Nutrition Research Reviews (2018), **31**, 291–301
doi:10.1017/S0954422418000136

Source and amount of carbohydrate in the diet and inflammation in women with polycystic ovary syndrome

Luigi Barrea[1]*, Paolo Marzullo[2], Giovanna Muscogiuri[1], Carolina Di Somma[3], Massimo Scacchi[4], Francesco Orio[5], Gianluca Aimaretti[6], Annamaria Colao[1] and Silvia Savastano[1]

[1]*Dipartimento di Medicina Clinica e Chirurgia, Unit of Endocrinology, Federico II University Medical School of Naples, Via Sergio Pansini 5, 80131 Naples, Italy*
[2]*Division of General Medicine, IRCCS Istituto Auxologico Italiano, Ospedale S. Giuseppe, 28921 Piancavallo-Verbania, Italy*
[3]*IRCCS SDN, Napoli Via Gianturco 113, 80143 Naples, Italy*
[4]*Department of Clinical Sciences and Community Health, Università di Milano, 20122 Milan, Italy*
[5]*Department of Sports Science and Wellness, "Parthenope" University Naples, Via Ammiraglio Ferdinando Acton 38, 80133 Naples, Italy*
[6]*Department of Translational Medicine, University of Piemonte Orientale, Via Solaroli 17, 28100 Novara, Italy*

Abstract

High carbohydrate intake and low-grade inflammation cooperate with insulin resistance and hyperandrogenism to constitute an interactive continuum acting on the pathophysiology of polycystic ovary syndrome (PCOS), the most common endocrine disorder in women of reproductive age characterised by oligo-anovulatory infertility and cardiometabolic disorders. The role of insulin in PCOS is pivotal both in regulating the activity of ovarian and liver enzymes, respectively involved in androgen production and in triggering low-grade inflammation usually reported to be associated with an insulin resistance, dyslipidaemia and cardiometabolic diseases. Although an acute hyperglycaemia induced by oral glucose loading may increase inflammation and oxidative stress by generating reactive oxygen species through different mechanisms, the postprandial glucose increment, commonly associated with the Western diet, represents the major contributor of chronic sustained hyperglycaemia and pro-inflammatory state. Together with hyperinsulinaemia, hyperandrogenism and low-grade inflammation, unhealthy diet should be viewed as a key component of the 'deadly quartet' of metabolic risk factors associated with PCOS pathophysiology. The identification of a tight diet–inflammation–health association makes the adoption of healthy nutritional approaches a primary preventive and therapeutic tool in women with PCOS, weakening insulin resistance and eventually promoting improvements of reproductive life and endocrine outcomes. The intriguing nutritional–endocrine connections operating in PCOS underline the role of expert nutritionists in the management of this syndrome. The aim of the present review is to provide an at-a-glance overview of the possible bi-directional mechanisms linking inflammation, androgen excess and carbohydrate intake in women with PCOS.

Key words: **Carbohydrates: Polycystic ovary syndrome: Low-grade inflammation: Hyperandrogenism**

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age[1]. PCOS is often associated with severe insulin resistance as well as with defects in insulin secretion, and this appears to be related to the modulation of the activity of the key regulatory enzyme of androgen biosynthesis, cytochrome P450c17[2]. In addition, hyperinsulinaemia inhibits the production of sex hormone-binding globulin, which increases local availability of bioactive testosterone[3], and works synergistically with increased levels of luteinising hormone to enhance androgen production[4]. The PCOS phenotype results in androgen excess, oligo-anovulatory infertility, polycystic ovaries on ultrasound examination, insulin resistance and cardiometabolic disorders, with overweight/obesity and visceral adiposity occurring in 30–70 % of PCOS women[5]. Metabolic flexibility, i.e. the ability of the organism to adapt fuel oxidation to fuel availability by switching from lipid oxidation to glucose oxidation and *vice versa*, is impaired in women with PCOS as the consequence of insulin resistance and compensatory hyperinsulinaemia[6]. In PCOS women, serum androstenedione levels are well correlated with insulin sensitivity, and the severity of glucose intolerance increases along with the severity of the hyperandrogenic phenotype[7]. In line with these observations, analysis of First National Health and Nutrition Examination Survey (NHANES I) data suggested that obesity and extreme obesity affecting women by the age of 20–24 years up to 32–41 years could suggest an underlying PCOS state which deserves appropriate workup[8].

Abbreviations: AT, adipose tissue; CRP, C-reactive protein; DASH, Dietary Approaches to Stop Hypertension; GI, glycaemic index; GL, glycaemic load; MNC, mononuclear immune cells; PCOS, polycystic ovary syndrome; ROS, reactive oxygen species.

* **Corresponding author:** Dr Luigi Barrea, email luigi.barrea@unina.it

PCOS shares a state of low-grade inflammation with other atherosclerosis-related non-transmissible chronic diseases, such as obesity, type 2 diabetes mellitus and CVD[9,10]. Among several environmental determinants, a number of nutrients are known to cause or modulate the inflammatory status and contribute to the onset and maintenance of cardiometabolic diseases[11–13]. Nevertheless, the spectrum of nutrients responsible for the onset of a pro-inflammatory state is also strictly associated with obesity, which *per se* is associated with chronic low-grade inflammation[11,14]. Besides the evidence linking inflammation and PCOS, uncertainty remains on the role of diet in controlling inter-individual variability in insulin resistance, hyperandrogenism and chronic low-grade inflammation in PCOS.

In light of the increased risk of reproductive and health-related issues in PCOS women across their life course, the aim of the present review is to provide an at-a-glance overview of the possible bi-directional mechanisms linking inflammation, androgen excess and carbohydrate intake in women with PCOS.

Nutrition and inflammation

General concepts

The innate (non-specific) immune system, the first-line defence mechanism against invading pathogens[11], is able of promoting a chronic low-grade systemic inflammation state[15,16], in the absence of any systemic or local infection[15], which is usually defined by the occurrence of 2- to 3-fold increase in plasma concentrations of cytokines and acute-phase proteins, with activation of a complex network of inflammatory signalling pathways. Among the environmental modifiable risk factors for chronic inflammation, unhealthy nutritional patterns are emerging for their association with the aberrant activation of the innate immune system triggering chronic low-grade systemic inflammation[17]. Strategic interest in diet-induced inflammation stemmed from both experimental and clinical evidence depicting a role for diet in driving atherogenesis through stimulation of the processes relating to initiation, progression and rupture of the atherosclerotic plaque[18]. Consequently, chronic low-grade systemic inflammation has been proposed as a potential link between insulin resistance, the metabolic syndrome, obesity, type 2 diabetes mellitus and CVD[19]. As summarised in a recent review[11], the International Life Sciences Institute's European Branch (ILSI Europe) has extensively investigated the interaction between nutrition, food and inflammation. However, the variability in results across different dietary studies did not allow to draw final conclusions on the understanding of diet/nutrient-driven inflammation[11]. Despite the overall consensus on the ability of several foods and nutrients to modulate inflammation both acutely and chronically, a debate currently exists on which circulating marker best reflects the low-grade inflammation, and which experimental condition most appropriately detects the diet/nutrient-driven inflammation, i.e. the fasted *v.* the postprandial state[20]. This controversy is further reinforced when considering that circulating inflammatory markers may not necessarily reflect the inflammation in tissue compartments or what happens locally in response to inflammatory challenges[11].

An increase in inflammation occurs acutely following meal ingestion and lasts for about 4–8 h, although it has been reported to occur several times a day following eating[21]. Unhealthy dietary patterns and single food components have been shown to induce inflammation through both direct and indirect effects, these latter being mediated by accumulation in white adipose tissue (WAT) of dysfunctional adipocytes and immune cell infiltration leading to the release of inflammatory cytokines[14,17,22]. Cell populations englobed in WAT consist of pre-adipocytes and mature adipocytes, as well as immune and stromal cells. Pre-adipocytes have functional characteristics and transcriptional patterns of multipotent cells that are similar to immune cells, and can transdifferentiate into macrophages both *in vitro* and *in vivo*[23,24]. Mature adipocytes share the ability with immune cells to secrete cytokines and activate the complement cascade much like mononuclear immune cells (MNC), then promoting a shift toward dominance of pro-inflammatory adipokines as opposed to anti-inflammatory adipokines[25]. Upon fat accumulation, adipose tissue (AT)-derived factors can activate $CD8^+$ T cells and promote macrophage infiltration, which perpetuates the inflammatory response within the AT[26]. WAT contains resident M2-like macrophages, which have a role in AT homeostasis, and recruits M1-like macrophages, which are clustered in crown-like structures and contribute to inflammation and insulin resistance[27–30]. Macrophage infiltration predominates in omental *v.* subcutaneous fat and becomes exaggerated with central obesity, which is at higher risk of insulin resistance[31]. Post-absorptively, abdominal adipocytes and monocytes/macrophages show the ability to respond to acute postprandial elevation of several metabolic components of the meal, for example, TAG, SCFA, oxysterols and glucose, through a transient inflammatory response that is crucial for the development of insulin resistance, the metabolic syndrome and atherosclerosis[21]. The resulting excess of body fat and ectopic fat storage could give rise to a condition of lipotoxicity and a pro-inflammatory/pro-oxidative state, linking nutrition to increased cardiovascular risk[11]. Because a detailed description of the inflammatory effects of each single nutrient is beyond the scope of the present review, we will focus in the next sections on the link between carbohydrates and inflammation, with particular regard to the interactions between nutrition, insulin resistance with compensatory hyperinsulinaemia, hyperandrogenism and low-grade inflammation in women with PCOS.

Carbohydrates and inflammation

Postprandial hyperglycaemia, an independent predictor of diabetes and CVD, may induce oxidative stress, i.e. the imbalance between free radical production and *in vivo* antioxidant defences[32], which displays a positive correlation with the degree of hyperglycaemia[33]. Both oxidative stress and inflammation have overlapping detrimental effects that make their individual effects virtually indistinguishable[34]. Acute hyperglycaemia induced by oral glucose loading has been demonstrated to increase inflammation and oxidative stress by generating reactive oxygen species (ROS) through different mechanisms, including non-enzymic glycation and imbalance in the NADH:NAD ratio induced by glucose[35], in several cell

https://doi.org/10.1017/S0954422418000136

types ranging from immune cells, including MNC, activated macrophages and T and B cells, and non-immune cells like adipocytes. In immune cells, ROS production is essential for eliminating invading pathogens, but it may also result in promoting sterile inflammation associated with the activation of phagocytes[36]. In particular, when an excess of glucose (or NEFA) reaches MNC and activated macrophages[37], a large number of reducing metabolites, including pyruvic acid and acetyl coenzyme A, are oxidised in mitochondria, leading to an enhanced activity of the electron transport chain and single electron transfer, which finally results in an increased ROS production[38]. ROS generation is an early key event in the onset and progression of a number of different diseases[39], and may cause oxidative modification of LDL-cholesterol, which is considered to be a main determinant of the development of atherosclerosis[40]. ROS can act as a potential activator of a class of proteins involved in innate immunity, known as Toll-like receptors, thereby mediating the activation and expression in MNC and activating macrophages of NF-κB, a family of transcription factors prone to control apoptosis and pro-inflammatory cytokine expression via dissociation from the inhibitory protein, inhibitory κB[36]. In immune and non-immune cells, activated NF-κB translocates to the nucleus and promotes the transcription of cytokine genes capable of enhancing the release of pro-inflammatory cytokines, such as TNF-α, a known mediator of insulin resistance, IL-6, IL-1β, monocyte chemotactic protein-1 and plasminogen activator inhibitor-1[41]. Other pro-inflammatory transcription factors are also activated, including activator protein-1, forkhead box P3, interferon regulatory factor and signal transducer and activator of transcription families[42]. Pro-inflammatory cytokines stimulate the liver to produce a variety of proteins known as acute-phase reactants, including C-reactive protein (CRP). CRP is involved in endothelial dysfunction and atherosclerotic process, and its level serves as an index of vascular inflammation and major predictor of CVD risk[43]. IL-6 plays a key role in the liver synthesis of CRP, and increased levels of IL-6 are correlated with a greater occurrence of cardiac events[44]. In addition, IL-6 regulates the secretion of TNF-α, which induces the expression of adhesion molecules, such as vascular cell adhesion protein-1 and intercellular adhesion molecule-1[45]. These latter have been involved in the development of atherosclerosis and production of other inflammatory cytokines[44].

Dietary carbohydrates and inflammation

The effect of postprandial glucose excursions mostly depends on the time of exposure to the postprandial glucose peak, a major contributor of chronic sustained hyperglycaemia, as well as on the magnitude of postprandial spikes, a reflection of glucose variability, with both contributing to protein glycation and activation of oxidative stress and inflammation. These two main mechanisms can lead to diabetic and cardiovascular complications[11]. Esposito *et al.*[46] reported that hyperglycaemic spikes are able to affect cytokine concentrations more than continuous hyperglycaemia, at least in the short term, suggesting that an oxidative mechanism could mediate the effect of hyperglycaemia. In a number of studies, the inflammatory effects of carbohydrates were analysed in association with the glycaemic index (GI) of foods, an index quantifying the postprandial blood glucose responses to the carbohydrate in different foods[47,48], and the glycaemic load (GL), the product of the GI of a specific food and its carbohydrate content[49], which provide an indication of glucose available for energy or storage following a carbohydrate-containing meal. There is evidence supporting the benefits of low-GI dietary patterns on insulin resistance[50,51], while foods with a high GI exert opposite effects[52]. Nevertheless, the relationship between dietary GI or GL and low-grade inflammation remains debatable, and the usefulness of GI and GL has been questioned due to the failure to consider the high intra- and inter-subject variation in insulin and glucose response to the ingestion of specific foods, as well as when foods are combined in a mixed meal[53].

Among the pro-inflammatory dietary patterns, particular concern has been raised by high-energy diets with high content in complex carbohydrates, as well as foods with a high GI scale, low in fibres, rich in refined carbohydrate, or high in fat, all of which are collectively included in the so-called Western diet[46,54–56]. The Western diet is responsible for supra-physiological postprandial spikes in glucose and lipids, resulting in a pro-inflammatory state[17,57,58]. Hu *et al.*[59] observed a positive association between dietary GI and oxidative stress markers as measured in healthy adults by two lipid peroxidation markers, such as malondialdehyde and F2-isoprostanes, thus concluding that a low-GI diet, not a low-carbohydrate diet, could be beneficial in reducing oxidative stress. The pro-inflammatory effects of high-GI diets have also been confirmed in large epidemiological studies. In particular, in the Harvard Women's Health Study, serum CRP levels increased progressively across quintiles of dietary GI[60]. In addition, high-GI carbohydrates have been reported to increase NF-κB activation and NF-κB binding in MNC of young, lean healthy subjects[61], such that levels of NF-κB were expressed at three times higher levels among lean subjects consuming high-GI meals when compared with controls[62]. On the other hand, studies have suggested that healthy eating patterns are characterised by reduced postprandial glycaemia and lipaemia, and are associated with reduced concentrations of low-grade inflammation markers. For example, dietary patterns with low GI[62,63] or high fibre consumption are associated with lower serum concentrations of CRP[64], which are conceivably related to a beneficial effect on glycaemia[65]. Likewise, diets low in GL and high in whole grains were found to exert a protective effect against inflammation in diabetic patients[66], and an inverse relationship was reported in epidemiological studies between CRP levels and dietary intake of fibre, such as in individuals receiving the Dietary Approaches to Stop Hypertension (DASH) diet, which is naturally high in fibre (g fibre/d) or consists of a fibre-supplemented standard diet (30 g psyllium fibre/d)[11]. At odds with these observations, the Women's Health Initiative Observational Study reported that a relatively high consumption of both soluble and insoluble fibre (24 g/d) was inversely associated with IL-6 and TNF-α but not with CRP levels[67]. Probably, the inflammatory response may vary depending on the type of carbohydrate. As such, Kallio *et al.*[68] reported that

https://doi.org/10.1017/S0954422418000136

a 12-week oat–wheat–potato diet resulted in a higher postprandial insulin response leading to late hypoglycaemia compared with a rye–pasta diet. Moreover, a carbohydrate-rich diet up-regulated genes relating to metabolic stress in abdominal subcutaneous AT of men and women with the metabolic syndrome, even in the absence of changes in body weight and insulin sensitivity[68]. Finally, it is important to consider that fructose, a common plant-derived sweetener that is habitually consumed in diets rich in carbohydrates and lipids, promotes a greater pro-inflammatory state than glucose, and its effects are amplified when it is associated with glucose and lipids. In fact, chronic consumption of fructose generates 100 times more ROS than glucose through different mechanisms, such as hepatic phosphate deficiency, and its hepatic metabolism generates potent glycation agents, such as methylglyoxal, leading to cellular stress and altered insulin signalling[69,70]. Hepatic phosphate deficiency leads to the accumulation of AMP resulting in the increased production of uric acid, which in turn stimulates the production of ROS via activation of transforming growth factor-β and NADPH oxidase 4[69]. In addition, fructose has been shown to promote the synthesis of SFA, such as palmitate[71], which are channelled to distinct cellular metabolic fates with direct and indirect involvement in the development of insulin resistance in adipocytes and skeletal muscle cells[72].

Nutrition and inflammation in polycystic ovary syndrome

A pro-inflammatory state has emerged as a key contributor to insulin resistance and CVD risk factors in PCOS women[10]. Besides the established role of abdominal adiposity, there is a suggestion that metabolic and ovarian dysfunction associated with PCOS could be enhanced by nutrient-induced oxidative stress and inflammation[73]. As well as in obesity and type 2 diabetes mellitus, also in PCOS inflammation contributes to generate insulin resistance and compensatory hyperinsulinaemia[74], although peculiar mediators such as hyperandrogenism play a pivotal role in metabolic outcomes related to the syndrome. Both hyperinsulinaemia and hyperandrogenism act as promoters of inflammation in PCOS, and the triad of insulin resistance, hyperandrogenism and low-grade inflammation works bi-directionally in a self-perpetuating vicious cycle that underlies the pathophysiology of PCOS[75]. The direct exposure of ovarian theca cells to pro-inflammatory stimuli *in vitro* increases androgen production, while *in vivo* circulating and molecular markers of oxidative stress and inflammation are highly correlated with circulating androgens[76]. Pioneering studies by Dunaif & Graf[77] demonstrated that circulating androgens are influenced by insulin levels independent of variations of gonadotropin release only in PCOS women, while such a correlation is not present in control women. It is also worth noting that up to 50 % of hyperandrogenic women with PCOS are of normal weight and insulin sensitive[78], and increased circulating androgens might exert anti-inflammatory effects through their lipolytic action[79]. It is also worth noting that the activity of the sympathetic nervous system, which controls resting energy expenditure at the systemic and local levels[80], is enhanced in PCOS as much as in obesity, insulin resistance and hypertension[81,82]. Rodent models of PCOS demonstrated an increased ovarian sympathetic outflow and elevated intra-ovarian synthesis of nerve growth factor, which may be involved in triggering ovarian disease[82]. Patients with PCOS have evidence of increased muscle sympathetic nerve activity, altered heart rate variability and attenuated heart rate recovery post-exercise, compared with age- and BMI-matched controls, suggesting a generalised increase in sympathetic nervous system activity[83]. Whether targeting sympathetic overactivity in this condition has favourable effects warrants further investigation.

A potential key role in the pathophysiology of PCOS is played by nutrients like glucose and saturated fat, which can promote inflammation in women with PCOS and stimulate ovarian androgen production independent of excess adiposity and insulin resistance[73,74]. Most studies examining markers of the pro-inflammatory state in PCOS have focused on the measurement of circulating CRP and adiponectin levels[84,85]. The antidiabetic, anti-inflammatory, anti-atherogenic and cardioprotective effects of adiponectin are widely recognised, where the high-molecular-weight isoforms represent the major relevant forms in its insulin-sensitivity activities[86]. However, previous reports on serum adiponectin levels in women with PCOS have provided conflicting results[87]. Like in CVD and obesity[88], also in PCOS patients CRP levels are a reliable circulating marker of chronic low-grade inflammation[11], although adiposity is a potential confounding determinant of CRP elevations in PCOS, and CRP is expressed at levels that are below the range predictive of metabolic or CVD risk[76]. Of note, MNC make use of ingested glucose and lipids for mitochondrial respiration during energy metabolism and generate NADPH oxidase, the ROS-producing enzyme, which in turn promotes the transcription of TNF-α and IL-6 genes. MNC have been extensively investigated in relation to the link connecting diet to inflammation in PCOS, especially when considering that dietary components, such as glucose and lipids, can trigger an inflammatory response in MNC[76]. Glucose ingestion is a promoting mechanism of inflammation in PCOS, as it has been shown to activate NF-κB in MNC and in MNC-derived macrophages migrating into the stromal–vascular compartment of expanded AT of obese individuals in response to cell hypoxia[28,74]. González *et al.*[74] demonstrated that glucose ingestion in women with PCOS stimulated ROS-related oxidative stress and increased NF-κB activation independent of obesity. These authors further observed that MNC-derived cytokine release was inversely related to insulin sensitivity and directly related to androgens, thus leading to the hypothesis that the glucose-stimulated inflammatory response from MNC played an independent role in promoting insulin resistance, hyperandrogenism, as well as inflammation in PCOS[74]. González[76] summarised the evidence that TNF-α and IL-6 release from circulating MNC is increased in PCOS both upon glucose ingestion *in vivo* and after glucose exposure *in vitro*, and is associated with insulin resistance, thus suggesting that diet-induced inflammation in PCOS is linked to insulin resistance and atherogenesis. In this scenario, nutrition could represent a complementary component of a new 'deadly quartet' of metabolic risk factors for PCOS in association with hyperinsulinaemia, hyperandrogenism and low-grade inflammation,

https://doi.org/10.1017/S0954422418000136

with hyperandrogenism possibly acting as a precursor of diet-induced inflammation[76]. The results of clinical trials set up to investigate *in vivo* the effects of anti-inflammatory therapy on circulating ovarian androgens in women with PCOS following lipid ingestion and glucose infusion will lead to an understanding of these intriguing nutritional–endocrine connections[89].

Indeed, diet is a key determinant of excessive body weight in PCOS and its relationship with PCOS is possibly influenced by geographical determinants[90]. A survey on overweight and obese US women with PCOS-related infertility showed poor dietary intake, particularly in terms of whole grains, fibre, and Fe, and eating behaviours inconsistent with achieving a healthy body weight, as well as low scores for PCOS-related quality of life[91]. Dissimilarly, a study on overweight and obese Italian PCOS women found no difference in terms of energy, macronutrient and advanced glycosylated end-product intake as compared with controls, yet PCOS women were characterised by a higher consumption of cheese and high-GI starchy sweets and a preference for raw oil rather than other cooked fats[5]. Women with PCOS showed impaired satiation and alterations in satiety–appetite hormones, for example, lower baseline levels and responsiveness of ghrelin to meals with varying carbohydrate content as well as higher leptin concentrations than BMI-matched controls[92–94]. On the other hand, it is widely recognised that body weight reduction yields marked beneficial effects on insulin resistance, hyperandrogenic phenotype and gynaecological problems of PCOS women[95] and PCOS may even resolve after weight loss induced by bariatric surgery[96]. A healthy dietary habit with an adequate ratio of complex to simple carbohydrates appears to be appropriate in light of the link between nutrition, hyperinsulinaemia, hyperandrogenism and chronic low-grade inflammation, and a low-fat/high-complex carbohydrate diet can promote weight loss and ameliorate metabolic, hormonal and reproductive homeostasis of PCOS[97]. There is, however, evidence that the chemical structure of food and botanical structure rather than the amount of fibre or the type of cereal in the food determine postprandial insulin responses to grain products and insulin resistance[98], and these effects may be mediated through glucose insulinotropic peptide and glucagon-like peptide-1[99,100]. It is also worth noting that metabolic inflexibility in insulin-resistant individuals fails to adequately oxidise fatty acids, and it diminishes the ability to switch from glucose to lipid oxidation during overnight fasting, thus leading to lipid accumulation in skeletal muscle and further impairment of insulin signalling[101]. Weight loss can improve insulin-mediated suppression of fatty acid oxidation in insulin-resistant individuals[102,103] and prevents the effects of hyperinsulinaemia on weight gain[104].

Dietary intervention in polycystic ovary syndrome

Dietary modifications that lead to a reduction in postprandial glucose and hyperinsulinaemia could have important implications in improving fatty acid oxidation, promoting weight loss, and preventing further weight gain in women with PCOS[105]. In a prospective study in infertile women seeking counselling, total carbohydrate intake and dietary GL were found to be positively related to ovulatory infertility in analyses adjusted for age, BMI, smoking, parity, physical activity, recency of contraception, total energy intake, protein intake and other dietary variables[106]. In PCOS women, uncertainty remains on whether manipulation of dietary components could aid the clinical management of the syndrome. Recent interest has stimulated research on moderate increases in dietary protein as a strategy to tackle global problems of PCOS, for example, glucose intake, androgen alterations, weight accrual and cardiometabolic risk[107,108]. In a cross-over study, Douglas *et al.*[109] reported that a low-carbohydrate diet (43 % of total energy) for 16 d can promote significant reductions in fasting and post-challenge insulin concentrations, which may over time improve the reproductive and endocrine outcomes of PCOS women. These results were confirmed by Marsh *et al.*[110] in ninety-six PCOS women, in which changes in insulin sensitivity and clinical outcomes were assessed during a dieting programme achieving similar weight loss (4–5 % of initial body weight) after consumption of a low-GI diet compared with a conventional healthy diet for 12 months. Both diets were designed as reduced-energy, low-fat, low-saturated fat, moderate-to-high-fibre diets with similar macronutrient distribution but differing carbohydrate content (GI, 40 *v.* 59 %; GL, 74 *v.* 109 g). Of interest, this study evidenced that with modest weight loss both the treatments led to similar improvements in blood lipids, androgens and markers of inflammation, but only women on a low-GI diet showed improvements in menstrual disorders, whole-body insulin sensitivity and levels of fibrinogen, an acute-phase protein of inflammation[110]. In evaluating the inflammatory pattern, Mehrabani *et al.*[111] investigated the effects of a high-protein, low-GL hypoenergetic diet (40 % carbohydrates with <20 GL, 30 % protein, 30 % fat) as compared with a conventional hypoenergetic diet (55 % carbohydrate, 15 % protein, 30 % fat) on reproductive hormones, inflammatory markers, lipids, glucose and insulin levels in sixty obese women with PCOS. Results demonstrated that both diets significantly led to reduced body weight and androgen levels, but only the combination of high-protein and low-GL foods led to a significant increase in insulin sensitivity and a decrease in high-sensitivity CRP levels[111]. Subsequently, Gower & Goss[112] evaluated if dietary restriction of carbohydrates would benefit body composition and metabolic health in thirty women with PCOS randomised to receive a low-fat diet (55, 18 and 27 % of energy from carbohydrate, protein and fat, respectively) or a low-carbohydrate diet (41, 19 and 40 %, respectively) for 8 weeks. The low-carbohydrate diet resulted in significant decreases in fasting insulin and glucose, and a significant increase in insulin sensitivity, while no changes were observed consuming the low-fat diet. While markers of inflammation did not change in response to either of the two diets, changes in intra-abdominal AT were associated with changes in TNF-α levels independent of changes in total body fat mass[112].

Different studies showed that carbohydrates from dairy products and starch-based foods caused greater postprandial insulin secretion than carbohydrates from non-starchy vegetables and fruits. In a prospective 8-week dietary intervention using a low-starch/low-dairy product diet, Pohlmeier *et al.*[113] reported that this approach proved useful in increasing fat

https://doi.org/10.1017/S0954422418000136

oxidation in overweight and obese women with PCOS. More recently, Eslamian *et al.*[114] investigated in a case–control study the association between dietary carbohydrate components and PCOS using a validated semi-quantitative FFQ. The results of this study showed higher dietary GI and GL values in women with PCOS than controls, while fibre intake was inversely associated with PCOS.

In a study investigating the effects of fructose in PCOS, Johnson *et al.*[115] examined whether an 8-week low-fructose, low-energy diet could be superior to a traditional low-energy diet based on fructose-rich liquid meal replacements, with respect to improvement of cardiometabolic risk factors and reproductive hormones. The authors failed to obtain significant differences between the two diet regimens in terms of body weight reduction, modification in cardiometabolic risk factors, including CRP levels and androgens. Little but positive experience has been reported on a low-energy ketogenic diet (consisting of fewer than 20 g carbohydrate per d) in PCOS women in terms of body weight, free testosterone, luteinising hormone:follicle-stimulating hormone ratio and fasting insulin[116]. It is also expected that manipulation of dietary protein content could favour psychological outcomes in PCOS women, namely depression and self-esteem, and predispose to improvement in satiety, dietary compliance and steroid production[117]. Regarding safety issues, it is until now unclear how low the carbohydrates content of a diet should be or for how long a low-carbohydrate diet can be administered so as to achieve optimal results without potential adverse events[118]. Challenging these previous views, however, there is suggestion that energy restriction seems more important than macronutrient composition, and there is still little evidence to support a universal role for high-protein diets on PCOS outcomes relating to fertility, endocrine/metabolic parameters and weight loss[119,120].

Since oxidative stress and inflammation occur in PCOS even in the absence of excess adiposity, a promising approach could be represented by dietary strategies that are capable of preventing inflammation, and hence insulin resistance. Anti-inflammation nutrition works upstream of primary molecular targets of inflammation to reduce the dietary factors that activate NF-κB to generate silent inflammation. Anti-inflammatory approaches encompassing low-GL foods, low *n*-6 fatty acids content and high *n*-3 fatty acids, combined according to the 1-2-3 nutritional rule-of-thumb proposed by the International Sports Sciences Association for macronutrients ratio (approximately one part fat, two parts protein and three parts carbohydrates), have been shown to improve insulin resistance and metabolic outcomes in the general population[121]. Also, dietary intake of nuts, a source of MUFA and *n*-3 PUFA, is increasingly seen as a strategy to exert beneficial effects on lipids, androgens and possibly inflammatory markers in PCOS women[122]. Growing interest is focusing on the effects of the Mediterranean diet on PCOS outcomes[123,124]. As such, energy restriction and a healthy lifestyle along with an anti-inflammatory nutrition approach are all reckoned as beneficial for PCOS outcomes, particularly when low-GI foods are associated with the Mediterranean diet, decreased red/processed meat, low sugar and saturated fats, phytochemicals and antioxidants, as well as small frequent meals[123]. A 12-week study in seventy-five overweight women using a Mediterranean-inspired low-GL hypoenergetic diet (25 % protein, 25 % fat and 50 % carbohydrate) showed favourable effects on body composition, menstrual cyclicity, blood pressure, glucose homeostasis, dyslipidaemia and surrogate measures of CVD risk[125]. Likewise, the DASH diet has gained increasing interest in the dietary management of PCOS patients due to its dietary content of antioxidant foods, such as fruits, vegetables, whole grains, low-fat dairy products and ions along with low saturated fats, cholesterol, refined grains and sweets[126]. Compared with a control group, consumption of a hypoenergetic DASH eating pattern for 8–12 weeks in overweight and obese women with PCOS resulted in the improvement of insulin resistance, TAG, VLDL-cholesterol and serum high-sensitivity CRP levels, and a significant increase in antioxidant levels along with improvements in abdominal fat accumulation[127–129]. Together, this evidence suggests that women with PCOS should be advised to consume a diet that includes an increase in fibre and a decrease in refined carbohydrates, as well as a decrease in *trans*- and saturated fats and an increase in *n*-3 (and *n*-9) fatty acids. Foods that contain anti-inflammatory compounds (fibre, *n*-3 fatty acids, vitamin E and resveratrol) could also help improving the metabolic and hyperandrogenic profile of PCOS patients[130]. In addition, vitamins such as vitamin C and β-carotene, inositol that belongs to the group of B vitamins, vitamin-like coenzyme Q10, minerals, such as Zn, Cu, Mg and Se, and other compounds, including resveratrol and N-acetyl cysteine, have been suggested as auxiliary antioxidants in PCOS. All these antioxidants could either stop directly the oxidation chain reaction or enhance the activity of main antioxidants; nevertheless, systematic reviews and meta-analyses of randomised controlled trials have been provided only on a restricted number of these compounds[131–134].

Conclusions

Epidemiological studies and large clinical trials have identified a number of potential diet-derived anti-inflammatory and pro-inflammatory components involved in the pathogenesis of PCOS, particularly those linking carbohydrate intake to low-grade chronic inflammation. Mutually with hyperinsulinaemia, hyperandrogenism and low-grade inflammation, an unhealthy diet should be thus viewed as a key component of the 'deadly quartet' of metabolic risk factors associated with PCOS pathophysiology, as depicted in Fig. 1. Although it is evident that the inflammatory response driven by carbohydrates is highly variable and that a full understanding of the source of heterogeneity is lacking, the results of large clinical trials set up to investigate *in vivo* the effects of anti-inflammatory therapy on circulating ovarian androgens in women with PCOS will lend support to the hypothesis of these intriguing nutritional–endocrine connections. The recognition of a robust diet–inflammation–health association makes the adoption of healthy nutritional approaches a key future preventive and therapeutic target in PCOS. A rational approach to the dietary management of women with PCOS under the guidance of registered dietitians will help the endocrinologists engage with these patients and increase the knowledge of how diet and lifestyle factors influence the disorder and how they may be changed to improve prognosis without exclusive reliance on only pharmacological treatments. Considering the substantial role of

https://doi.org/10.1017/S0954422418000136

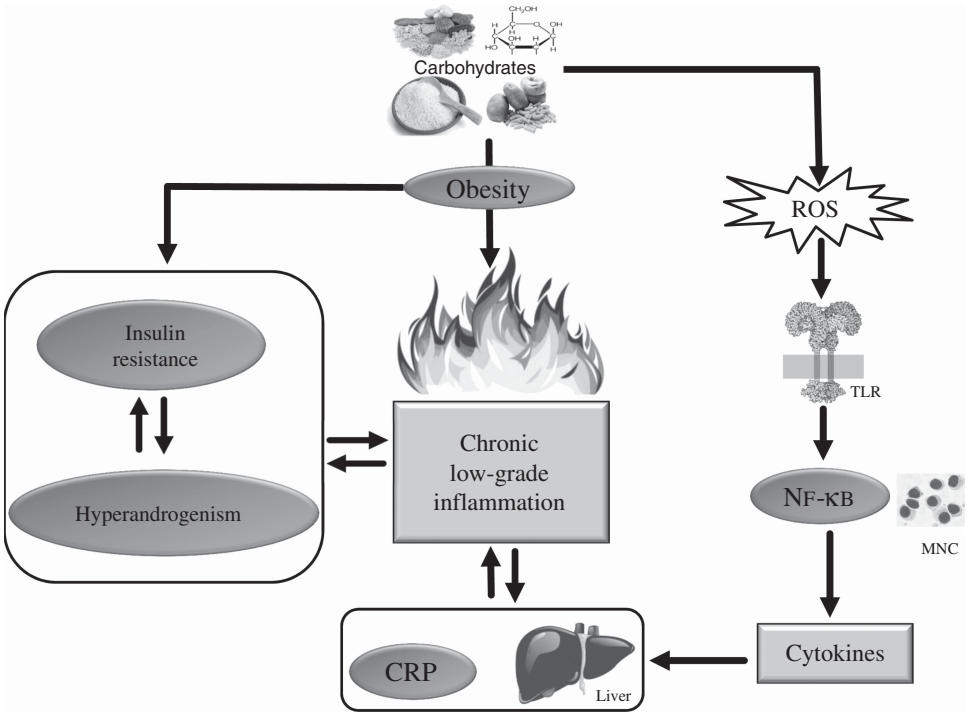

Fig. 1. The excess of glucose in the mononuclear cells (MNC) generates a large number of metabolites oxidised into mitochondria leading to an increase in reactive oxygen species (ROS) production[38]. ROS can act as a potential activator of Toll-like receptors (TLR), thereby mediating the activation and expression of NF-κB, a family of transcription factors controlling apoptosis and pro-inflammatory cytokine expression, with increased release of pro-inflammatory cytokines into the bloodstream. Pro-inflammatory cytokines stimulate the liver to produce a variety of proteins known as acute-phase reactants, including C-reactive protein (CRP) levels. Inflammation, when present in polycystic ovary syndrome (PCOS), contributes to the development of insulin resistance and compensatory hyperinsulinaemia[74], although with different peculiarities linked to the pivotal contribution of hyperandrogenism, one of the hallmark features of PCOS. In turn, hyperinsulinaemia and hyperandrogenism act as promoters of inflammation in PCOS[75]. On the other hand, nutrient-induced inflammation *per se* could stimulate the ovarian androgen production independent of excess adiposity and insulin resistance[73,74]. In this complex scenario, nutrition could act as an additive element in depicting a new 'deadly quartet' of metabolic risk factors together with hyperinsulinaemia, hyperandrogenism and low-grade inflammation, in the vicious cycle operating in the pathophysiology of PCOS, where hyperandrogenism might act as the progenitor of diet-induced inflammation in the disorder[76].

chronic low-grade inflammation in the pathogenesis of numerous chronic diseases, and acknowledging the health problems relating to PCOS in women across their entire life course, including infertility and long-term cardiometabolic consequences, there is a need to implement the strategic nutritional approach by expert dietitians, so as to design appropriate anti-inflammatory dietary interventions for the prevention and treatment of diet-induced inflammation in PCOS.

Acknowledgements

The present review received no specific grant from any funding agency, commercial or not-for-profit sectors.

The authors' responsibilities were as follows: L. B., P. M. and S. S. were responsible for the concept of this paper and drafted the manuscript; G. M., C. D. S., M. S., F. O., G. A. and A. C. provided a critical review of the paper. All authors contributed to and agreed on the final version of the manuscript.

There are no conflicts of interest.

References

1. Goodarzi MO & Azziz R (2006) Diagnosis, epidemiology, and genetics of the polycystic ovary syndrome. *Best Pract Res Clin Endocrinol Metab* **20**, 193–205.
2. Dunaif A (1997) Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. *Endocr Rev* **18**, 774–800.
3. Plymate SR, Matej LA, Jones RE, *et al.* (1988) Inhibition of sex hormone-binding globulin production in the human hepatoma (Hep G2) cell line by insulin and prolactin. *J Clin Endocrinol Metab* **67**, 460–464.
4. Nestler JE, Jakubowicz DJ, de Vargas AF, *et al.* (1998) Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndrome by activating its own receptor and using inositolglycan mediators as the signal transduction system. *J Clin Endocrinol Metab* **83**, 2001–2005.
5. Altieri P, Cavazza C, Pasqui F, *et al.* (2013) Dietary habits and their relationship with hormones and metabolism in overweight and obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* **78**, 52–59.
6. Di Sarra D, Tosi F, Bonin C, *et al.* (2013) Metabolic inflexibility is a feature of women with polycystic ovary syndrome and is associated with both insulin resistance and hyperandrogenism. *J Clin Endocrinol Metab* **98**, 2581–2588.
7. O'Reilly MW, Taylor AE, Crabtree NJ, *et al.* (2014) Hyperandrogenemia predicts metabolic phenotype in polycystic ovary syndrome: the utility of serum androstenedione. *J Clin Endocrinol Metab* **99**, 1027–1036.
8. Glueck CJ, Dharashivkar S, Wang P, *et al.* (2005) Obesity and extreme obesity, manifest by ages 20–24 years, continuing through 32–41 years in women, should alert

https://doi.org/10.1017/S0954422418000136

physicians to the diagnostic likelihood of polycystic ovary syndrome as a reversible underlying endocrinopathy. *Eur J Obstet Gynecol Reprod Biol* **122**, 206–212.
9. Wong BW, Meredith A, Lin D, *et al.* (2012) The biological role of inflammation in atherosclerosis. *Can J Cardiol* **28**, 631–634.
10. Escobar-Morreale HF, Luque-Ramírez M & González F (2011) Circulating inflammatory markers in polycystic ovary syndrome: a systematic review and metaanalysis. *Fertil Steril* **95**, 1048–1058.
11. Minihane AM, Vinoy S, Russell WR, *et al.* (2015) Low-grade inflammation, diet composition and health: current research evidence and its translation. *Br J Nutr* **114**, 999–1012.
12. Shivappa N, Hebert JR, Marcos A, *et al.* (2017) Association between dietary inflammatory index and inflammatory markers in the HELENA study. *Mol Nutr Food Res* **61**, 10.1002/mnfr.201600707.
13. Nasef NA, Mehta S & Ferguson LR (2017) Susceptibility to chronic inflammation: an update. *Arch Toxicol* **91**, 1131–1141.
14. Neale EP, Batterham MJ & Tapsell LC (2016) Consumption of a healthy dietary pattern results in significant reductions in C-reactive protein levels in adults: a meta-analysis. *Nutr Res* **36**, 391–401.
15. Hotamisligil GS (2006) Inflammation and metabolic disorders. *Nature* **444**, 860–867.
16. Chawla A, Nguyen KD & Goh YP (2011) Macrophage-mediated inflammation in metabolic disease. *Nat Rev Immunol* **11**, 738–749.
17. Galland L (2010) Diet and inflammation. *Nutr Clin Pract* **25**, 634–640.
18. Aravindhan V & Madhumitha H (2016) Metainflammation in diabetic coronary artery disease: emerging role of innate and adaptive immune responses. *J Diabetes Res* **2016**, 6264149.
19. Shah MS & Brownlee M (2016) Molecular and cellular mechanisms of cardiovascular disorders in diabetes. *Circ Res* **118**, 1808–1829.
20. Calder PC, Yaqoob P, Thies F, *et al.* (2002) Fatty acids and lymphocyte functions. *Br J Nutr* **87**, Suppl. 1, S31–S48.
21. Calder PC, Ahluwalia N, Brouns F, *et al.* (2011) Dietary factors and low-grade inflammation in relation to overweight and obesity. *Br J Nutr* **106**, Suppl. 3, S5–S78.
22. Paniagua JA (2016) Nutrition, insulin resistance and dysfunctional adipose tissue determine the different components of metabolic syndrome. *World J Diabetes* **7**, 483–514.
23. Cousin B, Munoz O, Andre M, *et al.* (1999) A role for preadipocytes as macrophage-like cells. *FASEB J* **13**, 305–312.
24. Charrière G, Cousin B, Arnaud E, *et al.* (2003) Preadipocyte conversion to macrophage. Evidence of plasticity. *J Biol Chem* **278**, 9850–9855.
25. Skurk T, Alberti-Huber C, Herder C, *et al.* (2007) Relationship between adipocyte size and adipokine expression and secretion. *J Clin Endocrinol Metab* **92**, 1023–1033.
26. Nishimura S, Manabe I, Nagasaki M, *et al.* (2009) $CD8^+$ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nat Med* **15**, 914–920.
27. Hill AA, Reid Bolus W & Hasty AH (2014) A decade of progress in adipose tissue macrophage biology. *Immunol Rev* **262**, 134–152.
28. Cinti S, Mitchell G, Barbatelli G, *et al.* (2005) Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. *J Lipid Res* **46**, 2347–2355.
29. Weisberg SP, McCann D, Desai M, *et al.* (2003) Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* **112**, 1796–1808.
30. Xu H, Barnes GT, Yang Q, *et al.* (2003) Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* **112**, 1821–1830.
31. Harman-Boehm I, Blüher M, Redel H, *et al.* (2007) Macrophage infiltration into omental versus subcutaneous fat across different populations: effect of regional adiposity and the comorbidities of obesity. *J Clin Endocrinol Metab* **92**, 2240–2247.
32. Mohanty P, Hamouda W, Garg R, *et al.* (2000) Glucose challenge stimulates reactive oxygen species (ROS) generation by leucocytes. *J Clin Endocrinol Metab* **85**, 2970–2973.
33. Ceriello A (2012) The emerging challenge in diabetes: the "metabolic memory". *Vascul Pharmacol* **57**, 133–138.
34. Siti HN, Kamisah Y & Kamsiah J (2015) The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease (a review). *Vascul Pharmacol* **71**, 40–56.
35. Ceriello A (1997) Acute hyperglycaemia and oxidative stress generation. *Diabet Med* **14**, Suppl. 3, S45–S49.
36. Lugrin J, Rosenblatt-Velin N, Parapanov R, *et al.* (2014) The role of oxidative stress during inflammatory processes. *Biol Chem* **395**, 203–230.
37. Dröge W (2002) Free radicals in the physiological control of cell function. *Physiol Rev* **82**, 47–95.
38. Zuo T, Zhu M & Xu W (2016) Roles of oxidative stress in polycystic ovary syndrome and cancers. *Oxid Med Cell Longev* **2016**, 8589318.
39. Alfadda AA & Sallam RM (2012) Reactive oxygen species in health and disease. *J Biomed Biotechnol* **2012**, 936486.
40. Parthasarathy S, Steinberg D & Witztum JL (1992) The role of oxidized low-density lipoproteins in the pathogenesis of atherosclerosis. *Annu Rev Med* **43**, 219–225.
41. Buyken AE, Goletzke J, Joslowski G, *et al.* (2014) Association between carbohydrate quality and inflammatory markers: systematic review of observational and interventional studies. *Am J Clin Nutr* **99**, 813–833.
42. Pahwa R & Jialal I (2016) Hyperglycemia induces Toll-like receptor activity through increased oxidative stress. *Metab Syndr Relat Disord* **14**, 239–241.
43. Soeki T & Sata M (2016) Inflammatory biomarkers and atherosclerosis. *Int Heart J* **57**, 134–139.
44. Teeman CS, Kurti SP, Cull BJ, *et al.* (2016) Postprandial lipemic and inflammatory responses to high-fat meals: a review of the roles of acute and chronic exercise. *Nutr Metab (Lond)* **13**, 80.
45. Güray U, Erbay AR, Güray Y, *et al.* (2004) Levels of soluble adhesion molecules in various clinical presentations of coronary atherosclerosis. *Int J Cardiol* **96**, 235–240.
46. Esposito K, Nappo F, Marfella R, *et al.* (2002) Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. *Circulation* **106**, 2067–2072.
47. Wolever TM, Jenkins DJ, Jenkins AL, *et al.* (1991) The glycemic index: methodology and clinical implications. *Am J Clin Nutr* **54**, 846–854.
48. Wolever TM, Vuksan V, Eshuis H, *et al.* (1991) Effect of method of administration of psyllium on glycemic response and carbohydrate digestibility. *J Am Coll Nutr* **10**, 364–371.
49. Sheard NF, Clark NG, Brand-Miller JC, *et al.* (2004) Dietary carbohydrate (amount and type) in the prevention and management of diabetes: a statement by the American Diabetes Association. *Diabetes Care* **27**, 2266–2271.

https://doi.org/10.1017/S0954422418000136

50. Rizkalla SW, Taghrid L, Laromiguiere M, *et al.* (2004) Improved plasma glucose control, whole-body glucose utilization, and lipid profile on a low-glycemic index diet in type 2 diabetic men: a randomized controlled trial. *Diabetes Care* **27**, 1866–1872.
51. Ebbeling CB, Leidig MM, Sinclair KB, *et al.* (2005) Effects of an *ad libitum* low-glycemic load diet on cardiovascular disease risk factors in obese young adults. *Am J Clin Nutr* **81**, 976–982.
52. Brynes AE, Mark Edwards C, Ghatei MA, *et al.* (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.
53. Venn BJ & Green TJ (2007) Glycemic index and glycemic load: measurement issues and their effect on diet–disease relationships. *Eur J Clin Nutr* **61**, Suppl. 1, S122–S131.
54. Cordain L, Eaton SB, Sebastian A, *et al.* (2005) Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr* **81**, 341–354.
55. Steckhan N, Hohmann CD, Kessler C, *et al.* (2016) Effects of different dietary approaches on inflammatory markers in patients with metabolic syndrome: a systematic review and meta-analysis. *Nutrition* **32**, 338–348.
56. Feliciano Pereira P, das Graças de Almeida C & Alfenas Rde C (2014) Glycemic index role on visceral obesity, subclinical inflammation and associated chronic diseases. *Nutr Hosp* **30**, 237–243.
57. Esposito K & Giugliano D (2006) Diet and inflammation: a link to metabolic and cardiovascular diseases. *Eur Heart J* **27**, 15–20.
58. Diamanti-Kandarakis E, Papalou O, Kandaraki EA, *et al.* (2017) Mechanisms in Endocrinology: Nutrition as a mediator of oxidative stress in metabolic and reproductive disorders in women. *Eur J Endocrinol* **176**, R79–R99.
59. Hu Y, Block G, Norkus EP, *et al.* (2006) Relations of glycemic index and glycemic load with plasma oxidative stress markers. *Am J Clin Nutr* **84**, 70–76.
60. Levitan EB, Cook NR, Stampfer MJ, *et al.* (2008) Dietary glycemic index, dietary glycemic load, blood lipids, and C-reactive protein. *Metabolism* **57**, 437–443.
61. Dickinson S, Hancock DP, Petocz P, *et al.* (2008) High-glycemic index carbohydrate increases nuclear factor-κB activation in mononuclear cells of young, lean healthy subjects. *Am J Clin Nutr* **87**, 1188–1193.
62. Buyken AE, Flood V, Empson M, *et al.* (2010) Carbohydrate nutrition and inflammatory disease mortality in older adults. *Am J Clin Nutr* **92**, 634–643.
63. Gaskins AJ, Mumford SL, Rovner AJ, *et al.* (2010) Whole grains are associated with serum concentrations of high sensitivity C-reactive protein among premenopausal women. *J Nutr* **140**, 1669–1676.
64. North CJ, Venter CS & Jerling JC (2009) The effects of dietary fibre on C-reactive protein, an inflammation marker predicting cardiovascular disease. *Eur J Clin Nutr* **63**, 921–933.
65. Bo S, Ciccone G, Guidi S, *et al.* (2008) Diet or exercise: what is more effective in preventing or reducing metabolic alterations? *Eur J Endocrinol* **159**, 685–691.
66. Qi L & Hu FB (2007) Dietary glycemic load, whole grains, and systemic inflammation in diabetes: the epidemiological evidence. *Curr Opin Lipidol* **18**, 3–8.
67. Ma Y, Hébert JR, Li W, *et al.* (2008) Association between dietary fiber and markers of systemic inflammation in the Women's Health Initiative Observational Study. *Nutrition* **24**, 941–949.
68. Kallio P, Kolehmainen M, Laaksonen DE, *et al.* (2007) Dietary carbohydrate modification induces alterations in gene expression in abdominal subcutaneous adipose tissue in persons with the metabolic syndrome: the FUNGENUT Study. *Am J Clin Nutr* **85**, 1417–1427.
69. Jegatheesan P & De Bandt J (2017) Fructose and NAFLD: the multifaceted aspects of fructose metabolism. *Nutrients* **9**, E230.
70. Barrea L, Di Somma C, Muscogiuri G, *et al.* (2017) Nutrition, inflammation and liver–spleen axis. *Crit Rev Food Sci Nutr* **11**, 1–18.
71. Sun SZ & Empie MW (2012) Fructose metabolism in humans – what isotopic tracer studies tell us. *Nutr Metab (Lond)* **9**, 89.
72. Kennedy A, Martinez K, Chuang CC, *et al.* (2009) Saturated fatty acid-mediated inflammation and insulin resistance in adipose tissue: mechanisms of action and implications. *J Nutr* **139**, 1–4.
73. González F (2015) Nutrient-induced inflammation in polycystic ovary syndrome: role in the development of metabolic aberration and ovarian dysfunction. *Semin Reprod Med* **33**, 276–286.
74. González F, Sia CL, Shepard MK, *et al.* (2014) The altered mononuclear cell-derived cytokine response to glucose ingestion is not regulated by excess adiposity in polycystic ovary syndrome. *J Clin Endocrinol Metab* **99**, E2244–E2251.
75. Shorakae S, Teede H, de Courten B, *et al.* (2015) The emerging role of chronic low-grade inflammation in the pathophysiology of polycystic ovary syndrome. *Semin Reprod Med* **33**, 257–269.
76. González F (2012) Inflammation in polycystic ovary syndrome: underpinning of insulin resistance and ovarian dysfunction. *Steroids* **77**, 300–305.
77. Dunaif A & Graf M (1989) Insulin administration alters gonadal steroid metabolism independent of changes in gonadotropin secretion in insulin-resistant women with the polycystic ovary syndrome. *J Clin Invest* **83**, 23–29.
78. Macut D, Bjekić-Macut J, Rahelić D, *et al.* (2017) Insulin and the polycystic ovary syndrome. *Diabetes Res Clin Pract* **130**, 163–170.
79. Wahrenberg H, Ek I, Reynisdottir S, *et al.* (1999) Divergent effects of weight reduction and oral anticonception treatment on adrenergic lipolysis regulation in obese women with the polycystic ovary syndrome. *J Clin Endocrinol Metab* **84**, 2182–2187.
80. Thorp AA & Schlaich MP (2015) Relevance of sympathetic nervous system activation in obesity and metabolic syndrome. *J Diabetes Res* **2015**, 341583.
81. Mancia G, Bousquet P, Elghozi JL, *et al.* (2007) The sympathetic nervous system and the metabolic syndrome. *J Hypertens* **25**, 909–920.
82. Lara HE, Dissen GA, Leyton V, *et al.* (2000) An increased intraovarian synthesis of nerve growth factor and its low affinity receptor is a principal component of steroid-induced polycystic ovary in the rat. *Endocrinology* **141**, 1059–1072.
83. Lansdown A & Rees DA (2012) The sympathetic nervous system in polycystic ovary syndrome: a novel therapeutic target? *Clin Endocrinol (Oxf)* **77**, 791–801.
84. Shen SH, Shen SY, Liou TH, *et al.* (2015) Obesity and inflammatory biomarkers in women with polycystic ovary syndrome. *Eur J Obstet Gynecol Reprod Biol* **192**, 66–71.
85. Ouchi N, Kihara S, Funahashi T, *et al.* (2003) Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. *Circulation* **107**, 671–674.

https://doi.org/10.1017/S0954422418000136

86. Nigro E, Scudiero O, Monaco ML, *et al.* (2014) New insight into adiponectin role in obesity and obesity-related diseases. *Biomed Res Int* **2014**, 658913.
87. Wickham EP 3rd, Cheang KI, Clore JN, *et al.* (2011) Total and high-molecular weight adiponectin in women with the polycystic ovary syndrome. *Metabolism* **60**, 366–372.
88. Bastard JP, Maachi M, Lagathu C, *et al.* (2006) Recent advances in the relationship between obesity, inflammation, and insulin resistance. *Eur Cytokine Netw* **17**, 4–12.
89. Gonzalez F (2017) Treating inflammation in polycystic ovary syndrome to ameliorate ovarian dysfunction (TIN-PCOS-AOD). https://clinicaltrials.gov/ct2/show/NCT03229408 (accessed June 2018).
90. Carmina E, Legro RS, Stamets K, *et al.* (2003) Difference in body weight between American and Italian women with polycystic ovary syndrome: influence of the diet. *Hum Reprod* **18**, 2289–2293.
91. Turner-McGrievy G, Davidson CR & Billings DL (2015) Dietary intake, eating behaviors, and quality of life in women with polycystic ovary syndrome who are trying to conceive. *Hum Fertil (Camb)* **18**, 16–21.
92. Brzechffa PR, Jakimiuk AJ, Agarwal SK, *et al.* (1996) Serum immunoreactive leptin concentrations in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* **81**, 4166–4169.
93. Marsh K & Brand-Miller J (2005) The optimal diet for women with polycystic ovary syndrome? *Br J Nutr* **94**, 154–165.
94. Moran LJ, Noakes M, Clifton PM, *et al.* (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.
95. Moran LJ, Pasquali R, Teede HJ, *et al.* (2009) Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. *Fertil Steril* **92**, 1966–1982.
96. Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F, *et al.* (2005) The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. *J Clin Endocrinol Metab* **90**, 6364–6469.
97. Anonymous (2000) Case problem: dietary recommendations to combat obesity, insulin resistance, and other concerns related to polycystic ovary syndrome. *J Am Diet Assoc* **100**, 955–957.
98. McKeown NM, Meigs JB, Liu S, *et al.* (2004) Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort. *Diabetes Care* **27**, 538–546.
99. Juntunen KS, Niskanen LK, Liukkonen KH, *et al.* (2002) Postprandial glucose, insulin, and incretin responses to grain products in healthy subjects. *Am J Clin Nutr* **75**, 254–262.
100. Barrea L, Annunziata G, Muscogiuri G, *et al.* (2017) Could hop-derived bitter compounds improve glucose homeostasis by stimulating the secretion of GLP-1? *Crit Rev Food Sci Nutr* **14**, 1–8.
101. Galgani JE, Moro C & Ravussin E (2008) Metabolic flexibility and insulin resistance. *Am J Physiol Endocrinol Metab* **295**, E1009–E1017.
102. Bonadonna RC, Groop LC, Zych K, *et al.* (1990) Dose-dependent effect of insulin on plasma free fatty acid turnover and oxidation in humans. *Am J Physiol* **259**, E736–E750.
103. Corpeleijn E, Saris WH & Blaak EE (2009) Metabolic flexibility in the development of insulin resistance and type 2 diabetes: effects of lifestyle. *Obes Rev* **10**, 178–193.
104. Mehran AE, Templeman NM, Brigidi GS, *et al.* (2012) Hyperinsulinemia drives diet-induced obesity independently of brain insulin production. *Cell Metab* **16**, 723–737.
105. Kopp HP, Kopp CW, Festa A, *et al.* (2003) Impact of weight loss on inflammatory proteins and their association with the insulin resistance syndrome in morbidly obese patients. *Arterioscler Thromb Vasc Biol* **23**, 1042–1047.
106. Chavarro JE, Rich-Edwards JW, Rosner BA, *et al.* (2009) A prospective study of dietary carbohydrate quantity and quality in relation to risk of ovulatory infertility. *Eur J Clin Nutr* **63**, 78–86.
107. Stamets K, Taylor DS, Kunselman A, *et al.* (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.
108. Moran L & Norman RJ (2004) Understanding and managing disturbances in insulin metabolism and body weight in women with polycystic ovary syndrome. *Best Pract Res Clin Obstet Gynaecol* **18**, 19–36.
109. Douglas CC, Gower BA, Darnell BE, *et al.* (2006) Role of diet in the treatment of polycystic ovary syndrome. *Fertil Steril* **85**, 679–688.
110. Marsh KA, Steinbeck KS, Atkinson FS, *et al.* (2010) Effect of a low glycemic index compared with a conventional healthy diet on polycystic ovary syndrome. *Am J Clin Nutr* **92**, 83–92.
111. Mehrabani HH, Salehpour S, Amiri Z, *et al.* (2012) Beneficial effects of a high-protein, low-glycemic-load hypocaloric diet in overweight and obese women with polycystic ovary syndrome: a randomized controlled intervention study. *J Am Coll Nutr* **31**, 117–125.
112. Gower BA & Goss AM (2015) A lower-carbohydrate, higher-fat diet reduces abdominal and intermuscular fat and increases insulin sensitivity in adults at risk of type 2 diabetes. *J Nutr* **145**, 177S–183S.
113. Pohlmeier AM, Phy JL, Watkins P, *et al.* (2014) Effect of a low-starch/low-dairy diet on fat oxidation in overweight and obese women with polycystic ovary syndrome. *Appl Physiol Nutr Metab* **39**, 1237–1244.
114. Eslamian G, Baghestani AR, Eghtesad S, *et al.* (2017) Dietary carbohydrate composition is associated with polycystic ovary syndrome: a case–control study. *J Hum Nutr Diet* **30**, 90–97.
115. Johnson LK, Holven KB, Nordstrand N, *et al.* (2015) Fructose content of low calorie diets: effect on cardiometabolic risk factors in obese women with polycystic ovarian syndrome: a randomized controlled trial. *Endocr Connect* **4**, 144–154.
116. Mavropoulos JC, Yancy WS, Hepburn J, *et al.* (2005) The effects of a low-carbohydrate, ketogenic diet on the polycystic ovary syndrome: a pilot study. *Nutr Metab (Lond)* **2**, 35.
117. Galletly C, Moran L, Noakes M, *et al.* (2007) Psychological benefits of a high-protein, low-carbohydrate diet in obese women with polycystic ovary syndrome – a pilot study. *Appetite* **49**, 590–593.
118. McGrice M & Porter J (2017) The effect of low carbohydrate diets on fertility hormones and outcomes in overweight and obese women: a systematic review. *Nutrients* **9**, E204.
119. Frary JM, Bjerre KP, Glintborg D, *et al.* (2016) The effect of dietary carbohydrates in women with polycystic ovary syndrome: a systematic review. *Minerva Endocrinol* **41**, 57–69.
120. Moran LJ, Ko H, Misso M, *et al.* (2013) Dietary composition in the treatment of polycystic ovary syndrome: a systematic review to inform evidence-based guidelines. *J Acad Nutr Diet* **113**, 520–545.

https://doi.org/10.1017/S0954422418000136

121. Sears B (2009) Anti-inflammatory diets for obesity and diabetes. *J Am Coll Nutr* **28**, Suppl., 482S–491S.
122. Kalgaonkar S, Almario RU, Gurusinghe D, *et al.* (2011) Differential effects of walnuts vs almonds on improving metabolic and endocrine parameters in PCOS. *Eur J Clin Nutr* **65**, 386–393.
123. Moran LJ, Grieger JA, Mishra GD, *et al.* (2015) The association of a Mediterranean-style diet pattern with polycystic ovary syndrome status in a community cohort study. *Nutrients* **7**, 8553–8564.
124. Muscogiuri G, Palomba S, Laganà AS, *et al.* (2016) Current insights into inositol isoforms, Mediterranean and ketogenic diets for polycystic ovary syndrome: from bench to bedside. *Curr Pharm Des* **22**, 5554–5557.
125. Salama AA, Amine EK, Salem HA, *et al.* (2015) Anti-inflammatory dietary combo in overweight and obese women with polycystic ovary syndrome. *N Am J Med Sci* **7**, 310–316.
126. Azadbakht L, Surkan PJ, Esmaillzadeh A, *et al.* (2011) The Dietary Approaches to Stop Hypertension eating plan affects C-reactive protein, coagulation abnormalities, and hepatic function tests among type 2 diabetic patients. *J Nutr* **141**, 1083–1088.
127. Asemi Z, Samimi M, Tabassi Z, *et al.* (2014) Effects of DASH diet on lipid profiles and biomarkers of oxidative stress in overweight and obese women with polycystic ovary syndrome: a randomized clinical trial. *Nutrition* **30**, 1287–1293.
128. Foroozanfard F, Rafiei H, Samimi M, *et al.* (2017) The effects of dietary approaches to stop hypertension diet on weight loss, anti-Müllerian hormone and metabolic profiles in women with polycystic ovary syndrome: a randomized clinical trial. *Clin Endocrinol (Oxf)* **87**, 51–58.
129. Azadi-Yazdi M, Karimi-Zarchi M, Salehi-Abargouei A, *et al.* (2017) Effects of Dietary Approach to Stop Hypertension diet on androgens, antioxidant status and body composition in overweight and obese women with polycystic ovary syndrome: a randomised controlled trial. *J Hum Nutr Diet* **30**, 275–283.
130. Liepa GU, Sengupta A & Karsies D (2008) Polycystic ovary syndrome (PCOS) and other androgen excess-related conditions: can changes in dietary intake make a difference? *Nutr Clin Pract* **23**, 63–71.
131. Thakker D, Raval A, Patel I, *et al.* (2015) N-acetylcysteine for polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled clinical trials. *Obstet Gynecol Int* **2015**, 817849.
132. Akbari M, Ostadmohammadi V, Lankarani KB, *et al.* (2018) The effects of vitamin D supplementation on biomarkers of inflammation and oxidative stress among women with polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Horm Metab Res* **50**, 271–279.
133. Maktabi M, Jamilian M & Asemi Z (2018) Magnesium–zinc–calcium–vitamin D co-supplementation improves hormonal profiles, biomarkers of inflammation and oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. *Biol Trace Elem Res* **182**, 21–28.
134. Banaszewska B, Wrotyńska-Barczyńska J, Spaczynski RZ, *et al.* (2016) Effects of resveratrol on polycystic ovary syndrome: a double-blind, randomized, placebo-controlled trial. *J Clin Endocrinol Metab* **101**, 4322–4328.

https://doi.org/10.1017/S0954422418000136