

Metabolic Consequences Of Obesity On The Hypercoagulable State Of Polycystic Ovary Syndrome: A Risk For Severe SARS-Cov-2 Infection?

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Abstract

Introduction: Polycystic ovary syndrome (PCOS) women have a hypercoagulable state and are also at high risk for severe COVID-19 leading to thromboembolic complications and increased mortality; however, whether this is intrinsically due to PCOS or, alternatively, a consequence of its metabolic complications is unclear.

Methods: We determined plasma coagulation pathway protein levels in PCOS (n=146) and control (n=97) women recruited to a PCOS biobank. Circulating levels of a panel of 18 clotting pathway proteins were determined by Slow Off-rate Modified Aptamer (SOMA)-scan plasma protein measurement.

Results: Cohorts were age matched, though PCOS had elevated body mass index (BMI)($p<0.001$), insulin ($p<0.001$) and C-reactive protein (CRP)($p<0.0001$). Eight pro-coagulation proteins were elevated in PCOS: plasminogen activator inhibitor-1 (PAI-1)($p<0.0001$), fibrinogen ($p<0.01$), fibrinogen gamma chain ($p<0.0001$), fibronectin ($p<0.01$), von Willebrand factor ($p<0.05$), D-dimer ($p<0.0001$), P-selectin ($p<0.05$), and plasma kallikrein ($p<0.001$). However, two anticoagulant proteins, vitamin K-dependent protein-S ($p<0.0001$) and heparin cofactor-II ($p<0.001$) were elevated and prothrombin was decreased ($p<0.05$). CRP, as a marker of inflammation, and insulin resistance (HOMA-IR) correlated with 11 and 6 of the clotting proteins, respectively ($p<0.05$). When matched for BMI<25 (16 PCOS, 53 controls) HOMA-IR remained elevated ($p<0.05$) and heparin cofactor-II was increased ($p<0.05$). In a multivariate analysis accounting for inflammation, insulin resistance and BMI, there was no correlation of PCOS with any of the coagulation proteins.

Conclusion: The hypercoagulable State in PCOS can be fully accounted for by BMI, inflammation and insulin resistance suggesting that only obese PCOS women would be predisposed to an enhanced risk for severe COVID-19-related disease.

Introduction

PCOS has been recognized as a reproductive-metabolic disorder given the excess prevalence of type 2 diabetes, hypertension, and cardiovascular diseases in this population at a later stage in life (1). Polycystic ovary syndrome (PCOS) patients have increased platelet aggregation and decreased plasma fibrinolytic activity, resulting in a prothrombotic propensity (2, 3). Elevated coagulation markers have been reported in PCOS in comparison to controls (4) and the coagulation parameters including prothrombin time, thrombin time and fibrin degradation products may be predictive of PCOS (5). It has been reported that coagulation proteins such as thrombin-activatable fibrinolysis inhibitor, PAI-1, D-dimer, Antithrombin III and thrombomodulin are significantly increased in women with PCOS compared with age- and BMI-matched controls (4). This suggests that PCOS, independent of its metabolic features, may be a risk factor for a hypercoagulable state, and thus PCOS women may be at high risk for severe COVID-19 infection (6, 7).

COVID-19 patients have a hypercoagulable state resulting in thromboembolic complications and increased mortality. Whilst the pathogenesis is not fully understood, evidence suggests a combination of endothelial injury, blood stasis and changes in circulating prothrombotic factors such as elevated D-dimer, factor VIII, fibrinogen and fibrin degeneration products and reduced antithrombin levels (8).

This study was undertaken to determine the parameters contributing to the hypercoagulable state reported for PCOS and the potential risk of developing severe COVID19 disease.

Materials And Methods

We determined plasma coagulation pathway protein levels in PCOS (n = 146) and control (n = 97) women recruited to a PCOS biobank (ISRCTN70196169). The diagnosis of PCOS was based on at least two out of three of the diagnostic criteria of the Rotterdam consensus as detailed previously (9); namely clinical and biochemical evidence of hyperandrogenism (Ferriman-Gallwey score >8; free androgen index >4, total testosterone >1.5 nmol/L), oligomenorrhea or amenorrhoea and polycystic ovaries on transvaginal ultrasound. Nonclassical 21-hydroxylase deficiency, hyperprolactinemia, Cushing's disease and androgen secreting tumors were excluded by appropriate tests. The baseline study measurements have been described in detail previously (10) and the demographic data for the PCOS and control women is shown in Table 1. All the control women had regular periods, no clinical or biochemical hyperandrogenism, no polycystic ovaries on ultrasound, no significant background medical history and none of them were on any medications including oral contraceptive pills or over the counter medications.

Circulating levels of clotting pathway proteins were determined by Slow Off-rate Modified Aptamer (SOMA)-scan plasma protein measurement, the details of which have been previously reported (11). Normalization of raw intensities, hybridization, median signal and calibration signal were performed based on the standard samples included on each plate, as previously described (12).

We used version 3.1 of the SomaScan Assay, specifically targeting those proteins involved in the coagulation pathways in the SomaScan panel of 18 proteins: antithrombin III, heparin cofactor 2, fibrinogen gamma chain, D-Dimer, P-selectin, fibronectin, fibronectin fragment 3, fibronectin fragment 4, vitamin K dependent protein S, alpha 2 antiplasmin, fibrinogen, von Willebrand factor, plasma kallikrein, prothrombin, coagulation factor Xa, tissue factor, coagulation factor XI and angiostatin (Table 2).

Statistics

Measured protein data were log transformed to ascertain normality. Proteins were regressed on the continuous variables CRP, HOMA-IR and BMI in separate models to assess the extent of association with each trait. A multivariate linear model incorporating all three traits and PCOS status was performed to evaluate the relationship between the measured proteins and PCOS whilst correcting for the traits. All analyses were performed using R version 4. P values were corrected for multiple testing using the false discovery rate (FDR).

Results

Cohorts were age matched, though PCOS had elevated BMI ($p < 0.001$), fasting glucose ($p < 0.05$), insulin ($p < 0.001$), C-reactive protein ($p < 0.0001$) and platelet number ($p < 0.01$).

Pro-coagulation proteins elevated in PCOS are shown in Figure 2 and include plasminogen activator inhibitor-1 (PAI-1) (2259 ± 137 vs 1457 ± 107 RFU, PCOS vs control, $p < 0.0001$), fibrinogen (177423 ± 2108 vs 169230 ± 2425 RFU, PCOS vs control, $p < 0.01$), fibrinogen gamma chain (63118 ± 946 vs 57328 ± 830 RFU, $p < 0.0001$), fibronectin (24594 ± 2627 vs 16041 ± 698 RFU, $p < 0.01$), von Willebrand factor (19849 ± 3038 vs 13159 ± 595 RFU, $p < 0.05$), D-dimer (13860 ± 185 vs 12708 ± 172 RFU, $p < 0.0001$), P-selectin (13843 ± 317 vs 12660 ± 412 RFU, $p < 0.05$), and plasma kallikrein (24868 ± 376 vs 22981 ± 447 RFU, $p < 0.001$). Prothrombin levels were decreased in PCOS (161458 ± 1275 vs 165233 ± 1958 RFU, $p < 0.05$) and the anticoagulant vitamin K-dependent protein S (4403 ± 69 vs 3989 ± 59 RFU, $p < 0.0001$) and heparin cofactor II (HCII) (4156 ± 64 vs 3821 ± 63 RFU, $p < 0.001$) were increased (Figure 1). Significant correlations of coagulation proteins with body mass index are shown in Table 2 and include antithrombin III ($p < 0.0001$), fibrinogen gamma chain ($p < 0.0001$), vitamin K dependent protein S ($p < 0.001$), D-dimer ($p < 0.001$), fibronectin ($p < 0.001$), prothrombin ($p < 0.01$), heparin cofactor 2 ($p < 0.01$), fibrinogen ($p < 0.05$), angiostatin ($p < 0.05$), fibrinogen fragment 3 ($p < 0.05$) and P-selectin ($p < 0.05$). Significant correlations of coagulation proteins with CRP, as a marker of inflammation, are shown in Table 2, that included antithrombin III ($p < 0.0001$), heparin cofactor 2 ($p < 0.0001$), fibrinogen gamma chain ($p < 0.0001$), D-dimer ($p < 0.0001$), P-selectin ($p < 0.001$), fibronectin ($p < 0.001$), and its fragments 3 and 4 ($p < 0.01$, respectively), vitamin K dependent protein S, alpha 2 antiplasmin and fibrinogen ($p < 0.05$, respectively). Significant correlations of coagulation proteins with insulin resistance, as determined by HOMA-IR, were also seen for antithrombin III ($p < 0.0001$), heparin cofactor 2 ($p < 0.001$), P-selectin ($p < 0.0001$), fibronectin ($p < 0.01$), vitamin K dependent protein S and alpha 2 antiplasmin ($p < 0.05$, respectively) (Table 2). However, in a multivariate analysis accounting for BMI, inflammation (CRP) and insulin resistance (HOMA-IR), there was no correlation with the coagulation proteins (Table 2).

To eliminate the confounding effect of obesity, a subset of women with BMI ≤ 25 kg/m² (16 PCOS and 53 controls) were compared. Here, HOMA-IR remained elevated in PCOS (1.6 ± 1.2 vs 1.1 ± 0.5 , $p < 0.05$), CRP did not differ, whilst heparin cofactor 2 (3979 ± 649 vs 3613 ± 585 RFU, $p < 0.05$) was elevated in the normal weight PCOS group.

Discussion

These data show that the hypercoagulable state in PCOS can be completely accounted for by BMI and its associated inflammation, and enhanced insulin resistance. In comparison to the normal controls, overall 10 pro-coagulation proteins were elevated in PCOS; plasminogen activator inhibitor-1 (PAI-1), fibrinogen, fibrinogen gamma chain, fibronectin, von Willebrand factor, D-dimer, P-selectin, plasma kallikrein, anticoagulant vitamin K-dependent protein S and heparin cofactor II, whilst prothrombin was decreased. These results are in accord with others who have reported changes in coagulation proteins in PCOS (4, 13), but underlying

pathophysiology has not been previously described and shows that in PCOS alterations in the coagulation factors appears complex and multifactorial. When normal weight ($BMI \leq 25$) PCOS patients were compared with normal weight control subjects, insulin resistance remained elevated and heparin cofactor 2, that is protective and inactivates thrombin in tissues, differed. These data are in accord with the association of heparin cofactor 2 with insulin resistance (14), indicating that normal weight PCOS subjects likely have no additional risk associated with a hypercoagulable state; however, obesity with associated inflammation markedly exaggerates the hypercoagulable state with an increased number of clotting parameters altered. The multivariate analysis showed that all of the changes in the coagulation proteins could be accounted for by BMI, inflammation and insulin resistance.

It is well recognized that obesity causes inflammation and increased insulin resistance (15, 16) and is associated with changes in coagulation parameters. For example, fibronectin is correlated to BMI (17) and obesity is associated with increased PAI-1 in PCOS (18). Others have reported, using a repeated fibrin formation and degradation functional assay, that "overall hemostatic potential" was BMI-dependent and not associated with PCOS (19). Central fat mass has been associated with fibrinogen, CRP, coagulation factor XIII, waist-to-hip ratio, plasminogen, PAI-1, plasmin inhibitor, and thrombin activatable fibrinolysis inhibitor (20)

Conversely, thrombin-activatable fibrinolysis inhibitor, PAI-1, D-dimer, Antithrombin III and thrombomodulin were reported to be significantly increased in women with PCOS compared with age- and BMI-matched controls, suggesting that alterations in these proteins are BMI-independent and due to other factors such as inflammation and insulin resistance, as reported here (4).

Inflammation (CRP) correlated significantly with antithrombin III, heparin cofactor 2, fibrinogen gamma chain, D-dimer, P-selectin, fibronectin, and its fragments 3 and 4, vitamin K dependent protein S, alpha 2 antiplasmin and fibrinogen. Inflammation crosstalk with coagulation leading to increased coagulopathy is well recognized; however, with the initiation of coagulation, the coagulation proteases may then modulate the inflammatory response (21, 22). In PCOS, both CRP and fibrinogen are predicted by BMI in accord with obesity initiating the increased inflammation (23) and particularly CRP, PAI-1, D-dimer, Antithrombin III with central fat mass as noted above (20).

In this study, insulin resistance (HOMA-IR) correlated with Antithrombin III, heparin cofactor 2, P-selectin, fibronectin, vitamin K dependent protein S and alpha 2 antiplasmin. It is recognized that insulin resistance is associated with enhanced thrombogenesis (24); however, it is difficult to determine the contribution of insulin resistance alone to its association with obesity and inflammation metabolic syndrome lipid parameters (25–27).

As noted above, there are reports of changes in coagulation proteins in PCOS (4, 13) and changes in functional assays (2, 3); however, conversely others have not found changes in the coagulation proteins between PCOS and controls (28). It can be seen from the data presented here that the likely reason for these discrepancies are due to the patient population being studied with the results dependent on the degree of obesity, inflammation and insulin resistance present. In addition, the PCOS phenotype may have an important role, with those having all three of the diagnostic criteria exhibiting the metabolic phenotype with increased insulin resistance in comparison to those with only two of the three diagnostic criteria (29)

The hypercoagulation state is in homeostasis with the pro-coagulation protein changes seen here in PCOS being balanced by the reduction in prothrombin and increased vitamin K-dependent protein S and heparin cofactor II that we also report; however, COVID-19 disease may shift this balance towards a hyper-procoagulant state. Patients infected with COVID-19 with acute respiratory distress syndrome (ARDS) show a procoagulant pattern of coagulation markers and elevation of fibrinogen and fibrin degradation products (D-dimers) which could drive organ failure and death (8).

Limitations of this study include that it was a cross sectional study but this was mitigated by the large number of subjects. In addition, only the proteins involved in the coagulation pathways were measured and no functional assays were undertaken in this study.

In conclusion, the hypercoagulable state in PCOS can be fully accounted for by BMI, inflammation and insulin resistance, suggesting that only obese PCOS women would be predisposed to an enhanced risk for severe COVID-19-related disease.

Declarations

Ethics approval and consent to participate: The Newcastle & North Tyneside Ethics committee approved this study. All patients gave written informed consent.

Consent for publication: All authors gave their consent for publication.

Availability of data and materials: All the data for this study will be made available upon reasonable request to the corresponding author.

Conflict of interests: No authors have any conflict of interest or competing interests to declare.

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Author contribution statement: ASMM and AEB analyzed the data and wrote the manuscript. TS supervised clinical studies and edited the manuscript. ID performed the statistical analysis. SLA and MAE contributed to study design, data interpretation and the writing of the manuscript. All authors reviewed and approved the final version of the manuscript. Alexandra E Butler is the guarantor of this work.

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Tables

Table 1: Demographics, baseline, hormonal and metabolic parameters of the PCOS subjects and controls

Baseline demographics	PCOS (n=146)	Controls (n=97)	P-value
	Mean (SD)	Mean (SD)	
Age (years)	29.1 (6.1)	29.6 (6.5)	0.09
BMI (Kg/m ²)	34.1 (7.5)	26.7 (6.6)	<0.0001
Weight (Kg)	96.5 (23.7)	74.4 (18.4)	<0.0001
Insulin (IU/ml)	10.2 (6.1)	6.2 (3.2)	0.001
HOMA-IR	3.8 (0.6)	1.6 (0.2)	<0.005
CRP (mg/L)	4.4 (4.2)	2.4 (3.9)	0.0008
SHBG (nmol/L)	42.5 (39.6)	77.5 (78.4)	0.0003
Testosterone (nmol/l)	1.6 (1.0)	1.05 (0.48)	<0.0001

BMI - Body Mass Index; *HOMA-IR* - Homeostasis model of assessment - insulin resistance; *CRP*- C reactive protein; *SHBG*- sex hormone binding globulin

Table 2. Correlation of coagulation proteins with (A) Body mass index (BMI). (B) inflammation (C reactive protein; CRP) and (C) insulin resistance (HOMA-IR). (D) shows the results of the multivariate analysis taking into account BMI, CRP and HOMA-IR.

A. BMI		B. CRP		C. HOMA-IR		D. CRP + BMI + HOMA-IR	
	p value		p value		p value		p value
Antithrombin.III	<0.00001	Antithrombin III	<0.00001	Antithrombin III	<0.00001	D.dimer	0.05967
Fibrinogen gamma chain	0.00004	Heparin cofactor.2	0.00002	Heparin cofactor 2	0.00068	Fibrinogen gamma chain	0.06575
Vitamin.K dependent protein S	0.00066	Fibrinogen gamma chain	0.00003	P.selectin	0.00099	Fibrinogen	0.07030
D.dimer	0.00077	D.dimer	0.00012	Fibronectin	0.00867	Plasma kallikrein	0.08567
Fibronectin	0.00077	P.selectin	0.00123	Vitamin.K dependent protein.S	0.01461	Fibronectin Fragment.4	0.12159
Prothrombin	0.00732	Fibronectin	0.00144	Alpha.2 antiplasmin	0.02270	Vitamin.K dependent protein.S	0.13821
Heparin.cofactor.2	0.00864	Fibronectin Fragment.3	0.00573	Prothrombin	0.05074	von Willebrand factor	0.13962
Fibrinogen	0.01267	Fibronectin Fragment.4	0.00715	Fibronectin Fragment.3	0.09201	Coagulation factor.Xa	0.18692
Angiostatin	0.01444	Vitamin K dependent protein.S	0.01838	Plasma kallikrein	0.18003	Antithrombin.III	0.18920
Fibronectin Fragment.3	0.02490	Alpha.2 antiplasmin	0.02004	Tissue Factor	0.19878	Fibronectin	0.24267
P.selectin	0.03856	Fibrinogen	0.02176	Fibrinogen gamma chain	0.23928	Fibronectin Fragment.3	0.30802
Alpha.2 antiplasmin	0.15769	von Willebrand factor	0.12158	Fibronectin Fragment.4	0.31789	Tissue.Factor	0.39938
Fibronectin Fragment.4	0.18185	Plasma kallikrein	0.18463	D.dimer	0.42608	Angiostatin	0.41172
Tissue.Factor	0.19238	Prothrombin	0.19448	Angiostatin	0.49776	Prothrombin	0.41800
von.Willebrand factor	0.26450	Coagulation factor.Xa	0.22468	Coagulation Factor.XI	0.80849	Alpha.2 antiplasmin	0.41905
Coagulation factor Xa	0.49408	Tissue.Factor	0.71352	Coagulation factor.Xa	0.82709	Heparin cofactor 2	0.58118
Coagulation Factor.XI	0.65951	Coagulation Factor.XI	0.73179	von Willebrand factor	0.86549	Coagulation Factor.XI	0.70381
Plasma kallikrein	0.96869	Angiostatin	0.73591	Fibrinogen	0.92833	P.selectin	0.70626

Figures

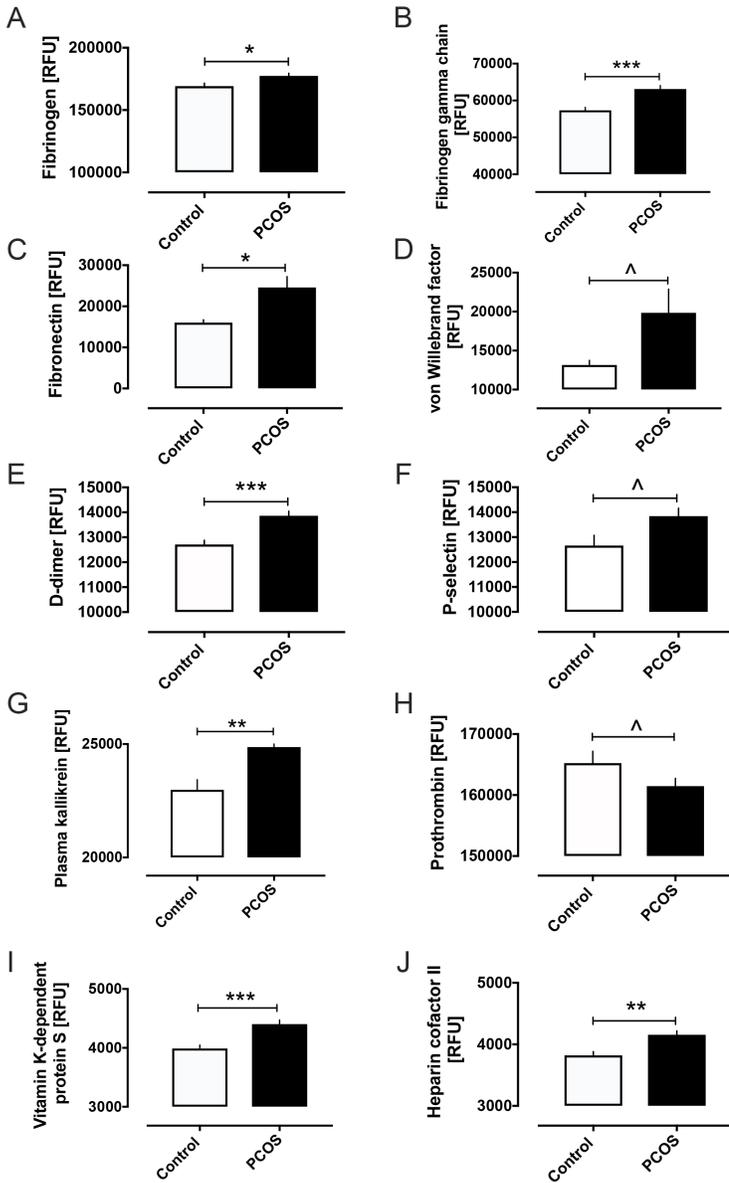


Figure 1

Figure 1. Clotting pathway proteins in women with and without polycystic ovary syndrome (PCOS). Levels of plasma fibrinogen (A), fibrinogen gamma chain (B), fibronectin (C), von Willebrand factor (D), D-dimer (E), P-selectin (F), plasma kallikrein (G) and prothrombin (H) in women with and without polycystic ovary syndrome (PCOS). RFU, relative fluorescent units. ^p<0.05, *p<0.01, **p<0.001, ***p<0.0001.