Characteristic and Defining Markers of PCOS

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Abstract: Polycystic Ovary Syndrome (PCOS) is one of the most frequently occurring endocrine disorders in women. The syndrome is diagnosed through a heterogeneous combination of androgen excess, anovulation, and ovarian dysfunction and is characterized by a host of resulting markers. This paper will paint the overall diagnostic picture of the condition and review a number of these markers to build an essential picture of PCOS. It will concentrate first on its principal metabolic markers then describe its physical, neurological and psychobehavioral markers. Each section will then abstract an essential picture from the data it presents. Finally, the review will conclude with a consolidation of the conclusions drawn in each section. The central theme that emerges is the inter-potentiated nature of PCOS markers.

Keywords: Polycystic Ovary Syndrome (PCOS), Hyperandrogenism, Central Obesity, Neuroticism, Autonomic Dysfunction.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women[1](Goodman et al. 2015) and, worldwide, affects between 7% and 12% of women of reproductive age[2] (Skiba et al. 2018). Conditional subsets of the following are used to diagnose the disorder: hyperandrogenism, oligo-anovulation, and polycystic ovaries. Which are required and in what combination depends on the diagnostic standard used, the NIH 1990 (Zawadski & Dunaif 1992), Rotterdam 2003 consensus (Fauser et al. 2004), or AE & PCOS guidelines (Azziz et al. 2009) (Table 1). Of the three, the Rotterdam consensus is the most accepted by the National Institute of Health (NIH) and scientific community (Teede et al. 2018), and the most widely used (Escobar-Morreale 2018).

Table 1: PCOS Diagnostic Criteria.

	Diagnostic Standard*		
Conditions	NIH (1990)	Rotterdam (2003) - if any 2 out of 3 criteria are met	AE & PCOS – HA + 1 of the 2 remaining criteria
Hyperandrogenism (HA)	+	+/-	+
Oligo-anovulation	+	+/-	+/-
Polycystic ovaries	Ø	+/-	+/-

* Legend: + indicates a necessary criterion; +/- indicates a criterion that may need to be present; Ø indicates an unnecessary criterion

The Rotterdam consensus divides PCOS into four phenotypes: 1) **A**-Classic PCOS (defined by oligo-anovulation, hyperandrogenism, and polycystic ovaries); 2) **B**-Classic non-polycystic ovary PCOS (defined by oligo-anovulation, hyperandrogenism, and normal ovaries); 3) **C**-Non-classic ovulatory PCOS (defined by regular menstrual cycles, hyperandrogenism, and polycystic ovaries); and 4) **D**-Classic mild or normoandrogenic PCOS (defined by chronic anovulation, normal androgens, and polycystic ovaries) (Fauser et al. 2004) (Table 2). Diagnostic phenotypes, though important, do not define the larger picture of PCOS. This paper will define metabolic, physical, neurological, and psychobehavioral markers of PCOS.

Characteristic Metabolic Markers

Hyperandrogenism

As Goodarzi et al. (2011) put it, hyperandrogenism is the *sine qua non* of the condition. About 80-85% of women with clinical hyperandrogenism have PCOS (Azziz et al. 2006, 2009). Hyperandrogenism expresses itself in elevated levels of metabolic androgen intermediates which include significantly higher levels of dehydroepiandrosterone (DHEA) (O'Reilly et al. 2014), dehydroepiandrosterone sulfate (DHEA-S) (Kumar et al. 2005; O'Reilly et al. 2014) and, more explicitly, higher levels of total testosterone (Barry et al. 2011b; Sverrisdo´ttir et al. 2008), free testosterone (Özkeçeci et al. 2016; Sverrisdo´ttir et al. 2008), and a higher free androgen index (FAI) (Carmina et al. 2009: O'Reilly et al. 2014). Furthermore, androgens (and their intermediates) are more bioavailable in PCOS women. Levels of Sex Hormone Binding Hemoglobin (SHBG), a glycoprotein that binds to these androgens and makes them unavailable, is significantly reduced (O'Reilly et al. 2014; Sverrisdo´ttir et al. 2008). The biochemical markers do not always express individually or in combination in every study (see Dag et al. (2015) and Tekin et al. (2008) for examples) but, compared to controls, elevated levels of such are found more frequently in women with PCOS.

Table 2: Phenotypes of PCOS - Rotterdam (2003) Criteria.

	PCOS Phenotypes*			
Conditions	A	B	C	D
Hyperandrogenism	+	+	+	Ø
Oligo-anovulation	+	+	Ø	+
Polycystic ovaries	+	Ø	+	+

* Legend: + indicates a required criterion; Ø indicates an unnecessary criterion

Insulin resistance (IR)

IR is the inability of insulin to regulate proper sugar levels in the body. The condition is present in over 50-70% (Yau et al. 2017) of cases. It is characterized by higher fasting blood glucose levels (FBG) (hyperglycemia) (Bansal 2015; Kuppusamy et al. 2015; O'Reilly et al. 2014; Saranya et al. 2014) and higher fasting insulin levels (hyperinsulinemia) (Dag et al. 2015; Kumar et al. 2005; Sverrisdo´ttir et al. 2008). Insulin resistance is a key cause of hyperandrogenism as it stimulates the secretion of ovarian androgen and inhibits SHBG production (Goodarzi et al. 2011). If IR persists, it can trigger a prediabetic state (Bansal 2015) and an upregulation in levels of total cholesterol (TC) and total triglycerides (TG), a pattern indeed seen in PCOS.

Gui & Wang (2017)'s meta-analysis found that TC and TG levels were significantly higher in women with PCOS, respectively (Hedges' g = 0.29, p = 0.01; 95% CI: 0.06 to 0.53; n=148 (PCOS), n=141 (controls)) and (Hedges' g = 0.51, p = 0.00001; 95% CI: 0.25 to 0.76; n=148 (PCOS), n=141 (controls)).

As is the case with hyperandrogenism, these markers do not always express consistently (see Tekin et al. (2008) and Özkeçeci et al. (2016) for examples), but they individually, in concert or combination, express significantly more in women with PCOS than in controls.

Conclusions

Hyperandrogenism and IR play identifying and as will be discussed, mediating roles in the overall physical and physiological nature of PCOS. Further, insulin resistance not only potentiates hyperandrogenism but the two, in a perpetual cycle, are hypothesized to reciprocally intensify and aggravate each other via intervening mediators[3] (Escobar-Morreale 2018; Yau et al. 2017), potentially upregulating the morbidity of the condition.

Characteristic Physical Markers

Body mass index (BMI)

Mean BMI is significantly higher in PCOS women compared to controls (e.g., 29.3 + 7.5 versus 25.6 + 5.8 kg/m2, $p < 0.001$, respectively) (Moran et al. 2013). The study yielding this result was part of the Australian Longitudinal Study on Women's Health (ALSWH). It compared the BMIs of 409 PCOS women and 7057 controls and is consistent with the findings of Gui & Wang's 2017 meta-analysis (Hedges' $g = 0.42$, $p = 0.004$; 95% CI: 0.14 to 0.701; n=243 (PCOS), n=211 (controls)). The BMIs of women with PCOS were nearly a half a standard deviation higher than that of controls (+ 0.49 SD).

Waist-to-hip ratio (WHR)

WHR's are significantly higher in PCOS women than controls (e.g., Franik et al. 2017; Glintborg et al. 2016; Hashim et al. 2015[4]; Saranya et al. 2014; Sverrisdo´ttir et al. 2008). WHR measurements in these studies ranged from 0.80 to 0.89, while controls invariably measured at ≤ 0.79. Gui & Wang's 2017 meta-analysis (Hedges' $g = 1.06$, $P = 0.0001$; 95% CI: 0.53 to 1.58; n=134 (PCOS), n=109 (controls)) reveals a significant effect size of + 1 SD with respect to higher WHR's in women with PCOS.

Lean body mass

Compared to age and/or weight-matched controls, significantly higher levels of lean body mass[5] have been reported in women with classic PCOS[6] compared to age and/or weight-matched controls (Carmina et al. 2009; Kogure et al.2015), but this has not been consistently reported (Katulski et al. 2014; Kirchengast et al. 2001; Mario et al. 2012).

Fat distribution pattern

Women with PCOS, be they of the lean phenotype or the classic phenotype, have a significantly more android fat configuration and more central abdomen adiposity than controls (e.g., Carmina et al. 2007, 2009; Ezeh et al. 2014; Glintborg et al. 2016; Godoy-Matos et al. 2009).

Bone mineral density (BMD)

Physically localized differences in BMD have been reported in PCOS women compared to age, weight, and ethnicity-matched controls (Good et al. 1999). Women with PCOS evidence significantly higher BMD in the upper skeleton. Di Carlo et al. (1992) demonstrated the same difference in amenorrheic women with PCOS compared to matched controls. Carmina et al. (2009), however, did not replicate the finding.

Strength differences

Women with PCOS show increased strength compared to controls, a difference that manifests independently of the level of lean body mass. PCOS women lift significantly higher 1 rep maximums in the bench press, leg extension, ($p<.01$) and isometric handgrip strength exercises ($p <0.03$) (Kogure et al. 2012, 2015).

Characteristic correlations

In Carmina et al. (2009), lean body mass in women with PCOS positively correlated with total fat, trunk fat, and % trunk fat ($r = 0.68, 0.67, 0.48$, respectively, all at $p < 0.01$); a similar association expressed with insulin levels and the free androgen index (FAI[7]) ($r = 0.48, 0.49$, respectively). The PCOS women in Carmina et al.'s study had higher insulin levels compared to controls (14 μU/ml +/- 5.2 and 9.6 μU/ml +/- 3, respectively; $p < 0.01$) and higher FAI levels (2.5 +/- 0.8 and 8.72 +/- 5.1, respectively; $p < 0.01$).

This pattern might be due to the obesogenic consequences of insulin resistance (IR) and its promotion of hyperandrogenism via the downregulation of sex hormone binding globulin (SHBG) and the *insulin*-like growth factor binding protein 1 (IGFPB-1). Down-regulation of IGFPB-1 ups IGF-1 availability, which potentiates the theca cells in the ovaries to produce more androgens, and down-regulation of SHBG potentiates the general bioavailability of androgens (Yau et al. 2017). The notion is that hyperandrogenism may have promoted the anabolism of more lean body mass. Consistent with this reasoning, Kogure et al. (2015) was able to find a significant correlation between FAI and lean muscle mass in women with PCOS ($r = 0.40$, $p < 0.05$)

A study by Glintborg et al. (2008) reinforces this, at least with regard to lean body mass. When PCOS women were given an insulin-sensitizing drug called pioglitazone, a decrease in lean body mass resulted.

Body to mass index (BMI)

In women with PCOS, BMI correlates significantly and positively with total testosterone levels, larger ovarian volume (Balen et al. 1995; Conway et al. 1989) and hirsutism ($p = 0.0002$) (Balen et al. 1995). In Kiddy et al. (1990), it has also significantly correlated with lower levels of SHBG. These relationships are consistent with obesity (qua BMI) as a major driver of PCOS pathophysiology (Yau et al. 2017). Higher BMI's increase the likelihood of lipotoxicity. In turn, this drives the generation of inflammatory cytokines, which potentiates insulin resistance and triggers the compensatory hyperinsulinemia that results (Yau et al. 2017). Hyperinsulinemia itself drives hyperandrogenism and the formation of ovarian cysts which contribute towards an increased ovarian volume.

Independent of PCOS, BMI has been found to inversely correlate with two time-domain measures of heart rate variability (HRV), pNN50 ($r= -.284$, $p =0.029$) and rMSSD ($r = -.270$, $p = 0.039$) (Koenig et al. 2014). Both measures are predominantly vagally mediated and correlate with increased parasympathetic tone about the ANS (Shaffer & Ginsberg 2017). Increased BMI has also been associated with increased sympathetic tone in the kidneys and skeletal muscle (Esler et al. 2006)[8]. This association, however, has not been directly observed in PCOS (Lambert et al. 2015).

Waist-to-hip ratio (WHR)

As might be expected (given the BMI differences), the WHR's of PCOS women directly correlate with their BMI's (e.g., Hashim et al. 2015[9]; Lu and Guo 2016; Mondragón-Ceballos et al. 2015) and, similarly to their BMI's, to lower values of a time-domain HRV index, SDNN[10] in this case.

Metabolic correlates of WHR, independent of PCOS, include higher free testosterone levels (Mondragon-Ceballos et al. 2015; van Anders and Hampson 2005) and lower levels of SHBG (Santoro et al. 2005). Franik et al. (2017), using women with classic PCOS with WHR's of ≥ 0.8, found significantly higher concentrations of glucose and insulin, and significantly higher insulin resistance levels in them compared to controls.

Central abdomen adiposity

Central abdomen adiposity in women with PCOS is associated with elevated fasting insulin levels (Mean Difference (MD): 95.00; 95 CI [54.81, 135.19], $p < 0.001$) and predicts the development of Type 2 diabetes and cardiovascular disease (see Lim et al. 2013 for a meta-analysis)

Central adiposity is also associated with FAI (von Ruesten et al. 2011) and, in some studies, significantly higher levels of total testosterone (TT) (Pasquali et al. 1994; Svendsen et al. 2008), but as Lim et al.'s (2013) meta-analysis noted, the association was not consistent (e.g., Godoy-Matos et al. 2009). No other endocrine parameter reached significance in the meta-analysis.

To the author's knowledge, a potential link between central adiposity and autonomic system functioning in PCOS women has not been established or studied though there is certainly that possibility. In a study comparing high BMI[11] abdominal visceral fat men (HVFM) with BMI controls, the HVFM produced 55% higher muscle sympathetic nerve activity (MSNA) activity. Furthermore, MSNA activity correlated with abdominal subcutaneous fat (r=0.27, $p < 0.05$) (Alvarez et al. 2002).

Conclusions

The composite picture points to a physical phenotype that is more likely overweight and, in fat distribution pattern, more android in configuration (i.e., more apple-shaped) with an increased concentration of central adiposity. PCOS women may further possess increased lean body mass coupled with increased physical strength and bone mineral density. As discussed, this is consistent with an insulin-resistant hyperandrogenic physiology.

Characteristic Neurological Markers

Several studies suggest that, relative to controls, women with PCOS have "differentially tuned" autonomic nervous systems (ANS). The differential may exhibit as augmented sympathetic nerve activity, reduced parasympathetic nerve activity, or some combination of both[12] (see Gui and Wang 2017 for a partial meta-analysis). Evidence of this condition expresses principally through muscle sympathetic nerve activity (MSNA) (e.g., Lambert et al. 2015; Shorakae et al. 2018) and heart rate variability (HRV) studies (e.g., Ferezini de Sa et al. 2011; Saranya et al. 2014).

Muscle sympathetic nerve activity (MSNA)

Microneurography is a direct measure of sympathetic nerve activity (Lansdown and Rees 2012). By placing electrodes in the skeletal muscle or skin, sympathetic bursts of activity can be recorded from efferent or afferent nerve axons embedded in these tissues (Lansdown and Rees 2012). Accordingly, when the activity is measured in the skeletal muscle, the term muscle sympathetic nerve activity (MSNA) is used and, when measured through the skin, the term skin sympathetic nerve activity (SSNA) applies (Wallin & Charkoudian 2007).

PCOS studies that have used microneurography have preferentially employed MSNA and, because of its accessibility, have used the peroneal nerve as a recording point, either the nerve itself or a muscle nerve fascicle connected to it (e.g., Lambert et al. 2015; Sverrisdo´ttir et al. 2008).

To date, multiple studies have examined MSNA in women with PCOS. Relative to age and weight-matched controls, PCOS women show a higher probability and frequency of sympathetic bursts relative to age and weight-matched controls (Lambert et al. 2015; Lansdown et al. 2019; Shorakae et al. 2018; Sverrisdo´ttir et al. 2008). Two of these studies (Lambert et al. 2015; Sverrisdo´ttir et al. 2008) were part of a larger meta-analysis by Gui & Wang (2017)[13]. The pooled 'probability of sympathetic bursts' data revealed a large and significant effect size (Hedges' g = 1.29, 95% CI 0.80 to 1.79, $p < 0.00001$) as did the 'frequency of firing' data (Hedges' g = 1.06, 95% CI 0.58 to 1.53, $p < 0.0001$).

Heart rate variability (HRV)

HRV[14] tends to be constricted in women with PCOS, and studies indicate there is less variation between heartbeat intervals when compared to controls (e.g., Hashim et al. 2015; Lambert et al. 2015; Saranya et al. 2014). This pattern manifests through two time-domain indices of HRV, SDNN and pNN50[15,16]; and through three frequency-domain parameters of HRV: low-frequency power (LF)[17], high-frequency power (HF)[18], and total powers[19] (see Gui & Wang (2017). Generally speaking, more variability in HRV indicates more parasympathetic dominance, while less variability indicates more sympathetic dominance (ETF 1996).

SDNN

The HRV index, SDNN, correlates with the state of overall cardiac autonomic modulation (ETF 1996). Lower SDNN values in PCOS women (e.g., Ferezini de Sa et al. 2011; Hashim et al. 2015[20]; Saranya et al. 2014) have been interpreted as a sign of increased sympathetic activity and decreased parasympathetic modulation of cardiac function.

Not all studies evince the finding (e.g., Ji et al. 2018; Özkeçeci et al. 2016), but Gui & Wang's (2017) meta-analysis reports the finding is consistent and sizeable. In a meta-analysis of 8 studies, women with PCOS had significantly lower SDNN than controls (Hedges' g = −0.51, p = 0.03; 95% CI: -0.96 to -0.05)

pNN50

As mentioned, lower pNN50 values have also been linked to PCOS women. Unlike SDNN, however, pNN50 correlates with decreased parasympathetic nervous activity (Shaffer & Ginsberg 2017). Women with PCOS, in other words, show significantly lower values compared to controls (e.g., Di Domenico et al. 2013; Hashim et al. 2015; Saranya et al. 2014). Gui & Wang's (2017) meta-analysis reveals that the effect size is large and the finding significant (Hedges' g = −1.04, p = 0.04; 95% CI: −2.01 to −0.06)

LF or LF_{nu} power

One of the HRV frequency parameters that correlate with sympathetic nerve activity is higher LF and/or LF_{nu}[21] power (ETF 1996). Though multiple studies show significantly higher LF and/or LF_{nu} powers in PCOS women (Ji et al. 2018; Kuppusamy et al. 2015; Yildirir et al. 2006), more consolidated studies do not.

The difference was present in Gui & Wang's meta-analysis, (3 data sets: n^{PCOS}=87; $n^{controls}$=84) but the effect size was not significant (Hedges' g = 0.49, 95% CI −0.05 to 1.03, p= NS) and the difference further only manifested with LF_{nu} power, not LF power (4 data sets: n^{PCOS}=110; $n^{controls}$=104). Ollila et al.'s (2019) megastudy comparing PCOS women and controls identified that differences in LF power actually manifested in the opposite direction (n=279 (PCOS); n=1577 (controls)), p=0.044.

HF or HF_{nu} power

Observations of HF and/or HF_{nu} power have been somewhat mixed as well. Some studies show significantly lower HF or HF_{nu} power in PCOS women than controls (Ji et al. 2018[22]; Kuppusamy et al. 2015; Yildirir et al. 2006), while others do not (Ferezini de Sa et al. 2011; Lambert et al. 2015). Ollila et al.'s (2019) megastudy however seems

to point to a clear difference (n=279 (PCOS); n=1577 (controls)). The PCOS sample had a significantly lower HF power than controls, HF: ms^2=172 (25Q: 75; 75Q: 399) vs ms^2=261 (25Q: 112; 75Q: 565); p=0.002.

Lower HF and HF_{nu} power correlate with decreased cardio-vagal[23] (parasympathetic) activity (ETF 1996; Shaffer & Ginsberg 2017). This mixed picture appears in Gui & Wang's (2017) meta-analysis as well. Though, compared to controls, differences were in the expected direction and the HF and HF_{nu} findings were not significant (HF: Hedges' g = −2.14, p=NS; 95% CI: −4.54 to 0.26, n=87 (PCOS); n=84 (controls)) ($HF_{nu:}$ Hedges' g = −0.43, p=NS; 95% CI: −1.09 to 0.22, n=80 (PCOS); n=74 (controls)).

LF/HF or LF_{nu}/HF_{nu} power ratio

LF/HF or LF_{nu} /HF_{nu} ratio differences also did not reach significance in Gui & Wang's meta-analysis (Hedges' g = 0.47, p=NS; 95% CI: −0.10 to 1.03). The LF/HF ratio is considered an index of the autonomic balance between the sympathetic and parasympathetic systems (sympathovagal balance) (ETF 1996; Shaffer & Ginsberg 2017). A high LF/HF ratio (e.g., LF > HF (von Rosenberg et al. 2017)) correlates with more dominant sympathetic nervous activity and a low ratio (e.g., LF < HF), with more dominant parasympathetic nervous activity (Shaffer & Ginsberg 2017). Four studies support a sympatho-dominant presentation (Ji et al. 2018; Kuppusamy et al. 2015; Saranya et al. 2014; Yildirir et al. 2006) and two do not (Di Domenico et al. 2013; Lambert et al. 2015).

Sympathetic skin response (SSR)

SSR reflects the sympathetic activation of sweat glands by recording electrical potential changes on the skin's surface (Kucera et al. 2004). This efferent activation is part of a polysynaptic reflex arch originating from myelinated sympathetic neuron fibers from the intermediolateral nucleus, between thoracic vertebra 1 (TH1) and lumbar vertebra 2 (L2). This change in potential is typically evoked by stimulating a peripheral nerve in an extremity. The stimulation triggers the afferent part of the reflex by activating myelinated sensory fibers (Kucera et al. 2004).

Two studies to date have examined SSR in women with PCOS with inconsistent results (Dag et al. 2015; Hashim et al. 2015). Relative to controls, Hachim et al. (2015)[24] observed significantly reduced latencies and higher amplitudes of palmar SSR (p<0.001, p=0.031, respectively) in PCOS women, while Dag et al. (2015) showed significantly increased latencies and lower amplitudes of palmar SSR (p<0.001, p< 0.01, respectively).

Heart rate recovery (HRR)

HHR post-exercise is a marker of parasympathetic nerve activity (Imai et al. 1994). PCOS women have significantly lower HRR values 1 minute after exercise than controls (Tekin et al. 2008). That is, they manifest significantly smaller heart rate changes post-exercise (28 ± 8 bpm vs. 20 ± 4, p< 0.0001). Further, their systolic blood pressure (SBP) values, though similar at rest, remained more elevated during exercise 172 ± 12 vs. 156 ± 14 mmHg, p <0.0001) and more elevated 1, 2, and 3 minutes after exercise (168 ± 13 vs. 148 ± 5 mmHg, 162 ± 13 vs. 136 ± 16 mmHg, 152 ± 17 vs. 127 ± 15 mmHg, respectively, p <0.0001).

Basal heart rate (BHR)

Significant BHR differences between PCOS women and controls are not a consistent finding. Gui & Wang (2017) revealed a non-significant trend in the direction of higher BHR's in PCOS women. Five out of eight studies from the meta-analysis evidenced the positive trend (Hedges' g = 0.42, p=NS; 95% CI: −0.04 to 0.87). The resting or basal heart rate is regulated by both parasympathetic and sympathetic nerve activity (Lahiri et al. 2008).

Parameter correlations

Muscle sympathetic nerve activity (MSNA)

In PCOS women, MSNA was directly related to total testosterone (TT) (r = 0.63, p < 0.005), free testosterone (r = 0.57, p < 0.01) and total cholesterol (TC) (r = 0.55, p <0.01) (Sverrisdo´ttir et al. 2008). In their regression analysis, both TT and TC were independently predictive of PCOS status, but TC did not correlate with TT. The significant positive relationship between MSNA and TT also manifested in Shorakae et al. (2018).

SDNN

SDNN, a time domain measure of HRV, significantly negatively correlates with BMI (r = -0.32, p <0.05), fasting insulin (r = -0.31, p <0.05), total triglycerides (TG) (r = -0.48, p <0.05), and TC (r = -0.35, p <0.05) (Ferezini de Sa et al. 2011). Hashim et al. (2015) reported a similar finding with WHR (r = -0.371, p = 0.047).

LF power

LF power, a frequency domain measure of HRV, significantly negatively correlates with BMI (r = -0.29, p <0.05), TG (r = -0.41, p <0.05), and TC (r = -0.33, p <0.05) (Ferezini de Sa et al. 2011)

HF power

HF power, a frequency domain measure of HRV, significantly negatively correlates with BMI (r = -0.34, p <0.05), TG (r = -0.40, p <0.05), and TC (r = -0.29, p <0.05) (Ferezini de Sa et al. 2011)

LF/HF power ratio

LF/HF ratio directly and significantly correlates with TT (Kuppusamy et al. 2015), BMI (Kuppusamy et al. 2015; Saranya et al. 2014), WHR (Saranya et al. 2014), BHR (Kuppusamy et al. 2015; Saranya et al. 2014), fasting blood glucose (FBG) (Saranya et al. 2014), insulin resistance (IR) (Kuppusamy et al. 2015), TG (Kuppusamy et al. 2015), and TC (Kuppusamy et al. 2015).

Plasma epinephrine

Hashim et al. (2015) found significant differences in plasma epinephrine levels (pg/ml) between PCOS women and obese controls across two physical positions; lying and standing (28.74 ± 17.43 vs. 6.87 ± 2.28, p <0.001; 37.33 ± 11.05 vs. 11.07 ± 5.63, p <0.001, respectively). Plasma norepinephrine levels are known to correlate with sympathetic nerve activity (Dodt et al. 1997)**.** This finding also exhibited in a non-PCOS sample of overweight hypertensives with sleep apnea (Rubinsztajn et al. 2003).

Plasma epinephrine levels in PCOS women also significantly correlated with BMI and WHR in the lying position (r = 0.398, p =-0.032; r = 0.428, p = 0.05, respectively), but this did not manifest with obese controls. In parallel with the earlier report, this finding compared to controls was also corroborated in a non-PCOS sample of overweight hypertensives with sleep apnea (Rubinsztajn et al. 2003).

Characteristic Psychobehavioral Markers

Emotional Lability (Neuroticism)

Neuroticism (‘*N’*) is the tendency to react quickly when stimulated and to inhibit emotions slowly once activated (Eysenck & Eysenck 1985). It is a major personality trait (or domain) comprised of the six cognitive subfactors: N1 - Anxiety, N2 - Anger, N3 - Depression, N4- Self Consciousness, N5 - Impulsiveness, and N6 - Vulnerability[25] (Goldberg 1999). Women with PCOS score 40.6% higher on *‘N’* than BMI and age-matched controls (7.89 (+/- 3.37) 5.61 (+/- 3.41) F=3.95, 2-tailed and p<0.05) (Barry et al. 2011b). Hans Eysenck, a noted psychologist, has long suggested that the expression of the trait correlates with the lability of the autonomic system (Eysenck 1967). Meta-analytic evidence (71 studies) indeed supports an association between *‘N’* and decreased PNS reactivity[26] (p < 0.083) (Chida & Hammer 2008). Longer recovery times after exposure to a stressor correlate with decreased PNS reactivity. This is consistent with evidence showing that longer cardiovascular recoveries after stressors are associated with ‘*N’* (r = .104; 95% CI = .029, .178; p = .007) (Chida & Hammer 2008).

Farmer et al’s (2013) findings were consistent with this conception. They showed that high *‘N’* was independently associated with longer cardiovagal tone[27] (CVT) and cardiac sympathetic index (CSI) recovery times. High-*N* patients evidenced prolonged CVT and CSI recovery times after esophageal intubation[28] compared to controls (112.5 s vs 46.5 s, p < 0.0001 and 549 s vs 223.5 s, p < 0.0001, respectively). Di Simplicio et al.’s (2012) findings were consistent with this pattern. High-*N* subjects in their study manifested a longer HF[29] recovery after exposure to negative images compared to controls (p=0.016).

Further, Chida & Hammer’s (2008) meta-analysis (71 studies) showed that anxiety, neuroticism, and negative affect were significantly associated with longer cardiovascular recoveries (r = .104; 95% CI = .029, .178; p = .007).

Impulsiveness[30]

Impulsiveness (or impulsivity) is *“... behavior characterized by little or no forethought, reflection, or consideration of the consequences of an action, particularly one that involves taking risks*” (VandenBos 2007, 243). It is a decision-making style that favors short-term decision horizons (Hinson et al. 2003). Though impulsiveness may be viewed as maladaptive in the absence of resource deprivation and under conditions where short-term reward opportunities can be deferred in favor of longer-term ones, it can be viewed as adaptive under conditions where the opposite applies (i.e., resource deprivation is high and opportunities for rewards are scarce or unpredictable). Under those circumstances, taking advantage of any reward opportunity may be more conducive to survival.

In a study investigating ADHD symptoms in PCOS women, Hergüner et al. (2015) found that they scored higher than controls on two subscales of the Adult ADHD Self-Report Scale (ASRS): 'Hyperactivity-Impulsivity' (15.28 +/- 6.02 vs. 12.03 +/- 4.67, p = .009) and 'Behavioral Problems/Impulsivity' (4.13 +/- 4.22 vs. 2.28+/- 2.62, p= .048).

In a study examining the relationship between impulsiveness and biochemical parameters, Özdil-Demiryürek et al. (2016)[31] found significant direct correlations in PCOS women between total testosterone (TT) levels and total impulsiveness scores on the Barratt Impulsiveness Scale (BIS): (r = 0.24, p = 0.027), and the same between free androgen index levels (FAI) and each of two subscales of the BIS: the 'motor impulsiveness' subscale (r = 0.27, p = 0.015) and the 'non-planning-related impulsiveness' subscale (r = 0.26, p = 0.017). Statistically significant negative correlations were also found between sex hormone binding globulin (SHBG) values and total impulsiveness scores (r = -0.256, p = 0.019), and between SHBG values and each of the subscales of 'non-planning-related impulsiveness' (r = -0.222, p = 0.042) and 'motor impulsiveness' (r = -0.221, p = 0.044).

The biochemical parameters of insulin and DHEA-S[32] evidenced significant correlations as well. Insulin and insulin resistance (IR) levels were directly correlated with scores on the 'non-planning-related impulsiveness' subscale (r = 0.26, p = 0.018; and r = 0.26, p = 0.019, respectively) and DHEA-S directly correlated with scores on the total impulsiveness subscale (r = 0.219, p = 0.045) and the 'attentional impulsiveness' subscale (r = 0.252, p = 0.021). Özdil-Demiryürek et al. (2016) concluded that PCOS women with high DHEA-S levels experienced more attention problems and made more impulsive decisions[33].

Criminal behavior

From data gathered from Swedish population-based registers (n = 12,730 (PCOS); n = 1,273,000 (controls)), the odds of women with PCOS committing any crime are 1.16 higher than that of controls (OR: 1.16; 95% CI: 1.10 to 1.23, p = 0.05) and 1.27 higher for violent crime compared to controls (OR: 1.27; 95% CI: 1.08 to 1.49, p = 0.05) (Ohlsson-Gotby et al. 2015).

Anxiety[34]

Anxiety is "… *an emotion characterized by apprehension and somatic symptoms of tension in which an individual anticipates impending danger, catastrophe, or misfortune." It is "…considered a future-oriented, long-acting response broadly focused on a diffuse threat."* (APA Dictionary 2019, 66). Threat is defined as the presence (or potential presence) of predators, resource scarcity (e.g., famine), social rejection, social stigma, illness, open spaces, strangers, and the unspoken negative intentions of others (Nettle 2007).

Anxiety in evolutionary terms relates to the detection and identification of threat signals and to the management of the associated error. Anxiety functions much like a smoke alarm (Nesse 2005). Under the analogy, missing threats and dangers (i.e., an actual fire) have higher fitness costs than identifying threats and dangers that are in fact not real (i.e., false alarms). Were the anxiety system to err, it would be biased, because of the error asymmetry, towards the less expensive error (false alarms) and biased against false negatives (not alarming during an actual fire). Sustaining multiple false alarms is less expensive than missing a fire (a false negative). Essentially, the anxiety system is designed not to miss true positives and be biased, when it errs, against false negatives. By analogy, heightened sensitivity of the alarm is equivalent to heightened anxiety and a bias towards identifying more non-threats as actual threats.

In their meta-analysis of nine studies looking at anxiety symptoms in women with PCOS, Cooney et al. (2017) reported that they were almost 6 times more likely than controls to experience anxiety symptoms (Odds ratio (OR): 5.62; 95% CI: 3.22 to 9.80, p < 0.05) and 6.55 times more likely to experience moderate to severe anxiety symptoms (OR: 6.55; 95% CI: 2.87, 14.93, p < 0.05; five studies). The median prevalence of any anxiety symptom was 41.9% (Interquartile range (IQR): 13.6, 52.0%) in the PCOS group and 8.5% (IQR: 3.3, 12.0%) in the control group.

Anger[35]

Anger is defined as "…*an emotion characterized by tension and hostility arising from frustration, real or imagined injury by another, or perceived injustice*…" (APA Dictionary 2019, 55). It may motivate behavior designed "*... to remove the object of the anger (e.g., determined action) or express the emotion itself (e.g., swearing)*" (APA Dictionary 2019, 55).

Relative to controls, women with PCOS exhibit more anger (2.82 (+/-1.36) vs. 2.02 (+/-1.36) 2.69, p <.05- 2 tailed) and a greater tendency to suppress it (1.41 (+/- 0.96) vs. 0.84 (+/- 0.92) 4.71, p <.05- 2 tailed) (Barry et al.

2011b). Further, their trait anger scores directly correlated with DHEA-S, insulin, insulin resistance (IR), total testosterone (TT), and FAI (respectively, r= 0.272, p = 0.012; r=0.221, p = 0.044; r=0.226, p = 0.039; r=0.408, p < 0.001, and r=0.507, p < 0.001) (Özdil-Demiryürek et al. 2016). Özdil-Demiryürek et al. (2016) also found a statistically significant negative correlation between trait anger scores and SHBG (r= - 0.293, p = 0.007) and anger control scores and SHBG (r=0.230, p = 0.035).

Conclusions

These data suggest that the PCOS women, because of their generally higher '*N'* and resulting higher false positive bias, may be more reactive to potential threats and dangers and, given the general adaptation syndrome (GAS) (Selye 1950), may experience the alarm stage more frequently than individuals with lower '*N'*. This may equate to sustaining more sympathetic "bursts of activity."

Because of the decreased parasympathetic reactivity, PCOS women may take longer to return to homeostasis or alternatively, because of the longer recovery, may remain in the resistance stage longer (i.e., remain vigilant longer, and thus potentially be more likely to reach the exhaustion stage).

In a study that examined stress responses in PCOS patients to a public speaking task, PCOS women expressed enhanced ACTH and cortisol stress responses compared to controls (ACTH: $F = 3.6$, $p < 0.05$; for serum cortisol: $F = 2.7$, $p < 0.05$) (Benson et al. 2009). The study also found that they demonstrated a significantly enhanced stress-induced heart-rate response ($F = 3.6$, $p < 0.05$) with significantly increased heart rates both pre-task and at two intervals post-task ($F = 4.9$, $p < 0.05$; group effect). These effects are consistent with a higher reactivity to stress and a longer recovery period post-stressor.

Looking specifically at the '*N'* finding, one would expect to find higher rates of mood disorders in PCOS. That is, in fact, the case. There is a significantly increased prevalence of major depressive (or unipolar) disorder (MDD)[36] (Cooney et al. 2017; Hung et al. 2014), bipolar disorder (Cesta et al. 2016), anxiety, and personality disorders among PCOS women (Cesta et al. 2016; Scaruffi et al. 2014).

The impulsiveness[37] data suggest that PCOS women may exhibit lower behavioral thresholds before acting, be it to take advantage of a reward or avoid punishment, and because of that may reflect an "activation" bias. This lends itself towards earlier rather than later action and thus may contribute towards more of a short-term rather than long-term decision-making style. This style may be better suited towards surviving in a higher deprivation state where opportunities for rewards are fewer and predicting them less reliable.

This tendency may have a basis in testosterone metabolism. As reported earlier, significant direct correlations have been found between impulsiveness scales and both TT and the FAI, and a negative correlation between those scales and SHBG levels (Özdil-Demiryürek et al. 2016). The same study reported the same with respect to anger and the same forms of testosterone including DHEA-S.

Final Conclusions

This paper attempted to define the metabolic, physical, neurological, and psychobehavioral markers of PCOS. The compiled picture highlights as follows:

1. Hyperandrogenism is the most common and defining condition of PCOS.
2. Metabolic dysfunction involving insulin and glucose metabolism is present in most PCOS cases.
3. Women with PCOS possess higher concentrations of central adiposity, which may drive in a vicious cycle, an inflammatory process whereby hyperandrogenism, insulin resistance, and central adiposity all come to potentiate each other.
4. They may also have a sturdier constitution with a higher level of physical strength, an increased level of bone density, and more lean body mass.
5. Women with PCOS may have differentially calibrated autonomic nervous systems, ones with a tendency towards augmented sympathetic nerve activity, reduced parasympathetic nerve activity, or a combination of both.
6. PCOS women are likely more neurotic than controls (e.g., more anxious and impulsive with a bias towards assuming the presence of threats and dangers.

Notes

[1] Though PCOS is more commonly studied in reproductive age women, it is also observable in adolescents (Rothenberg et al. 2018; Diamanti-Kandarakis 2010) and may express as soon as prenatally (Barsky et al. 2021; Siemienowicz 2018; Abbott et al. 2005).

[2] Its prevalence depends on the diagnostic criteria used and the geography of the population being studied (Bozdag et al. 2016). The Rotterdam consensus has the most inclusive criteria and accounts significantly for the upper range of the estimate (Dumesic et al.; Skiba et al. 2018)
[3] These mediators are discussed later in the paper in the BMI section.
[4] This only reflected in Hachim et al's 2015 sample of overweight PCOS women and controls.
[5] Lean body mass was calculated by dividing total lean mass by height in centimeters (Carmina et al. 2009)
[6] The classic PCOS phenotype includes all the following criteria: chronic anovulation, hyperandrogenism, and polycystic ovaries (El Hayek et al. 2016)
[7] FAI: total testosterone (nmol/l)/SHBG (nmol/l) x 100) (Carmina et al. 2009)
[8] PCOS connections to the autonomic nervous system will be explored later in the paper.
[9] This only was evident in Hachim et al's 2015 overweight sample of PCOS women and controls.
[10] SDNN is defined as the standard deviation of the mean interval between heartbeats (ETF 1996). More variable SDNN correlates with a more dominant parasympathetic presence about the ANS (ETF 1996)
[11] BMI's of ≥ 35
[12] Higher PNS activity may be associated with a lower, higher, or no SNS activity at all and vice-versa. The relative activity of the two branches is not a zero-sum relationship, but a dynamic one (Shaffer & Ginsberg 2017)
[13] Gui and Wang (2017) examined cardiovascular autonomic dysfunction in women with PCOS.
[14] HRV is the variation of the time intervals between consecutive heartbeats in a given amount of time, usually about 15 minutes or 24 hrs. (Shaffer & Ginsberg 2017).
[15] The NN term refers to the interval of time between heartbeats (ETF 1996).
[16] pNN50 refers to the percentage derived by dividing the number of interval differences of successive heartbeat intervals greater than fifty *ms* by the total number of heartbeat intervals (ETF 1996).
[17] Low frequency power is a low frequency oscillatory component of heart rate (Reyes Del Paso et al. 2013)
[18] High frequency power is a high frequency oscillatory component of heart rate (Reyes Del Paso et al. 2013)
[19] 'Total powers' is considered equivalent to SDNN in diagnostic value and as such it will not be covered (ETF 1996)
[20] This was seen observed in Hachim et al's 2015 overweight sample of PCOS women and controls.
[21] LF_{nu} is LF in normalized units (ETF 1996).
[22] The finding only held for HF_{nu} not HF.
[23] The vagus nerve is a principal component of the parasympathetic nervous system (Breit et al. 2018)
[24] This was only observed in Hachim et al's 2015 overweight sample of PCOS women and controls.
[25] For the purposes of overall length and relatedness to the other sections, only the cognitive facets of impulsiveness, anger, and anxiety (and their related behaviors) will be covered here.
[26] Parasympathetic nerves activate more rapidly (<1 s) than sympathetic nerves (>5 s) (Shaffer & Ginsberg 2017)
[27] Because HR is a mixed measure of ANS tone, Farmer et al. (2013) used CSI and CVT as surrogate markers of ANS recovery.
[28] Most people find esophageal intubation particularly stressful while conscious. For that reason, it is considered an acute autonomic nervous system (ANS) stressor (Farmer et al. 2013)
[29] Higher values reflect increased parasympathetic (vagal) activity (ETF 1996)
[30] Impulsiveness is a sub-facet of Neuroticism (Costa & McCrae 1995).
[31] To the author's knowledge, this is the only study that has examined the relationship between androgens and impulsiveness in women with PCOS.
[32] Dehydroepiandrosterone sulfate.
[33] Impulsivity more generally is related to a greater probability of being arrested for criminal offenses. See Ellis et al. (2019) for a review.
[34] Anxiety is also a sub-facet of Neuroticism (Costa & McCrae 1995).
[35] Anger is also a sub-facet of Neuroticism (Costa & McCrae 1995).
[36] In the case of unipolar disorder, obesity further may function as an exacerbator (Veltman-Verhulst et al. 2012; Barry et al. 2011a)
[37] Two individuals may measure as equally "neurotic" in terms of the major factor *N* but vary in their distribution across the six sub-factors that make it up (Costa & McCrae 1995).

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