Dietary treatment of the metabolic syndrome – the optimal diet. *Br J Nutr* **83**, Suppl. 1, S143–S148.

Roberts SB (2000) High-glycemic index foods, hunger, and obesity: is there a connection? *Nutr Rev* **58**, 163–169.

Robinson S, Henderson AD, Gelding SV, Kiddy D, Niththyananthan R, Bush A, Richmond W, Johnston DG & Franks S (1996) Dyslipidaemia is associated with insulin resistance in women with polycystic ovarian syndrome. *Clin Endcrinol* **44**, 277–284.

Rossetti L, Rothman D, DeFronzo R & Shulman G (1989) Effect of dietary protein on in vivo insulin and liver glycogen repletion. *Am J Physiol* **257**, E212–E219.

Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* **81**, 19–25.

Sabate J (2003) The contribution of vegetarian diets to health and disease: a paradigm shift? *Am J Clin Nutr* **78**, Suppl. 502S–507S.

Sabuncu T, Vural H & Harma M (2001) Oxidative stress in polycystic ovary syndrome and its contribution to the risk of cardiovascular disease. *Clin Biochem* **34**, 401–413.

Saldana TM, Siega-Riz AM & Adair LS (2004) Effect of macronutrient intake on the development of glucose intolerance during pregnancy. *Am J Clin Nutr* **79**, 479–486.

Salmeron J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, Stampfer MJ, Wing AL & Willett WC (1997a) Dietary fibre, glycaemic load and risk of NIDDM in men. *Diabetes Care* **20**, 545–550.

Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL & Willett WC (1997b) Dietary fibre, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *J Am Med Assoc* **277**, 472–477.

Salomaa V, Ahola I, Tuomilehto J, Aro A, Pietinen P, Korhonen HJ & Penttila I (1990) Fatty acid composition of serum cholesterol esters in different degree of glucose intolerance. *Metabolism* **39**, 1285–1291.

Samaha FF, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, Williams T, Williams M, Gracely EJ & Stern L (2003) A low-carbohydrate as compared with a low-fat diet in severe obesity. *N Engl J Med* **348**, 2074–2081.

Sampson M, Kong C, Patel A, Unwin R & Jacobs HS (1996) Ambulatory blood pressure profiles and plasminogen activator inhibitor (PAI-1)

activity in lean women with and without the polycystic ovary syndrome. *Clin Endocrinol* **45**, 623–629.

Schulze MB, Manson JE, Willett WC & Hu FB (2003) Processed meat intake and incidence of type 2 diabetes in younger and middle-aged women. *Diabetologia* **46**, 1465–1473.

Skov AR, Toubro S, Ronn B, Holm L & Astrup A (1999) Randomized trial on protein vs carbohydrate in *ad libitum* fat reduced diet for the treatment of obesity. *Int J Obes* **23**, 528–536.

Slabber M, Barnard HC, Kuyl JM, Dannhauser A & Schall R (1994) Effects of a low-insulin response, energy-restricted diet on weight loss and plasma insulin concentrations in hyperinsulinemic obese females. *Am J Clin Nutr* **60**, 48–53.

Song Y, Manson JE, Buring JE & Liu S (2004) A prospective study of red meat consumption and type 2 diabetes in middle-aged and elderly women: the Women's Health Study. *Diabetes Care* **27**, 2108–2115.

Spieth LE, Harnish JD, Lenders CM, Raezer LB, Pereira MA, Hangen SJ & Ludwig DS (2000) A low-glycemic index diet in the treatment of pediatric obesity. *Arch Pediatr Adolesc Med* **154**, 947–951.

Stamets K, Taylor DS, Kunselman A, Demers LM, Pelkman CL & Legro RS (2004) A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome. *Fertil Steril* **81**, 630–637.

Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, Williams M, Gracely EJ & Samaha FF (2004) The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Int Med* **140**, 778–785.

Strowitzki T, Halser B & Demant T (2002) Body fat distribution, insulin sensitivity, ovarian dysfunction and serum lipoproteins in patients with polycystic ovary syndrome. *Gynecol Endocrinol* **16**, 45–51.

Swinburn BA, Metcalf PA & Ley SJ (2001) Long term (5 year) effects of a reduced-fat diet intervention in individuals with glucose intolerance. *Diabetes Care* **24**, 619–624.

Talbott E, Clerici A, Berga SL, Kuller L, Guzick D, Detre K, Daniels T & Engberg RA (1998) Adverse lipid and coronary heart disease risk profiles in young women with polycystic ovary syndrome: results of a case-control study. *J Clin Epidemiol* **51**, 415–422.

Talbott E, Guzick D, Clerici A, Berga S, Detre K, Weimer K & Kuller L (1995) Coronary heart disease risk factors in women with polycystic ovary syndrome. *Arterioscler Thromb Vasc Biol* **15**, 821–826.

Talbott EO, Zborowski JV, Guzick DS, *et al.* (2000) Increased PAI-1 levels in women with polycystic ovary syndrome: Evidence for a specific 'PCOS' effect independent of age and BMI. In *Programs and Abstracts of the 40th Annual Conference on Cardiovascular Disease Epidemiology and Prevention*, p. 13. San Diego, CA: American Heart Association.

Tsunehara CH, Leonetti DL & Fujimoto WY (1991) Animal fat and cholesterol intake is high in men with IGT progressing to NIDDM. *Diabetes* **40**, Suppl., 427A.

Tuomilehto J, Lindstrom J, Eriksson JG, *et al.* (2001) Prevention of type 2 diabetes by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* **344**, 1343–1350.

van Dam EW, Roelfsema F, Veldhuis JD, Helmerhorst FM, Frolich M, Meinders AE, Krans HM & Pijl H (2002) Increase in daily LH secretion in response to short-term calorie restriction in obese women with PCOS. *Am J Physiol* **282**, E865–E872.

Vessby B (2000) Dietary fat and insulin action in humans. *Br J Nutr* **83**, Suppl. 1, S91–S96.

Vessby B, Aro A, Skarfors E, Berglund L, Salminen I & Lithell H (1994*a*) The risk to develop NIDDM is related to the fatty acid composition of the serum cholesterol esters. *Diabetes* **43**, 1353–1357.

Vessby B, for the Kanwu Study Group (1999) Effect of dietary fat on insulin sensitivity and insulin secretion. The Kanwu Study. *Diabetologia* **42**, Suppl. 1, A46.

Vessby B, Tengblad S & Lithell H (1994*b*) The insulin sensitivity is related to the fatty acid composition of the serum lipids and the skeletal muscle phospholipids in 70 year old men. *Diabetologia* **37**, 1044–1050.

Wahrenberg H, Ek I, Reynisdottir S, Carlström K, Bergqvist A & Arner P (1999) Divergent effects of weight reduction and oral anticonception treatment on adrenergic lipolysis regulation in obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab* **84**, 2182–2187.

Wang L, Folsom AR, Zheng Z-J, Pankow JS & Eckfeldt JH (2003) ARIC Study Investigators. Plasma fatty acid composition and incidence of diabetes in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr* **78**, 91–98.

Weerakiet S, Srisombut C, Bunnag P, Sangtong S, Chuangsoongnoen N & Rojansakul A (2001) Prevalence of type 2 diabetes mellitus and impaired glucose tolerance in Asian women with polycystic ovary syndrome. *Int J Gyneacol Obstet* **75**, 177–184.

Wijeyarante CN, Nirantharakumar K, Balen AH, Barth JH, Sheriff R & Belchetz PE (2004) Plasma homocysteine in polycystic ovary syndrome: does it correlate with insulin resistance and ethnicity? *Clin Endocrinol* **60**, 560–567.

Wild RA (1995) Obesity, lipids, cardiovascular risk, and androgen excess. *Am J Med* **98**, S27–S32.

Wild RA, Alaupovic P & Parker LJ (1992) Lipid and apolipoprotein abnormalities in hirsute women I. The association with insulin resistance. *Am J Obstet Gynecol* **166**, 1191–1196.

Wild S, Pierpoint T, McKeigue P & Jacobs HS (2000) Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: a retrospective cohort study. *Clin Endocrinol* **52**, 595–600.

Wolever TM (1992) Beneficial effect of a low glycemic index diet in type 2 diabetes. *Diabet Med* **9**, 451–458.

Wolever TM, Jenkins DJ, Vuskan V, Jenkins AL, Wong GS & Josse RG (1992) Beneficial effect of low-glycemic index diet overweight NIDDM subjects. *Diabetes Care* **15**, 562–564.

Wolever TMS & Mehling C (2002) Long-term effect of varying the source or amount of dietary carbohydrate on postprandial plasma glucose, insulin, triacylglyerol, and free fatty acid concentrations in subjects with impaired glucose tolerance. *Am J Clin Nutr* **77**, 612–621.

World Cancer Research Fund (1997) *Food, Nutrition and Cancer: a Global Perspective*. Washington, DC: American Institute of Cancer Research.

Wu CL, Nicholas C, Williams C, Took A & Hardy L (2003) The influence of high-carbohydrate meals with different glycaemic indices on substrate utilization during subsequent exercise. *Br J Nutr* **90**, 1049–1056.

Yang EJ, Kerver JM, Park YK, Kayitsinga J, Allison DB & Song WO (2003) Carbohydrate intake and biomarkers of glycemic control among US adults: the third National Health and Nutrition Examination Survey (NHANES III). *Am J Clin Nutr* **77**, 1426–1433.

Yildirim B, Sabir N & Kaleli B (2003) Relation of intra-abdominal fat distribution to metabolic disorders in nonobese patients with polycystic ovary syndrome. *Fertil Steril* **79**, 1358–1364.

Zheng W, Kushi LH, Potter JD, Sellers TA, Doyle TJ, Bostick RM & Folsom AR (1995) Dietary intake of energy and animal foods and endometrial cancer. *Am J Epidemiol* **142**, 388–394.