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Diet and Nutrition in Polycystic Ovary Syndrome (POCS): Pointers for Nutritional Management

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Introduction

The most common endocrine disorder, PCOS is becoming commoner due to increased awareness and the global increase in the prevalence of overweight and obesity. It is a heterogeneous disorder that has been difficult to define because there is no single abnormality or diagnostic test that defines the syndrome. While precise definitions are important for scientific studies, as a working definition the syndrome may be diagnosed if at least two of the following are present:

- Oligomennorhoea or amenorrhoea associated with decreased ovulation. PCOS is the commonest cause of anovulatory infertility.
- Hyperandrogenaemia or clinical features of androgen excess, in the absence of other underlying disease states.
- Abnormal ovarian ultrasound with 12 or more follicles in each ovary each having a diameter of 2-9mm, or increased ovarian volume.
- Increased LH with increased LH/FSH ratio.

The diagnosis is more certain with the presence of increasing number of features. Many overweight or obese women have menstrual irregularity, decreased fertility or hirsutism without fulfilling diagnostic criteria for PCOS. The pathogenesis and management of these is the same as for women with PCOS. Specific treatments for hirsutism and subfertility have substantially improved management of PCOS in recent years but do not generally influence the underlying condition which is largely due to over-nutrition and insulin resistance. Even PCOS patients who are not overweight are often insulin resistant, and modest weight loss improves outlook in patients of near normal body weight. The association of PCOS with the abnormalities of metabolic syndrome (central obesity, dyslipidaemia, hypertension and glucose intolerance) is

responsible for the documented relationship with type 2 diabetes, cardiovascular disease and hormonally-responsive cancers in later life. [1 2] This article reviews our understanding of nutritional aspects of PCOS, and proposes an approach to diet management and nutritional therapy in patients with PCOS. The optimal approach to dietary management of patients with PCOS remains to be defined. [3] This review sets out some general principles around which a tailored approach to the individual patients can be designed.

Prevalence and Association with Obesity

The prevalence of PCOS varies between populations, as does the strength of the association between PCOS and insulin resistance or obesity. These differences may arise from genetic factors and from differences in lifestyle. Furthermore, cultural differences in attitudes to fertility and racial differences in hirsutism may influence presentation. PCOS prevalence amongst young women in the reproductive years is generally quoted at 5 – 10%. [1] There may also be variation within populations with ethnic groups who are at high risk of metabolic syndrome also being at high risk of PCOS. This may apply, for example, to individuals of Asian descent in the UK and to the black population of the US. A study from USA [4] in an unselected population showed that the prevalence of PCOS for black and white women were 8.0 and 4.8%, respectively. Furthermore, the features of PCOS may vary amongst different racial groups because of differences in body mass, diet, and exercise habit. [5]

Insulin resistance is present in women with PCOS independent of body mass. However, obesity in PCOS is associated with greater insulin resistance, and higher

incidence of dyslipidaemia and diabetes. The incidence of diabetes and lipid disorders is higher. At least 50% of women with PCOS are overweight or obese. [6] Abdominal adiposity or android pattern obesity (waist-hip ratio > 0.85) is also common in PCOS. [7 8] Android fat distribution is also present in 70% of lean women with PCOS, placing them at risk of metabolic disturbances. [7] Risk of glucose intolerance among women with PCOS patients is 5- to10-fold higher than normal, and the typical age of onset of impaired glucose tolerance or diabetes is in the third or fourth decades, earlier than in the general population. [9] In later life, the risk of developing type 2 diabetes is potentially increased seven-fold in patients who have had PCOS. [10] As in the non-PCOS population, obesity in PCOS is associated with endothelial dysfunction, decreased adiponectin and other changes in adipokines that contribute to metabolic and cardiovascular risk. [5] Several mechanisms have been proposed for insulin resistance in PCOS, including peripheral target tissue resistance, reduced hepatic clearance or increased pancreatic sensitivity. [11] In obesity, free fatty acids and tumor necrosis factor-α (TNF-α), released from adipose tissue may play a key role in pathogenesis of insulin resistance. [12] Other pro-inflammatory cytokines are also increased, including interleukin-6 [13] and interleukin-18. [14 15] As with metabolic syndrome and type 2 diabetes, plasma adiponectin is decreased and there is increase leptin and resistin. [13] The complex pathogenesis of the condition and its relationship with metabolic syndrome is demonstrated by a recent study [16] where gene expression profiling of visceral fat from patients with PCOS was carried out. The was increased expression of pro-inflammatory genes, as well as those involved in regulating immune function, oxidative stress, lipid metabolism, and insulin signaling.

Obesity has significant effects on clinical manifestations of PCOS: Menstrual/ ovulatory disturbances tend to be more marked in the obese; Androgen levels are higher contributing to hirsutism and acanthosis nigricans; [17] Fertility is decreased and the rate of spontaneous abortion increased. [18] Obesity is clearly a major determinant of many of the long-term consequences of PCOS including glucose intolerance and risk of cardiovascular disease. Both obesity and insulin resistance are major influences on whether patients with PCOS have features of the metabolic syndrome. [19 20] The increased risk of endometrial carcinoma in patients with PCOS is may also be more marked in patients who are obese and insulin resistant. [21] Patients with PCOS who become pregnant are at increased risk of developing gestational diabetes. [22] Emotional factors including stress, depression, and distorted body image are important determinants of symptoms and presentation, but also of response to treatments, including lifestyle interventions. [23-26] The influence of psychological factors must always be taken into account when considering treatment options. Low self esteem and impaired quality of life are common amongst women with PCOS, [27] and if the effect of these factors is not appreciated lifestyle interventions, in particular, are likely to prove ineffective.

Calorie Requirements and Restriction

Many studies in overweight and obese subjects have shown beneficial effects of even modest (5% or more) weight loss on well-being, insulin sensitivity, and cardiovascular risk profile. There is every reason to believe that these benefits extend to women with PCOS. [3] Studies in patients with PCOS confirm that modest weight loss improves glucose tolerance, cardiovascular risk profile and reproductive function.

[28-31] Modest weight loss achieved in the short term may also improve some of the endocrine abnormalities associated with PCOS: Hyperinsulinaemia contributes both to increased androgen production in response to LH in the ovary and also to the increased levels of free androgen by decreasing SHBG. Peripheral aromatisation of androgens to oestrogen adds to the relatively high oestrogen state which may increase the long-term risk of certain cancers, and exacerbate the endocrine abnormalities seen in patients with PCOS. Short periods of calorie restriction lead to decreased androgen levels, and this is sufficient in some patients to restore normal LH pulse frequency and amplitude with consequent restoration of normal menstruation. However, LH secretion remains abnormal in some patients suggesting that they may have intrinsic abnormalities of pituitary-ovarian axis function. [32 33] Leptin is a hormone that is produced exclusively by adipocytes and is responsible, in the physiological state, for decreased feeding, and therefore energy intake, when the organism is replete. It is also involved in regulation of reproductive function and decreased leptin production with weight loss may help to normalise reproductive function. Ghrelin is a 28 amino acid acylated peptide secreted by the stomach in response to imminent feeding. It is an endogenous ligand for the growth hormone receptor and secretion prior to meals stimulates feeding, decreases energy expenditure and stimulates gastric motility and acid secretion. Increased ghrelin levels in patients with PCOS may be part of the abnormal state of energy balance, and this abnormality is again restored toward normal with calorie restriction and weight loss. [29]

In approaching dietary management, it is important to take into account the calorie requirements of the individual. The recommended daily intake for women is

summarized in Table 1. Calorie requirements are higher for women with higher body mass and, and increase in relation to activity. It is often useful to initially focus on the eating pattern and the macronutrient content of the diet rather than to try too quickly to promote both healthy eating and weight loss. Energy deficit can be achieved either by limiting nutrient intake or by increasing calorie expenditure. The best approach is a combination of the two. A daily calorie deficit of as little as 200 kcal per day will prevent weight gain and promote weight loss in the longer term. A deficit of 500 kcal per day is needed for the average person to lose 0.5 kg per week, while a 1,000 kcal deficit is needed for 1 kg weight loss per week. These deficits are often hard to achieve in practice, explaining why many patients find it difficult to achieve satisfactory weight loss. There is a distinct impression, but it is not clear from published evidence, that women with PCOS find it harder than average to lose weight. It is important to recognize that improved abdominal obesity and insulin sensitivity may occur without an overall change in body weight. In particular, body composition of patients who exercise regularly may change with increased lean body mass and decreased fat mass, but no overall change in weight. Increased lean body mass (muscle) increases resting energy expenditure and may help improve hormonal and metabolic parameters in women with PCOS. While the benefits of modest weight loss have become more widely appreciated in recent years, this should not preclude us from aiming for as near normal body weight and composition as possible where this is feasible. To that end, our range of dietary options is increasing. For example, short-term meal substitution to achieve calorie deficit is now recognized as an option for women with PCOS. [34]

Dietary Fat and Protein

Fat is the most energy-rich macronutrient component of the diet containing 9 kilocalories per gram, compared with only 4 kilocalories per gram for carbohydrate and protein. Furthermore, the body has virtually infinite capacity to store fat, particularly in hyperinsulinaemic individuals. Experiments with fat overfeeding suggest that fat excess decreases carbohydrate oxidation with no apparent change in fat oxidation. When carbohydrate is present in excess, or is inadequately oxidized, fat deposition is increased through the process of *de novo* lipogenesis. Cross sectional studies indicate that higher fat intake is associated with impaired insulin sensitivity, but this relationship is mainly due to obesity. [35] [36] By contrast, intervention studies showed that a reasonable increase in total fat intake (from 20% to 40%) had no major impact on insulin sensitivity. [35] Hence, a potential criticism regarding the deleterious effects of high-protein low-carbohydrate diets on increasing fat intake may be not applicable, at least in short-term interventions. [37]

Increased consumption of unsaturated fatty acids has been reported to improve insulin sensitivity in healthy (Vessby et al. 2001), obese and type 2 diabetic subjects (Summers et al. 2003). However, the beneficial effects of the fat quality on insulin sensitivity were observed in individuals with less than 37% of total energy intake as fat. [38] A recent investigation [39] focused on a diet supplemented in polyunsaturated fatty acids (PUFA) which have been associated with positive health benefits in a number of studies. Administration of a diet supplements with walnuts to increase levels of linoloeic and α-linolenic acids, surprisingly increased glucose levels, both fasting and during an oral glucose tolerance test. One explanation might be that total

fat intake in that study was more than 37% (39 ± 1%). There was no change in levels of insulin or of reproductive hormones. The longer chain PUFAs, eicosapentaenoic acid and docosahexaenoic acid which are found in fish oil have beneficial effects on metabolic parameters in patients with diabetes, but specific evidence relating to PCOS is not available at this stage. While the Mediterranean diet, rich in monounsaturated fatty acids (MUFA), has been widely accepted as a gold standard for healthy diets, its potential benefits in patients with PCOS have not been documented, although decreased features of obesity and insulin resistance have been noted in Italian compared with American patients with PCOS. [5] Overall, dietary fat should account for no more than 30% of the calorie content of the diet, with a maximum of 10% of calories coming from saturated fat. The remainder of the fat content should be as a balanced mixture of unsaturated fat including cooking oils and spreads. Consumption of trans fats – unsaturated fats which, because of internal resonance in the molecule between double bonds, behave like unsaturated fats – has been recently linked with increased risk of anovulatory infertility. [40]

Diets that are either low in fat or low in carbohydrate almost inevitably deliver an increased proportion of calorie intake as protein. Although it has been controversial, recent evidence suggests that higher intake of protein improves the glucose and insulin responses to a glucose load. [41 42] Higher protein intake also increases satiety and may contribute to increasing postprandial thermogenesis, as well as decreasing abdominal fat. Adequate protein intake is important to protect lean body mass and to increase muscle in response to exercise. There have been recent concerns about high intake of red meat as increased body stores of iron have been linked to risk of

developing type 2 diabetes. General advice is that the diet should deliver 20% of its calories as protein, this may be increased at the expense of other dietary components for short-term diets designed to help the patient lose weight or improve glucose tolerance.

Dyslipidaemia in patients with PCOS is an important determinant of long-term cardiovascular risk. This is most commonly manifest as low HDL-cholesterol but because triglycerides are often relatively low, a full atherogenic lipid profile is often not expressed. However, subtle abnormalities including alterations in lipoprotein particle size and increase LDL II and IV subclasses may contribute to susceptibility to macrovascular disease. [43] Combined oral contraceptives including combinations of the antiandrogenic progestagen cyproterone acetate with ethinyloestradiol are often used to achieve cycle control, decrease androgenic symptoms, to protect the endometrium, as well as for their contraceptive action. Their effect on glucose tolerance and lipid profile is complex and controversial. It is clear that, in some individuals, they can increase glucose intolerance and circulating triglyceride levels. [44] Increased weight during oral contraceptive use may also have an adverse effect on long-term cardiovascular risk. [45] The dyslipidaemic effect of combined oral contraceptive treatment is prevented by concurrent use of a statin drug which also decreases the low-grade inflammation (increased C-reactive protein) that often accompanies PCOS. [46] A recent report also suggests that statins may have beneficial effects on the endocrine profile in PCOS, including decreasing circulating testosterone levels. [47] Low circulating sex hormone binding globulin (SHBG) has been advocated as a marker for the dyslipidaemia associated with insulin resistance

(including PCOS), [48] although variability in measured values might preclude its use in routine practice. [49]

Dietary Carbohydrate

The glycaemic load of a diet is defined as the amount of carbohydrate multiplied by the glycaemic index (GI). Foods with high GI deliver carbohydrate rapidly following ingestion. High glycaemic load is associated with increased risk of diabetes and with poor glycaemic control in patients with established diabetes. Glycaemic load can be decreased either by decreasing the amount of carbohydrate (in an isocaloric diet an increased proportion of calories are as MUFA or as protein) or by consuming foods of lower GI. The latter has been shown to improve insulin sensitivity, decrease post prandial hyperglycaemia, decease triglycerides and increase HDL-cholesterol. [3] Apart from the fact that they are low GI, whole grain foods may have a specific role in protecting against development of diabetes. Low-carbohydrate diets have been controversial and public interest in these diets has preceded and, to an extent driven, scientific interest. We have recently reviewed the literature relating to the use of these diets in people who have or are at risk of type 2 diabetes [50] Low carbohydrate diets are effective in promoting weight loss when used for periods up to six months. They are only effective if they deliver fewer calories than are being used (i.e. they are hypocaloric). They appear to be safe for short-term use and, indeed, improve cardiovascular risk profile. The diets used vary in the degree of carbohydrate restriction. A period of relatively strict carbohydrate restriction helps at the start of the diet, but the diet does not have to be severely restricted in carbohydrate to be effective. Care should be taken to limit the intake of fat, particularly saturated fat and

the diets work best when they moderately restrict calorie intake and are used alongside a suitable exercise programme.

Many studies with low-carbohydrate diets have been carried out over relatively short periods of time. This limitation has been overcome by more recent studies. Thus, greater weight loss with a low-carbohydrate diet compared with conventional diet after 6 months has been reported, [51 52] but the difference between the two diets was not sustained at 12 months. [53 54] Further investigations in obese patients demonstrated inconsistency in terms of weight reduction after 12 months on low-carbohydrate diets. [37 55] The effects of high-protein low-carbohydrate versus low-protein high-carbohydrate diets on PCOS have been evaluated only in two experiments. [30 56] Both of these studies reported no significant differences in weight loss in terms of the different protein content of the diets. However, these studies were very short term (one and three months respectively).

No significant differences were observed between low-carbohydrate and high-carbohydrate diets on fasting insulin levels, or insulin sensitivity as assessed by homeostatic model assessment (HOMA). [42 57 58] However, a lower postprandial insulin response was reported in subjects consuming a low-carbohydrate diet. [42 57] In one recent study, [31] both fasting and post-challenge insulin levels were decreased by low-carbohydrate diet. More marked improvement in triglycerides [51] and HDL-cholesterol [54] have been noted with low-carbohydrate diets compared with conventional diets. Other studies have reported improvements in LDL-cholesterol particle size, [59] LDL concentration, [37 60] and postprandial blood-lipid profile. [37] Low-

carbohydrate diets have been associated with deleterious effects on lipid profile when used long-term, [61] and thus severe carbohydrate restriction should be regarded as a short-term measure to achieve weight loss. Recent trials confirm that restriction of dietary carbohydrate can lead to improved adipokine levels towards values that indicate a more normal, insulin-sensitive state, [62] and along with this there is an improvement in cardiovascular risk profile. [63]

Regulation of appetite is complex and fluctuations in blood glucose may play a part in stimulating appetite and increasing energy intake. Both insulin and blood glucose fluctuate more widely in patients with insulin resistance. This fluctuation commonly gives rise to reactive hypoglycaemia. For example, Altuntas et al. [64] studied 64 lean women with PCOS and showed that reactive hypoglycaemia occurred in 50% following a glucose load. The phenomenon was associated with lower levels of androgen and prolactin and tended to occur in women with higher levels of β cell function. Many women with PCOS describe carbohydrate cravings and cite this as a reason for their difficulty in losing weight. Hypoglycaemia is known to stimulate feeding behaviour, increasing both total food and fat intake. [65] Glucose sensing neurones are present in the hypothalamus, basal ganglia, limbic system, and nucleus tractus solitarius. [66] Glucose responsive neurones express the components of the sulphonylurea receptor (Kir 6.2 and SUR) and glucokinase, and sense increased glucose in a manner akin to the pancreatic β cell. Another population of glucose sensing neurones fire in response to decreased glucose. The components of the glucose sensing mechanism (glucokinase and sulphonylurea receptor) are also present in neurones that secret neuropetide Y (NPY) or pro-opiomelanocortin (POMC), both

of which are involved in appetite regulation. Orexins, a group of hormones that stimulate feeding behaviour, both stimulate glucose-sensitive neurones, [67] and are secreted by these neurones. [68] The neurones also respond to the potent orexigenic peptide, ghrelin. [69] Changes in feeding behaviour during the menstrual cycle have been well documented with increased fat and total energy intake during the luteal phase. This may relate to increased energy requirement and loss of this cyclical change in energy utilisation may contribute to the increase in weight that commonly occurs following the menopause. [70] Hyperglycaemia may also play a direct role by stimulating release of cytokines such as TNF-α which may be involved in the pathogenesis of insulin resistance and hyperandrogenaemia. [71] Fluctuations in blood glucose may thus arise from the changes that occur in PCOS but may also contribute to development of these changes through altered feeding behaviour, body composition, and insulin responses.

Eating Pattern

The importance of frequency and regularity of eating patterns is often neglected. There has been, in recent years a move away from regular and social eating patterns to more irregular eating with increased consumption of convenience and energy-dense snack foods. [72] There has been surprisingly little research on the influence of eating pattern on metabolic parameters but available evidence suggests that it may be an important determinant of overall nutrient intake and may, to an extent, govern the metabolic response to food. In a study of nearly 16,000 adults, [73] meal and snack patterns were good markers for overall nutrient intake. Those who ate frequently during the day had higher intakes of carbohydrate, fibre, and a range of

micronutrients. Those who ate less frequently had higher intakes of fat, cholesterol, protein and sodium. Lower micronutrient intake was associated with skipping breakfast. Our recent experiments on lean [74] [75] and obese [76] women showed that a regular meal frequency leads to higher postprandial energy expenditure, lower energy intake and impaired improved insulin sensitivity compared with irregular eating in two week interventions. In a further study, [77] breakfast consumption was associated with a lower energy intake and improved insulin sensitivity compared with breakfast omission. If such effects seen after only two weeks of irregular eating or omitting breakfast are sustained in the long term, they could lead to weight gain and thus contribute to the development of obesity. Chapelot et al. [78] have confirmed that less frequent major eating episodes may lead to increased fat mass and increased levels of leptin. The optimal frequency of food intake has yet to be determined, but a regular pattern with low intake from snacks seems to be desirable. Ghrelin levels increase in response to anticipation of food, [79] and this response is learned. Since this and other orexigenic hormones increase energy intake and decrease energy expenditure, there is a strong argument for regular but not too frequent eating episodes in individuals who wish to control or lose weight. The importance of breakfast may not just relate to distribution of energy intake and thermic response to food, individuals who missed breakfast in the Göteburg Adolescence Study [80] were more likely to smoke, drink alcohol, ate more carbohydrate and had decreased micronutrient intake. Although further long-term studies in obese and PCOS are required, it appears that regular eating including breakfast can help in weight management and also improve insulin sensitivity.

Exercise and PCOS

There is a surprisingly scant literature on the role of exercise in managing patients with PCOS. What we know, and what we recommend, must therefore come largely from studies involving non-PCOS subjects. We currently recommend 30 minutes of exercise on at least five days of the week to maintain weight, and for healthy lifestyle. Recent studies showed that 60 - 75 minutes of moderate-to-high intensity of physical activity promotes a greater long term (12-18 months) weight loss compared with the conventional recommendation for optimum health. [81] [82] Accumulation of exercise in frequent short periods of physical activity appears to have similar influence in long term weight loss programmes. Activity related to daily living and leisure time activity is an important determinant of body weight but not of the response to weight management programmes. A realistic approach to exercise depends on assessment of the patient's current exercise habits, preferences regarding type of exercise, and inclination to undertake exercise. The following options for exercise should be discussed with the patient:

- Aerobic exercise. This is important for cardiovascular fitness and to increase energy expenditure as part of a weight loss programme. It is important to recognise that the overweight and unfit patient may have limited capacity for aerobic exercise.
- Exercises to increase suppleness and flexibility. Although they may not greatly increase calorie expenditure, such exercises may increase engagement with an exercise programme, decrease risk of injury with exercise, and promote a sense of well-being.

- Endurance exercise. For patients who cannot manage high-intensity exercise, prolonged lower level activity is an appropriate way to gain fitness and to increase energy expenditure. Walking with a pedometer can be a very useful approach to begin to increase energy expenditure.
- Resistance training. Increasing muscle strength and mass with weight training has been neglected as a means of improving function and body composition until recently. The high metabolic rate of muscle means that muscle mass is an important determinant of resting energy expenditure and resistance training is now regarded as a highly acceptable way opt influence weight, body composition, and insulin sensitivity. [83] [84]

Drug Therapy

Pharmacological treatment should obviously only be considered as an adjunct to lifestyle management, and only when the latter has been shown not to have controlled symptoms and signs on its own. However, the benefits which accrue when insulin sensitivity is improved with drug therapy can be useful to demonstrate what could be achieved with sustained lifestyle interventions. Also, there is increasing evidence that drug treatments to improve insulin sensitivity are a useful adjunct to lifestyle interventions. Specific aspects of PCOS such as menstrual irregularity, anovulatory infertility and hirsutism may require specific treatment. For many patients, the greatest symptomatic relief, as well as improved long-term prognosis, could be gained by dealing with the underlying causes of the condition – insulin resistance and overweight/obesity. These two aspects can be treated separately with modern drugs,

and both the patient and the clinician should be informed about the likely benefits and limitations of each.

Management of insulin resistance is with metformin, a biguanide drug, or with the thiazolidindiones (rosiglitazone or pioglitazone) which are agonists at the peroxisome proliferator activator receptor-γ (PPARγ) receptor. Use of these drugs should be considered at an earlier stage in patients who have impaired fasting glucose or impaired glucose tolerance to prevent or delay progression to type 2 diabetes, and in patients who have developed diabetes to improve diabetic control. Metformin is extensively used in patients with PCOS, not only because of its effects on glucose homeostasis, but also because by decreasing insulin resistance it leads to favourable changes in androgens and gonadotrophins. [85] The latter has proved to be useful in restoring ovulatory function and thus fertility, either used alone or in combination with clomiphene citrate. This effect of metformin is not necessarily confined to women who are either overweight or who have overt insulin resistance. [86] Metformin does not specifically promote weight loss. Metformin added to a hypocaloric diet may specifically decrease some of the features of abdominal obesity – specifically decreased leptin levels consistent with loss of visceral fat may contribute to improvement in a number of features of PCOS. [87] [88] The drug is usually well tolerated, although up to 30% of patients experience gastrointestinal side effects. Lactic acidosis is a very rare side effect but sufficiently serious to warrant the drug not being used in patients with cardiac, renal or hepatic failure. One of the difficulties in using metformin or other insulin sensitising drugs for PCOS is the lack of a readily available marker to document successful treatment or to guide dosing. Recent

evidence suggests that the combination of metformin and lifestyle intervention has sustained beneficial effects on weight maintenance and cardiovascular risk profile that might last for up to four years. [89] [90] In addition to affording some protection from macrovascualr damage, use of metformin with suitable lifestyle advice has been shown to improve microvascular function. [91] [92] The drug has been shown to decrease systemic levels of advanced glycation end products (AGEs) which contribute to vascular and renal complications of insulin resistant states. [93] As confidence with use of metformin in PCOS grows, and as scientific evidence supporting its use accumulates, the drug is increasingly being used in younger patients, including adolescents, with PCOS. [94-96]

There is increasing evidence for the use of thiazolidinediones in patients with PCOS. Side effects include weight gain, peripheral oedema, anaemia and changes in liver tests. Rosiglitazone has been shown to improve glucose tolerance and insulin sensitivity in patients with PCOS, although it does not necessarily produce marked improvement in other endocrine parameters. [97] In a head-to-head study with metformin, rosilgitazone was reported to be more useful where the features were predominantly those of insulin resistance, while metformin additionally ameliorates features of a high androgen state. [98] It may, however, usefully be combined with oestrogen and/or antiandrogen treatment to produce benefits in features related to insulin resistance and hyperandrogenaemia. [99] Pioglitazone tends to have more marked beneficial effect on cardiovascular risk factors, and may be beneficial in insulin-resistant patients who fail to respond to metformin. [100] [101] The drug may be used singly or in combination with metformin. Increased weight with the glitazone

drugs relates to increased subcutaneous fat which is due to the drugs increasing fat cell differentiation and growth in fat depots that do not contribute, or have a beneficial effect on, cardiovascular risk. The resultant decrease in circulating triglycerides and non-esterified fatty acids contributes to improved insulin sensitivity but has no influence on the overall body composition and energy expenditure. [102] Decreased adiponectin and increased resistin are features of PCOS and insulin resistance, [103 104] and these features are partly normalised during treatment with thiazolidinediones. [105] Additionally, these drugs can decrease some of the changes found in association with non-alcoholic steatohepatitis (NASH) and low-grade inflammation. [106]

Modern drugs to assist with weight loss and maintenance are certainly effective in some patients, and appear to be safe if used within guidelines. Orlistat is a gastrointestinal lipase inhibitor that decreases absorption of ingested fat by up to 30%. Although its use leads to gastrointestinal side effects in up to one third of cases, it appears to be a very safe drug and is now widely used in treatment of PCOS. The beneficial effect on insulin resistance and in decreasing androgen levels is equivalent to that achieved by metformin. [107] Advanced glycation end products are reactive molecules produced by glycation of proteins and lipids, and are involved in pathogenesis of diabetic complications. Orlistat may decrease assimilation of these products for the diet. [108] Sibutramine is a centrally-acting inhibitor of serotonin and noradrenaline uptake. It is marginally more effective than orlistat as a weight controlling drug but its use is limited to 1 – 2 years since it consistently increases pulse rate and blood pressure. It should not be used in patients with uncontrolled hypertension. Used in patients with PCOS, sibutramine improves glucose tolerance

and decreases androgen levels. [109] [110] It also decreases levels of leptin and resistin and increases adiponectin, all of which are associated with improved insulin sensitivity and decreased risk of type 2 diabetes. [111] Other drugs to assist with weight control are in development. The most immediately promising of these is rimonabant, an inhibitor of the cannabinoid-1 receptor (CB-1). This drug has been shown in extensive trials, both in Europe and North America, to promote weight loss and improvement in cardiovascular risk profiles in overweight patients. [112-114] Although there is no specific evidence relating to PCOS at present, there is every reason to believe that rimonabant will prove useful in this condition. There is a distinct possibility that eight management drugs will not only prove useful overall, but that specific agents might be selected to match the underlying problem with calorie intake and that these drugs may be useful singly or in combination with other drugs to treat the features or natural history of PCOS. There are no specific data at present relating to the role of bariatric surgery in managing patients with PCOS. While surgically-induced weight loss clearly may restore fertility and improve cardiovascular risk profile, potential risks have to be considered carefully. [115]

Conclusions

PCOS is a complex disorder due, in part but not exclusively to, insulin resistance and overweight. In practice, its management is often not entirely satisfactory from the

patient's point of view. Treatment of PCOS may be divided as follows: 1) Attention to lifestyle factors including diet and exercise. 2) Management of specific aspects such as menstrual irregularity, anovulatory infertility, and hirsutism. 3) Dietary and exercise interventions to promote weight loss and improve glucose tolerance. 4) Pharmacological interventions to improve insulin sensitivity or to assist with weight loss. A scheme for management of the overweight or insulin resistant patient with PCOS is proposed in Figure 1. Although there has been a general increased interest in the role of lifestyle modification to favourably alter the clinical features of PCOS, much of what has been learned is by inference from the non-PCOS population. There is relatively little specific information on nutritional recommendations for patients with PCOS. [116] [117] The focus, to date, has been on the macronutrient components of the diet. There is beginning to emerge evidence that micronutrients are also important. Thus, there may be benefits to supplementation with omega-3 fatty acids and antioxidants, [116] and low vitamin D levels in some patients may contribute to the metabolic features of the syndrome. [118] Some early evidence supports non-pharmacological treatment including herb and nutritional supplements. [119] [120]

As PCOS is principally a disease of over-nutrition, the primary management in most cases should centre on a nutritional approach. Based on published information summarised in this review, certain recommendations can be made about diet and exercise in patients with PCOS. These are summarised in Figure 2. An approach which deals with the fundamental problem in PCOS will help to improve the multiple facts of the problem and to protect the patient from the long-term consequences including, type 2 diabetes and cardiovascular disease. A rational approach to lifestyle

management in PCOS will help the practitioner engage with the patient, and allow both practitioner and patient to approach this complex disorder in a rational manner. PCOS is largely a disease of lifestyle. As it becoming more commonly diagnosed, it is mandatory for health professionals dealing with PCOS patients to have some knowledge of how lifestyle factors influence the disorder and how they may be changed to alter prognosis without an undue reliance on the short-term use of pharmacological treatments.

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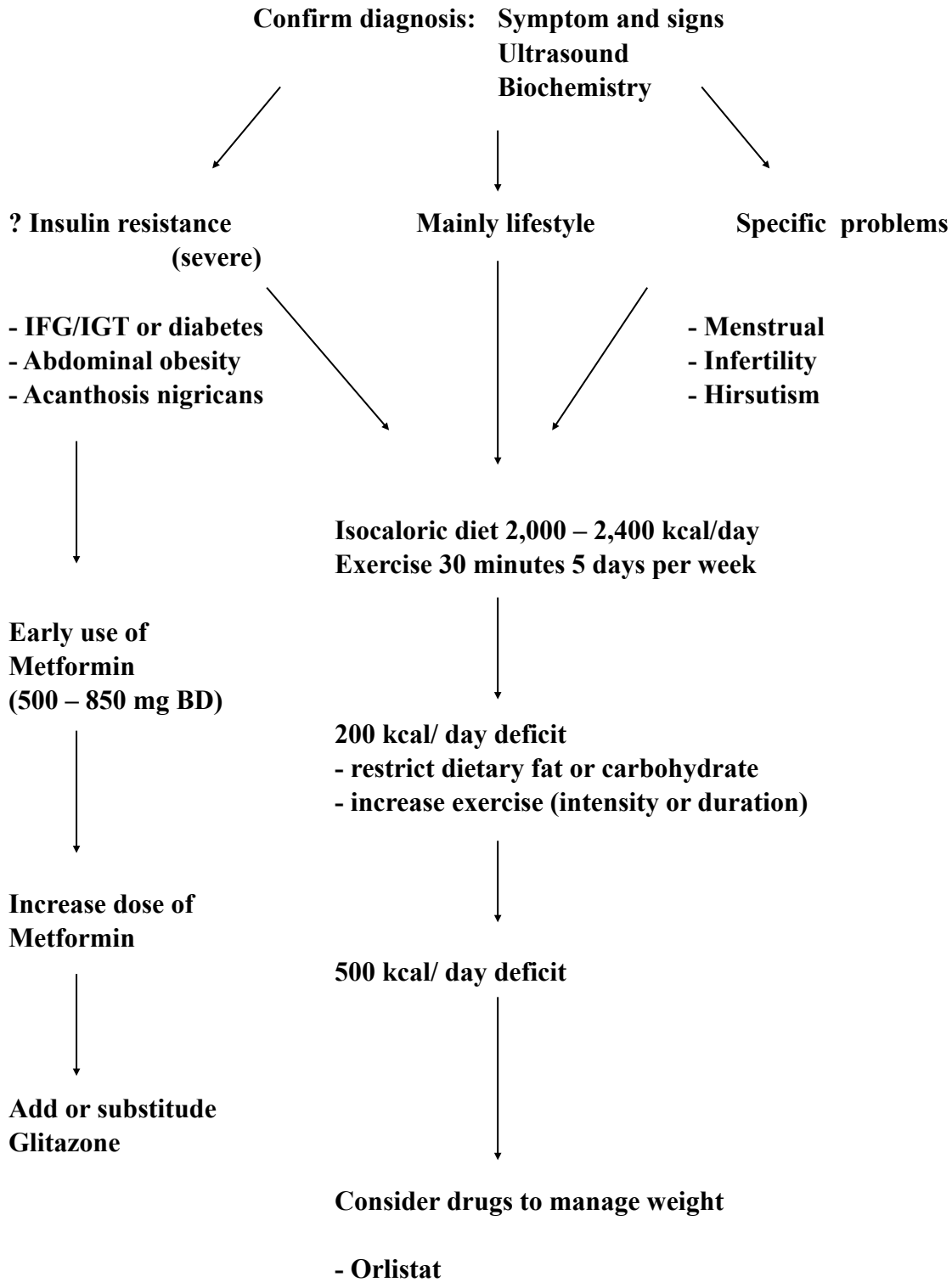
Table 1: Recommended Calorie Intake for Lean Adult Females

	Activity Level		
Age (years)	**Sedentary**	**Moderate**	**Active**
19 – 30	2,000	2,000 – 2,200	2,400
31 – 50	1,800	2,000	2,200
51 +	1,600	1,800	2,000 – 2,200

Values are based on BMI of 21.5 kg/m^2, women with higher BMI have greater calorie requirement. Sedentary is equivalent to just carrying out activities of daily living. Moderately active is equivalent to walking 1.5 to 3.0 miles per day at 3 – 4 miles per hour. Active is equivalent to walking greater than 3.0 miles per day at that pace.

Figure 1: Approach to the Patient with PCOS



- Sibutramine

Figure 2: Diet and Exercise in PCOS

1. Daily energy requirement of 2,000 – 2,400 kcal for patient of average build who is not too active. Avoid restricting this too much to start with.

2. Exercise regularly. 30 minutes of moderate exercise daily will help to maintain body weight. More prolonged or vigorous exercise may be needed to produce weight loss.

3. Eat no more than 30% of daily calories as fat, restricting saturated fat to less than 10% total calories. Use low fat spreads and dairy products.

4. Carbohydrate should count for 45 – 55% of the diet initially. Keep intake of refine carbohydrate down. Concentrate of low glycaemic index (GI) foods, those high in fibre and wholegrain foods.

5. Diet of higher protein content may improve satiety and insulin sensitivity. Start with 20% of daily energy as protein, but this may be increased by substituting for carbohydrate in those who have difficulty controlling eating or maintaining weight.

6. Avoid too much red meat. Eat oily fish at least once per week to supply long-chain essential fatty acids (omega-3 polyunsaturated fatty acids).

7. Eat at least five portions of fruit or vegetable per day. This promotes satiety, supplies fibre and maintains the micronutrient content of the diet.

8. Eat regularly and focus food intake on three (maximum four) meals per day. Breakfast is an important meal.

9. Avoid calorie dense snacks as they promote hyperinsulinaemia and drive hunger. Make sure that drinks are counted in daily calorie intake estimated – fruit juices and alcoholic drinks are often forgotten but are rich in calories and carbohydrates.

10. Even modest weight loss has health benefits. Achieving this requires energy restriction – modest 200 kcal restriction (decreased intake or increased output with a suitably constituted diet will lead to 5% weight loss n six months for many. 500 kcal per day energy deficit usually equates to weight loss of up to 0.5 kg per week.