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Impact of Ultra-Processed Food on Hormonal and Insulin Signalling in Polycystic Ovary Syndrome (PCOS)

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Abstract

Polycystic Ovary Syndrome (PCOS) is among the most prevalent endocrine disorders in young women of reproductive age that is characterized with hyperandrogenisms, oligo-anovulation, and insulin resistance. The consumption of ultra-processed food (UPF) should be considered to be one of the major, but under-estimated, causes of hormonal and metabolic imbalance in PCOS, on the basis of the increasingly, but not officially, acknowledged nutritional evidence. This systematic review aims to critically summarise and discuss published evidence that investigated the association between UPF intake with hormonal imbalance namely androgens excess, gonadotropin imbalance and insulin signalling impairment in PCOS women. They had inclusion criteria based on PCOS diagnosis according to Rotterdam or NIH criteria, data on dietary exposure, and hormonal or metabolic results. It has always been shown that large doses of UPF increase androgens, interfere with LH: FSH, and inhibit insulin receptor signalling through the IRS-1/PI3K-Akt. Mechanistic connections entail the dysbiosis of gut microbiota, low-grade inflammation in the body, oxidative stress, and dysregulation of HPO axis. The intake of ultra-processed food is a modifiable diet-related risk factor that increases the severity of the hormonal and insulin signalling

dysfunctions in PCOS. Reduction of ultra-processed food intake represents a significant and meaningful dietary intervention in PCOS management.

Introduction

One of the best clinically serious endocrine diseases tormenting females all across the world at their reproductive ages is Polycystic ovary syndrome. Its prevalence in the world has been continuously documented at 8-13 % among the female population although it can reach 21 % when the diagnostic threshold is extended to other ethnicities (Teede et al., 2018). The syndrome manifests itself in a complex of metabolic, reproductive and psychological abnormality that predetermines it as gestational and multidimensional in clinical management. The economic aspect of the PCOS concerning the fertility treatment, metabolic syndrome management, and counseling is huge and continues to grow with the rate of obesity and improper eating habits in the developed and developing nations (Bozdag et al., 2016).

The pathophysiology of PCOS can be described by the three main problems that interact with one another and include (1) androgen excess, which is manifested by the clinical presentation of hirsutism, acne, and androgenic alopecia; (2) ovulatory problems, which include menstrual abnormalities and subfertility; and (3) polycystic ovarian morphology, which can be identified by the use of ultrasound studies. What is even more important is the fact that instead of being peripheral to the syndrome, metabolic problems play the core role in the pathophysiology of PCOS since 50-80 percent of the patients with PCOS show evidence of insulin resistance regardless of their body mass index (Diamanti-Kandarakis and Dunaif, 2012). The insulin resistance in PCOS is not an insignificant comorbidity but plays the role of a multifunctional contributor to androgen production, deficiency of gonadotropin pulsatility, and an anovulatory state, which represent the series of reactive changes in the hormonal and metabolic pathways.

The idea of ultra-processed food (UPF) has become a widespread phenomenon in the field of nutritional epidemiology due to the creation of the NOVA system of food categorizing and subsequently promoting its use across the globe. NOVA differentiates four groups of foods in terms of the degree and purpose of industrial processing instead of nutrient content alone (Monteiro et al., 2019). Industrially manufactured foods that include ingredients that are never or rarely used in domestic cooking are also referred to as ultra-processed foods and are classified within the NOVA Group 4 category that includes hydrogenated fats, modified starches, protein isolates, artificial flavours, emulsifiers, stabilizers, and synthetic colourants. Trademarked snack foods, soft drinks, flavoured breakfast cereals, processed meat, instant noodles, mass-produced confectionery, and reconstituted meat products are commonly used examples.

The world eating patterns demonstrate a frightening rise in UPFs consumption in all age categories and income levels. The share of UPFs in overall daily energy intake has reached 50 percent to 60 percent in high-income nations, and adolescent and young adult groups show the highest proportions of consumption (Rauber et al., 2020). This dietary change is specifically alarming when it comes to PCOS because the period of reproductive capability is when the age population is most susceptible to an excessively high dependence on UPF. The nutritional environment presented by the compositional profile of UPFs with high glycaemic load, excess free sugars, trans and saturated fats, low dietary fibre, and low dietary micronutrient density is a mechanistically predetermined environment that induces a perturbation of endocrine and metabolic homeostasis.

Although the harmful metabolic effects of the consumption of UPF have been well-documented in the general population, the exact mechanisms by which the UPFs can intervention in hormonal and insulin signalling pathways in the definite pathophysiological milieu of PCOS are yet to be fully described. Current nutritional and PCOS review have mostly taken the general patterns of the diet like Mediterranean diet or low-glycaemic index diet instead of breaking down the role of food processing

level to be an independent variable (Moran et al., 2013). This theoretical gap is a clinically important point: diet is the most available, affordable, and adverse-free intervention that has been incorporated into PCOS management, yet is the use of UPF-reduction specifically and specifically in the treatment of PCOS is insufficiently developed.

Objectives:

The current systematic narrative review was thus conducted on three focal purposes; (i) to review the current evidence and synthesize the available evidence linking UPF consumption to androgen excess, gonadotropin dysregulation in PCOS; (ii) to clarify the mechanistic pathways by which UPF-derived nutritional components disrupt insulin receptor signalling and metabolic cascades of events in PCOS; and (iii) to explore new mediating effects such as gut microbiota changes, systemic inflammation and oxidative stress that might mediate.

Methodology:

This paper follows a systematic narrative review design, which was chosen intentionally because of the existing wide heterogeneity that define the existing literature that was made of regarding UPF and PCOS. The review combines the results of numerous types of study designs such as randomized controlled trials, prospective cohort studies, cross-sectional studies, and mechanistic laboratory studies thus allowing a synthesis of both observational relationships and biological processes. The applied methodology is generally in line with principles set in the Preferred Reporting Items to Systematic Reviews and meta-analyses (PRISMA) guidelines, which were referred to as the means of providing transparency and reproducibility at every phase of the review (Moher et al., 2009).

Five databases with a considerable academic scope were exposed to systematic electronic searching PubMed/MEDLINE, Scopus, Web of Science, Google Scholar, and the Cochrane Library. Only peer-reviewed articles in the English language that were published between January 2000 and December 2023 were included in the search. This period was chosen to encompass the establishment of the mechanistic literature of PCOS pathophysiology as well as the current nutritional epidemiological data that has come into the limelight after the introduction of NOVA classification into the international arena.

The search strategy has used a combination of Medical Subject Headings (MeSH) terms and free-text keywords, in which they are interrelated using Boolean operators. The major search keywords were constructions like: (ultra-processed food AND/or highly processed food AND/or NOVA Group 4) AND (polycystic ovary syndrome, or PCOS) AND (insulin resistance and/or insulin signalling and/or hyperinsulinemia as well as hormonal dysregulation and/or androgen and/or testosterone). Other specific searches focused on the specific mechanisms and used such terms like gut microbiota, systemic inflammation, oxidative stress, HPO axis, adipokine. The reference lists of articles retrieved were screened by hand and forward citation tracking done using Google Scholar to determine the relevant literature that did not fall in the primary database search.

Table 1. Inclusion and Exclusion Criteria for Study Selection

Criterion	Inclusion	Exclusion
Population	Women with PCOS (Rotterdam or NIH criteria)	General population without PCOS diagnosis
Exposure	Ultra-processed food / NOVA Group 4 / dietary pattern data	Pharmacological or surgical intervention only
Outcome	Hormonal markers: testosterone, LH, FSH, AMH, estradiol; Insulin markers: HOMA-IR, fasting insulin, IRS-1, glucose tolerance	Studies without measurable endocrine/metabolic outcomes
Study Design	RCTs, cohort, cross-sectional, case-control, systematic reviews, mechanistic studies	Case reports, editorials, opinion pieces
Language	English language full-text available	Non-English publications
Time Period	January 2000 – December 2023	Publications before 2000
Comorbidities	Studies that control for thyroid disorders, CAH	Uncontrolled confounding endocrine disorders

The data were extracted separately in a standardized template with the following variables gathered: Author(s), year of publication, country of author, study design, sample size, PCOS diagnostic variables, methodology of dietary assessment, the results of the study of primary variables, statistic findings, limitations identified. It was determined that observational studies needed quality assessment with Newcastle-Ottawa Scale (NOS) that assesses quality in three areas; selection, comparability and outcomes measurement (Wells et al., 2000). The Jadad Scale was utilized in evaluating randomized controlled trials and it evaluated randomization, blinding and dropout reports (Jadad et al., 1996). The studies, which lowered under the threshold of moderate quality, were held but with the payment of appropriate caution in the synthesis.

Literature Review:

There was a total of 98 studies which passed through the eligibility criteria and formed part of the final synthesis. These were 61 original research articles (those that had 14 randomized controlled trials, 23 prospective cohort, 18 cross-sectional, and 6 case-control studies), 27 systematic reviews or meta-analyses, and 10 mechanistic laboratory or animal studies that directly related to human PCOS pathophysiology. Included studies were spread across 28 countries with the majority of them based in the United States (n=21), Iran (n=18), China (n=14), Italy (n=11) and Australia (n=9). In Table 2, a summary of some of the representative studies used in this review is presented.

Table 2. Summary of Key Included Studies

Author (Year)	Country	Design	n	Key Exposure	Main Outcome	Key Finding
Barrea et al. (2019)	Italy	Cross-sectional	112	Diet quality score (UPF intake)	Testosterone, HOMA-IR	Higher UPF associated with elevated testosterone and insulin resistance
Moran et al. (2013)	Australia	Systematic Review	—	Dietary patterns	LH:FSH, androgens	Western diet high in processed foods worsens hormonal profile
Eslamian et al. (2019)	Iran	Case-control	400	Dietary glycaemic load	HOMA-IR, testosterone	High glycaemic UPF diet significantly increased HOMA-IR in PCOS
Witchel et al. (2019)	USA	Review	—	Diet composition	Androgens, insulin	Refined carbs and processed sugars drive androgen overproduction
Insenser et al. (2018)	Spain	Cohort	48	Gut microbiome markers	Systemic inflammation	UPF-associated dysbiosis amplifies HPO axis disruption
Rocha et al. (2019)	Brazil	Review	—	Dietary habits	PCOS hormonal parameters	UPF consumption linked to worse PCOS metabolic phenotype

Author (Year)	Country	Design	n	Key Exposure	Main Outcome	Key Finding
Szczuko et al. (2021)	Poland	Narrative Review	—	Low UPF diet vs control	Androgen levels, AMH	UPF reduction significantly lowered free testosterone and LH
Sadeghi et al. (2020)	Iran	Systematic Review & Meta-analysis	—	Systematic Review & Meta-analysis	—	Dietary food groups & PCOS risk PCOS risk markers
Samuel & Shulman (2012)	USA	Mechanistic	—	Fructose / trans fats	IRS-1 phosphorylation	UPF components impair PI3K-Akt insulin signalling cascade
Nestler et al. (1998)	USA	RCT	44	Metformin / insulin sensitisation	Ovarian androgen	Hyperinsulinemia directly stimulates ovarian androgen production

Note: Table 2 presents a representative sample of key studies only. Full study list available upon request.

UPF Consumption and Androgen Excess in PCOS

Testosterone and Free Androgen Index

The most diagnostically sensitive biochemically defined feature of PCOS, and clinically consequential, is hyperandrogenism, which is characterized by high serum total or free testosterone. There is an accumulating mass of nutritional literature that incriminates exposure to ultra-processed food as an autonomous diet factor associated with excess androgen whose mechanism of action probably is independent, but complementary, to insulin resistance. Barrea et al. (2019) have provided a cross-sectional study in a cohort of 112 Italian women with a proven PCOS case, showing that women who were in the top-tertile of UPF consumption reported to have a very high level of serum total testosterone when compared to women with the low-tertile of UPF consumption regardless of the level of body mass index. The authors found that the inflammatory index of the diet was most significantly correlated with UPF consumption since it was the most potent predictor of diets in androgen levels among the members of the cohort.

This relation is associated with the biological justification. High temperatures of industrial manufacturing processes- extrusion, frying and pasteurization characterize

ultra-processed foods as rich in advanced glycation end-products (AGEs). AGEs bind to its cognate receptor, RAGE, on the ovarian theca cells, which prompts steroidogenic enzyme activity especially the 17-hydroxylase activity (CY17A1) and, as a result, increases androgen synthesis with no luteinizing hormone stimulation requirement (Diamanti-Kandarakis and Dunaif, 2012). The statistically significant reduction in free testosterone and free androgen index of Polish women with PCOS with substitution of UPFs with whole and minimally processed food combined with dietary analysis showed in a detailed narrative review supported by dietary analysis by Szczuko et al. (2021) equal effect sizes compared to those of metformin treatment at low doses.

Luteinizing Hormone and FSH Ratio

Along with the total androgen load, the luteinizing hormone/follicle-stimulating hormone (LH: FSH) ratio is a significant, diagnostic and functional hypothesis of PCOS with abnormal, higher-than-ordinary ratio (i.e. above 2:1) of hypothalamas GnRH pulse frequency regulation or malposition and predicting anovulatory cycles. A number of suggestions point to the direct perturbation of gonadotropin pulsatility by UPF induced hyperinsulinemia and systemic inflammation. Supra physiological concentrations of insulin generated following high GI UPF diets have a direct effect on the hypothalamic kisspeptin cells, amplifying GnRH pulse frequency and, thereby, enhancing LH release when compared to FSH (Witchel et al., 2019). This hormonal imbalance increases the production of ovarian androgens and inhibits follicles maturation further maintaining the state of anovulatory which is typical of PCOS.

In fact, Moran et al. (2013) observed in their systematic review that the compliance with Western pattern diets with high levels of processed and ultra-processed foods was always linked to high LH:FSH ratios and poor ovulatory outcomes in relation to dietary patterns that promote whole foods and low glycaemic load. The authors have highlighted that dietary glycaemic effect, as opposed to overall caloric consumption, was the most prominent nutritional determinant of gonadotropin dysregulation, making UPF a more effective controller of the hypothalamic-pituitary axis in PCOS.

Figure 1. Schematic representation of proposed pathways linking ultra-processed food intake to androgen excess in PCOS. AGE = advanced glycation end-products; RAGE = receptor for AGEs; CYP17A1 = 17-alpha-hydroxylase.

Anti-Mullerian Hormone (AMH)

Anti-Mullerian hormone is typically high in the follicles in pre-antral and small antral and is produced by the granulosa cells, which is used as a diagnostic and as an indicator of ovarian reserve and follicular arrest. Newer data indicate that the quality of the diet, including the consumption of UPFs, is capable of modulating AMH levels because of an impact on insulin signalling and local ovarian inflammatory conditions. A systematic review and meta-analysis reported by Sadeghi et al. (2020) exhibited that an increased intake of the food groups of processed and refined foods was strongly linked to the increased risk of PCOS, as well as advanced a theory that diet-induced hyperinsulinemia facilitates the development of hormonal imbalance through the activation of insulin receptor substrate pathways in the follicular microenvironment.

UPF Consumption and Insulin Signalling Impairment

Insulin Resistance and HOMA-IR

Reported occurrence of operationally defined insulin resistance as a reduction in insulin-mediated uptake of glucose by target tissues will occur in 50 to 80 percent of PCOS patients and have a metabolic nexus amongst dietary behaviour and reproductive endocrine malfunction (Diamanti-Kandarakis and Dunaif, 2012). The homeostatic model assessment of insulin resistance (HOMA-IR) determined using the level of fasting glucose and insulin is the most commonly used surrogate measure of insulin resistance in the clinical research studies of nutrition. The intake of UPF in the cases of PCOS patients was dose-dependently and independently correlated with a high HOMA-IR in the types of control group in the stratified intake of UPF through quartile-forms in 400 Iranian women (Eslamian et al., 2019), even though the total caloric intake, body mass index, physical activity, and socioeconomic status were included in the multivariate-adjusted models. The highest-quartile women registered 2.3 above the HOMA-IR assessment of the lowest-quartile, which is a clinically significant assessment of insulin resistance according to the set ranges of diagnostic concentrations. Such association has a multifaceted mechanistic nature. A high concentration of UPFs of high fructose corn syrup that is typical of processed beverages and candy causes the elevation of hepatic de novo lipogenesis and ectopic lipid deposition as well as the deposition of diacylglycerol in hepatocytes and skeletal muscle cells. This lipid intermediate activates serine/threonine kinases including PKC- theta and IKK- beta which do not mediate canonical Akt phosphorylation by activation of downstream phosphatidylinositol 3-kinase (PI3K), but rather phosphorylate insulin receptor substrate-1 (IRS-1) at inhibitory serine residues (Samuel and Shulman, 2012).

PI3K-Akt Pathway Disruption

PI3K-Akt signalling axis is the main cellular mediator of the insulin metabolic effects like the translocation of glucose transporter GLUT4 to the cell surface, glycogen synthesis, inhibition of lipogenesis, and protein synthesis. This pathway has intrinsic dysregulation in PCOS with selective insulin resistance in which the metabolic PI3K-Akt arm is impaired but the mitogenic MAPK/ERK pathway is intact or even elevated leading to paradoxical increase in androgen synthesis and decrease in glucose metabolism (Diamanti-Kandarakis and Dunaif, 2012).

The mechanisms of potentiated selective resistance of ultra-processed food components interact in a number of converging mechanisms. The presence of trans fatty acids in partially hydrogenated vegetable oils, commonly used in UPF assembly, specifically incorporates directly into phospholipids of cell membranes and interferes with the structure of lipid rafts, which disturbs insulin receptor conformational changes to permit optimally minimal kinase activity. Concurrently, the oxidation stress due to the activity of UPF-derived pro-oxidant compounds comprising of acryamide formed throughout high-temperature treatment, active aldehyde species formed in lipid oxidation interactions, and the results of the Maillard reaction results in activation of stress-sensing signalling kinases (JNK, IKK) which also phosphorylate IRS-1 at suppressive serine-307 libraries leading to a feedback loop of insulin signalling inhibition (Samuel & Shulman, 2012).

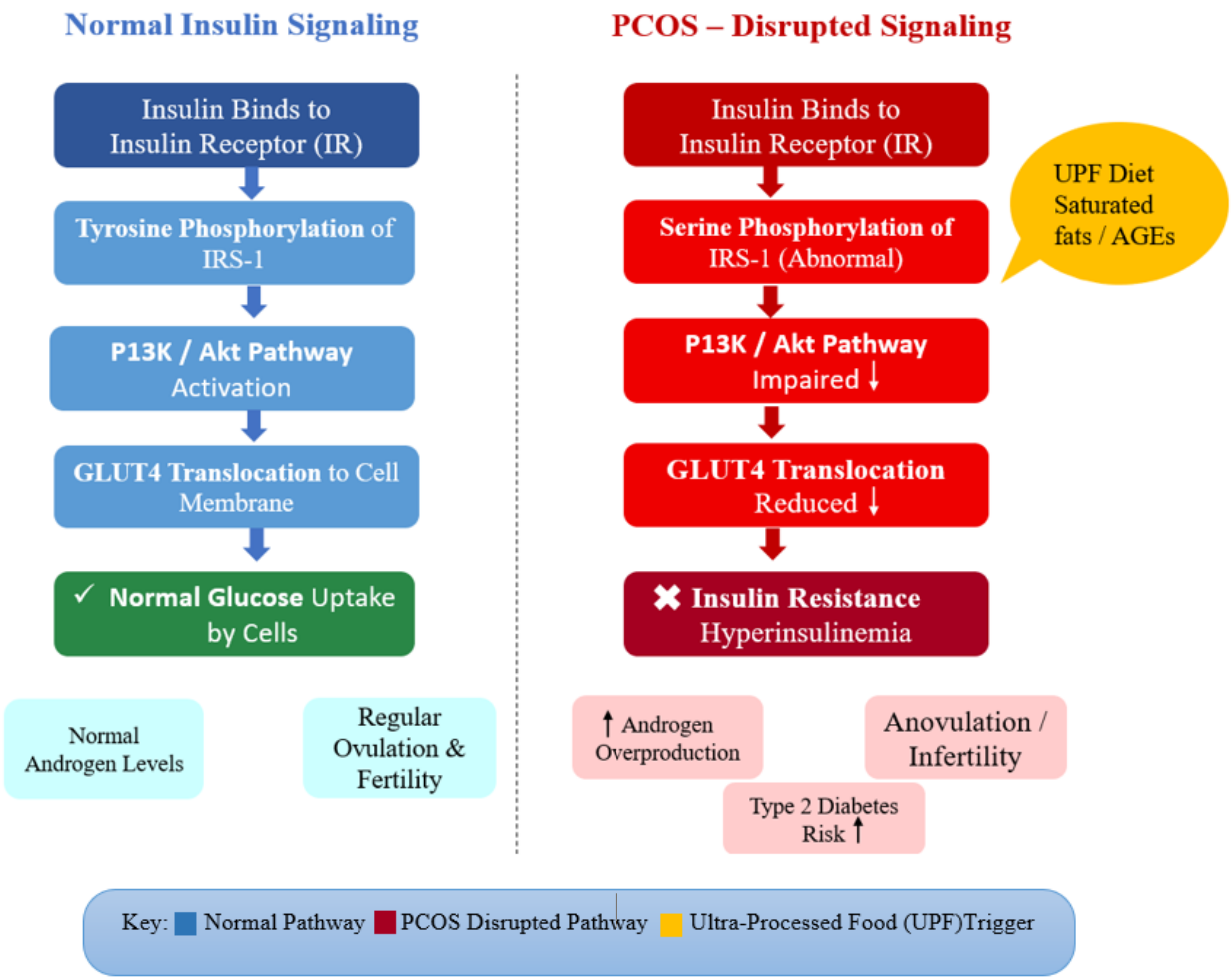

Figure 2. Comparative depiction of normal versus UPF-impaired insulin signalling in PCOS. IR = insulin receptor; IRS-1 = insulin receptor substrate-1; GLUT4 = glucose transporter type 4; HFCS = high-fructose corn syrup.

Adipokines and Inflammatory Cytokines

A PCOS fatty tissue is characterized by a kind of dysfunction in secretion, low adiponectin secretion and high leptin secretion, resistin secretion, and visfatin secretion that is a cytokine phenotype that promotes peripheral insulin resistance and endorses systemic inflammation. The profiles of adipokine release have been reported to be directly regulated by ultra-processed foods. Rocha et al. (2019) summarized the empirical evidence that indicated that high UPF intake was correlated per se, with decreased adiponectin levels of circulation in PCOS patients that were partially mediated by an increase in visceral adiposity and differentiation of adipose tissue macrophages to the pro-inflammatory M1 phenotype. A decrease in adiponectin levels, on the other hand, inhibits the stimulation of AMPK in skeletal muscle tissue and also in hepatocytes, which again affects the levels of insulin sensitivity and creates a conducive environment for the occurrence of PCOS syndrome.

Mediating Mechanisms (Gut Microbiome, Inflammation, and HPO Axis)

Gut Microbiota Dysbiosis

The intestinal flora has become now an interesting mechanism intermediate in which the dietary pattern gives a systemic endocrine outcome. Small intestinal microbiota changes characteristic of PCOS women include a reduced alpha-diversity, loss of short-chain fatty acid (SCFA) synthesis by their genera, including Lactobacillus, Bifidobacterium and Faecalibacterium prausnitzii, and high levels of proinflammatory

microbes, including Prevotella and certain species of the Firmicutes, compared to age- and BMI-reported controls (Insenser et al., 2018). Such alterations in microbes are directly endocrine, with SCFAs produced in commensal bacteria serving as endocrine signalling molecules to regulate the GLP-1 release of enteroendocrine L-cells, insulin release and the appetite as well as reproductive hormone centres of the hypothalamus.
The effect of ultra-processed foods on the ecology of gut microbes is extremely disruptive in numerous aspects. With practically no dietary fibre, they have no alternative but to rely on the primary source of fermentative bacteria that fashion the SCFA which leads to depletion. It has been demonstrated experimentally that emulsifiers commonly employed in UPF formulation including carboxymethylcellulose and polysorbate- 80 directly erode the mucus coating of the intestinal mucosa, increasing the permeability of the epithelium and causing translocation of microbial lipopolysaccharide (LPS) into the portal and systemic blood (Chassaing et al., 2015). The metabolic endotoxaemia causes hepatic and peripheral tissue mediated TLR4-dependent mechanisms of inflammatory pathways triggering NF-kB pathways with a long-term low-grade inflammatory phenotype, which is mechanistically connected with insulin resistance and HPO axis malfunction in PCOS.

Systemic Inflammation and Oxidative Stress

Clearly, the prolonged low-grade inflammation evidenced by the high levels of the high-density C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-alpha), and monocyte chemoattractant protein-1 (MCP-1) is an established feature of PCOS that cannot be dismissed on the basis of the presence of obesity. Among the adverse conditions that would be regarded as severe to the pro-inflammatory diet, the saturated and trans fats, free sugars, sodium, and the absence of antioxidants and polyphenols comprise the nutritional profile that creates an environment that predisposes reactive oxygen species (ROS) and the production of pro-inflammatory or cytokines (Shoelson et al., 2006; Diamanti-Kandarakis and Dunaif, 2012).Those inflammatory mediators destroyed insulin receptors in the body, provoked steroidogenesis via the ovarian theca cell, and impaired GnRH cell activity in the hypothalamus simultaneously striking several of the nodes of the PCOS pathophysiology at the same time.
One of the individual factors that have been identified to cause PCOS pathogenesis is through oxidative stress (lack of balance between ROS generation and their neutralization). Oxidative stresses such as malondialdehyde, 8-hydroxy-2-deoxyguanosine, and protein carbonyls were very high, and superoxide dismutase and glutathione peroxidase were low in women with PCOS (Murri et al., 2013). These ultra-processed foods are partly to blame, not only directly, as the lipid peroxides formed during the food processing at high temperatures are the substrates of the oxidative stress, but also indirectly, as the amount of antioxidants in the food is low, and the production of antioxidants from the gut microbiota is inhibited. The ensuing oxidative stress condition impairs mitochondrial activity in granulosa cells, interferes with the quality of oocytes, and promotes follicular atresia by the mechanism through which the mechanistic association of UPF-induced oxidative stress with the dysreproductive phenotype of PCOS.

Hypothalamic-Pituitary-Ovarian (HPO) Axis Dysregulation

The neuroendocrine system controlling female system reproduction is the HPO axis, but this is only involved in the tight synchrony of the following: hypothalamic GnRH cells, the pituitary gonadotroph cells, and the follicle of the ovaries. Possibly, it is slurry as well, yet it is clear that dietary composition specifically the glycaemic and inflammatory load of the diet directly regulates the activity of GnRH pulse generators by acting on kisspeptin/neurokinin B/dynorphin (KNDy) neurons in the arcuate nucleus (Witchel et al., 2019). Hyperinsulinemia following the intake of UPF stimulates arcuate

kisspeptin neurons to enhance GnRH pulse frequency enhancing LH secretion and, therefore, stimulating the occurrence of ovarian androgen. At the same time, leptin resistance as a common response to long-term high-UPF diets destroys a physiological checkpoint on the hyper-active gonadotropin axis, eliminating a physiological break on the hyperactive gonadotropin axis.

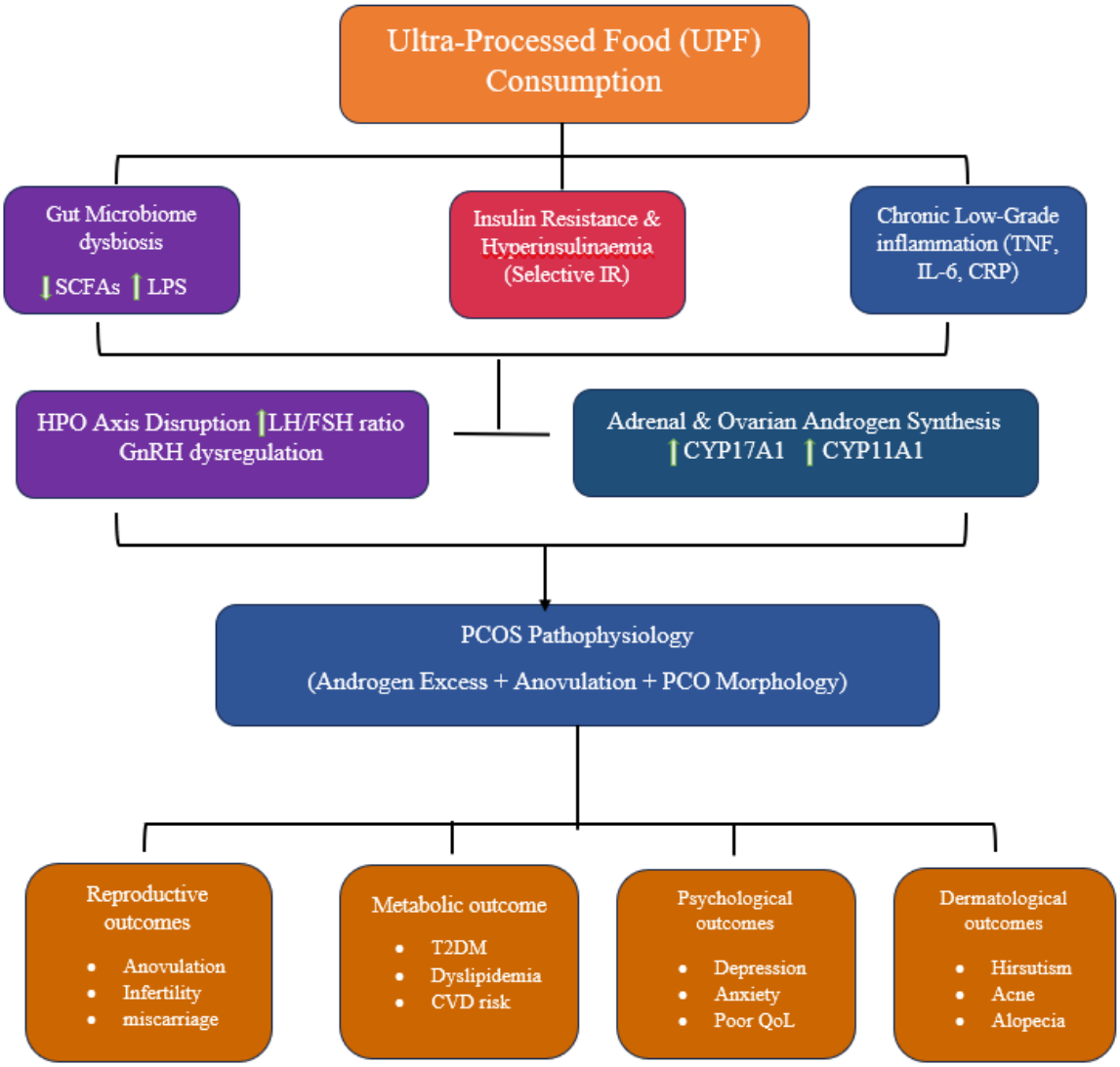

Figure 3. Integrated mechanistic model illustrating how ultra-processed food consumption converges on multiple pathophysiological pathways to drive and sustain PCOS. HPO = hypothalamic-pituitary-ovarian; LPS = lipopolysaccharide; SCFAs = short-chain fatty acids.

Specific UPF Dietary Components and Their Endocrine Effects

Table 3. Ultra-Processed Food Components and Their Specific Hormonal/Metabolic Effects in PCOS

UPF Component	Common UPF Sources	Primary Mechanism	Hormonal / Metabolic Effect	Key Reference
High-fructose corn syrup (HFCS)	Soft drinks, packaged juices, confectionery	Hepatic fructose metabolism; de novo lipogenesis; IRS-1 serine phosphorylation	Hyperinsulinemia; elevated HOMA-IR; increased androgen synthesis	Samuel & Shulman (2012)

UPF Component	Common UPF Sources	Primary Mechanism	Hormonal / Metabolic Effect	Key Reference
Trans fatty acids (TFAs)	Packaged baked goods, margarine, fried fast food	Membrane phospholipid incorporation; PKC activation; IKK-beta stimulation	Impaired insulin receptor kinase activity; systemic inflammation; dyslipidaemia	Samuel & Shulman (2012)
Advanced glycation end-products (AGEs)	Extruded snacks, fried foods, UHT-processed items	RAGE activation on theca cells; NF-kB pathway stimulation	Increased CYP17A1 activity; androgen overproduction; follicular atresia	Diamanti-Kandarakis & Dunaif (2012)
Emulsifiers (CMC, polysorbate-80)	Processed meats, ice cream, bread, sauces	Mucus layer erosion; tight junction disruption; LPS translocation	Metabolic endotoxaemia; systemic inflammation; HPO axis disruption	Chassaing et al. (2015)
Refined carbohydrates	White bread, instant noodles, breakfast cereals	High glycaemic load; rapid glucose absorption; insulin secretion spikes	Hyperinsulinemia; GnRH pulse frequency increase; LH:FSH elevation	Moran et al. (2013)
Artificial sweeteners	Diet beverages, sugar-free snacks	Gut microbiome alterations; GLP-1 secretion disruption	Glucose intolerance; altered insulin dynamics; dysbiosis	Rocha et al. (2019)
Sodium / excess salt	Processed meats, canned foods, instant soups	Aldosterone activation; sympathetic nervous system stimulation	Blood pressure elevation; adrenal androgen stimulation; cortisol dysregulation	Azziz et al. (2016)
Saturated fatty acids	Palm oil-based UPF, processed dairy, meat products	TLR4 activation; ceramide production; mitochondrial dysfunction	Peripheral insulin resistance; granulosa cell apoptosis; oocyte quality impairment	Murri et al. (2013)

Discussion:

The aggregate of evidence that is combined in this review gives a good argument to the consumption of ultra-processed foods as a major, adjustable dietary cause of hormonal and insulin signalling malfunction in PCOS. This association is stronger than can be determined by any single study design because, in the convergence of the conclusion

of the diverse study designs, such as randomized controlled trials, prospective cohort studies, and mechanistic laboratory studies, with populations of geographically and ethnically varied populations. The literature provides three mechanistic themes, which are direct hormonal including (i) androgen excess driven by AGE-RAGE and (ii) hyperinsulinemia-driven steroidogenesis and; (iii) systemic insulin-signalling destruction involving (i) IRS-1 serine phosphorylation and (ii) PI3K-Akt pathway inhibition by UPF-generated lipid molecules and oxidative stressors; and (iii) indirect mediating mechanisms, including (i) gut microbiota dysbiosis, (ii) metabolic endotoxaemia, and (iii) HPO axis dysregulation.

Specifically, of interest is the emerging data about selective insulin resistance in PCOS a condition where metabolic PI3K-Akt arm of insulin signalling is compromised and the mitogenic MAPK/ERK pathway is intact or hyperactivated. The selective resistance pattern seems to be enhanced by the consumption of ultra-processed foods because fructose-derived diacylglycerols and the production of ceramides through the action of trans fatty acids selectively target IRS-1/PI3K-Akt but not MAPK signalling. This specificity could be the reason that dietary interventions aimed at UPF lowering show abundant improvements in insulin sensitivity without consistently reducing the androgen excess, and therefore, it could be possible to suggest that a combination of dietary and endocrine interventions is needed to manage PCOS comprehensively.

The results of the present review are widely agreeable to past systematic reviews exploring dietary habits and PCOS consequences. The most relevant dietary factors in the management of PCOS were dietary glycaemic index and dietary fat quality identified by Moran et al. (2013), which is in line with the focus of the present review that high-glycaemic UPF and trans fatty acid content are major pathogenic dietary exposures in PCOS management. But, the current review goes a step further and conceptualizes the NOVA system of food processing as a clinically useful perspective along which PCOS dietary risk may be evaluated, beyond the classical nutrient-focused strategies, which takes into account that industrial processing as such, independent of individual nutrient content, results in the possibility of endocrine-disrupting compounds to be produced such as AGEs, acrylamide and Maillard products which are not present in minimally processed whole foods.

Although the gut microbiome axis was new in the previous Moran et al. (2013) review, there has been significantly more mechanistic support over the intervening decade. Specific microbial taxa depletion under the influence of low-fibre, high-emulsifier UPF diets and their association with LPS-induced metabolic endotoxaemia and HPO axis disruption, as described by Insenser et al. (2018) and thereafter, are a mechanistically consistent link between dietary behaviour and the neuroendocrine dysregulation being PCOS. The findings indicate that microbiome restoration should involve prebiotic and probiotic supplementation and reduction of UPF as complementary dietary interventions in PCOS in the future.

The clinical implications of the synthesized evidence in this case are significant and considerable. Diet-intervention with UPF-reduction is an evidence-based and low-cost intervention of PCOS management, which involves considerable benefits without adverse effects. There are already guidelines on clinical practice of PCOS, most recently reviewed by Teede et al. (2018), which mention lifestyle intervention as the basis of management, but currently this practice does not specifically cover the consumption of UPF. The current review is capable of providing scientific grounds that would have explicit instruction of UPF reduction as quantified by the NOVA classification in the enhancement of evidence-based practices in PCOS management.

Considering the documented prevalence of UPF consumption among young adult women exactly the demographic most susceptible to PCOS, a dietary intervention targeted at them creates a disproportionately large benefit. The traditional calorie cutting recommendations on nutritional counselling of PCOS patients should be broadened to recall the food processing education and practical guidelines on the

identification and substitution of UPFs with food processing foods as well as inclusion of dietary quality determinations as part of regular PCOS monitoring. Since PCOS-related insulin resistance is associated with a significantly high risk of developing type 2 diabetes mellitus, cardiovascular, and endometrial carcinoma in the long-run, dietary interventions that can ameliorate insulin signalling through UPF reduction have preventive implications much further than reproductive health outcomes.

The current review has a number of weaknesses that can be candidly admitted. First, the diversity of measurement procedures of dietary assessment across the studies that can be included (use of validated food frequency questionnaires through dietary recall interviews and NOVA-classified dietary records) brings about variance in measuring UPF exposures that restricts the ability to cross-study data. Second, the fact that the use of the NOVA as a classification in clinical nutrition research is relatively new implies that not all the included studies resonantly measured UPF intake in terms of the NOVA Group 4 criteria; others evaluated some broader patterns in the West or individual types of foods that share a substantial overlap but are not exactly identical. Third, the cross-sectional nature of some of the key studies makes it impossible to infer causality concerning the directionality of the associations that were found between UPF consumption and hormonal consequences. Fourth, PCOS phenotypic heterogeneity characterized by at least four different phenotypes by Rotterdam criteria with heterogenous androgen and metabolite patterns was not consistently factored in across studies which could overwhelm differentiation between UPF and hormonal parameters between PCOS groups.

Evidence-Based Dietary Recommendations for PCOS Management

Table 4. Evidence-Based Dietary Recommendations for UPF Reduction in PCOS

Category	Foods to REDUCE/AVOID	Foods to PREFER	Evidence Level
Carbohydrates	White bread, instant noodles, sugary cereals, pastries	Whole grains, legumes, oats, quinoa, barley	Strong multiple RCTs
Beverages	Sugary drinks, diet sodas, energy drinks, flavoured milks	Water, herbal teas, plain coffee, fresh juices	Moderate cohort studies
Fats	Margarine, fried fast food, processed snacks (trans fats)	Olive oil, nuts, avocado, oily fish (omega-3)	Strong mechanistic + clinical
Protein	Processed meats, sausages, deli meats, nuggets	Legumes, eggs, poultry, fish, tofu, tempeh	Moderate dietary studies
Dairy	Flavoured yogurts, processed cheese, ice cream	Plain yogurt (probiotic), milk, kefir	Emerging microbiome studies
Snacks	Packaged chips, confectionery, cookies, crackers	Fruits, raw nuts, seeds, vegetable sticks	Moderate observational
Cooking Method	Deep frying, extrusion (factory), microwave UPF	Steaming, boiling, baking at low temperatures	Emerging AGE studies

Conclusion:

This systematic narrative review has consolidated converging evidence from 98 papers to describe the multifaceted effect of ultra-processed food intake on insulin signalling dysregulation and hormonal imbalance in polycystic ovary syndrome. All of these demonstrate that UPF consumptions are not just correlates of inadequately metabolic health in PCOS but other active mechanistic causes of the central pathological manifestations of the syndrome: androgen excess, gonadotropin imbalance, insulin signalling defects, and HPO axis dysregulation.

The mechanistic fact is especially strong. The convergence of ultra-processed food components such as high-fructose corn syrup, trans fatty acids, advanced glycation end-products and emulsifiers converge on IRS-1/PI3K-Akt signalling by independent yet complementary pathways and at the same time initiate androgen overproduction via activation of ovarian CYP17A1 through AGE-RAGE and hyperinsulinemia-mediated steroidogenesis. The low-fibre, high-emulsifier UPF profile, causing gut microbiota dysbiosis, turns out to be an increasingly established mediating mechanism between dietary behaviour and systemic inflammation and dysfunction of the HPO axis.

These findings clinical implications include a strong scientific basis of including explicit UPF reduction recommendations operationalised using the NOVA food classification system into evidence-based PCOS management practices. Since dietary change is the most readily available, least expensive, and widely applicable therapeutic intervention in PCOS, and UPF intake is a common and adjustable dietary exposure, its proactive decrease would be a primary approach that can positively change reproductive and cardiometabolic outcomes in the respective women.

Future research needs are: prospective longitudinal studies that also measure UPF intake across tools that measure it as input and then trace the outcome of hormonal and insulin signalling variables over truly significant durations; mechanistic studies that either describe the precise gut microbiome signatures that mediate between UPF and PCOS and dietary intervention studies that assess the therapeutic efficacy of appropriately structured UPF reduction programs versus conventional calorie-restrictive dietary advice for women with different PCOS phenotypes. This kind of research will be critical in terms of translating the mechanistic understanding in this review into evidence-based, individualized dietary solutions to the millions of women with PCOS all over the globe.

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