Insulin resistance and insulin secretory defect among Bangalee PCOS women: a case-control study

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Abstract

Insulin resistance (IR) is a well-recognized covariate of Polycystic Ovarian Syndrome (PCOS) with varying burden and risk factors among populations. The relationship of insulin secretory defect or ISD with PCOS is less understood. The presence of IR and ISD as well as their covariates have been explored in the present case-control study among young adult to early middle-aged, normal weight to obese, Bangalee women with PCOS. A number of 158 PCOS [age 23 (15–34) years, Median (Range)] and 126 Non-PCOS [24 (19–34) years] females were recruited purposively with PCOS diagnosed following Modified Rotterdam Criteria 2003. Hormones were measured by CLIA method and lower abdominal ultrasonography was done by trained personnel. IR and ISD were assessed by homeostasis model assessment with 75th percentile values of HOMA-IR (2.4) and HOMA%B (143) in Non-PCOS group considered as the cut-off values. Hyperandrogenism (HA) was measured by calculating Fasting Androgen Index (FAI). HOMA-IR was high among 52% of PCOS and 28% of Non-PCOS women. Body Mass Index (BMI) and HA were independently associated covariates of IR ($p < 0.001$). HOMA%B was compromised among 48% of PCOS subjects and the deficiency showed independent association ($p < 0.001$) with 2 h glycemia on OGTT in Non-PCOS and HA in PCOS groups. The data suggest insulin resistance as a major risk factor for PCOS among Bangalee women with obesity and hyperandrogenemia as its major covariates. The findings also indicate that presence of impaired insulin secretion is a major determinant of hyperglycemia and, consequently, of higher T2DM risk among young women in this population.

Keywords PCOS, HOMA-IR, HOMA%B, Hyperandrogenism

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Introduction

Polycystic Ovary Syndrome (PCOS) is the most prevalent endocrine disorder among reproductive-aged women [1]. Its prevalence is reported to vary widely (2.2 − 48%) [2, 3] which seems to be due to genuine racial differences and subject groups as well as due to different diagnostic criteria used in various studies [4]. Anovulation/oligomenorrhea (AO/OM), polycystic ovarian morphology (POM) and hyperandrogenism (HA) are the three diagnostic phenotypic features of PCOS; however, their mandatory inclusion in the clinical diagnosis of the disorder varies depending on the criteria used. Three diagnostic criteria

are mainly used worldwide in case of PCOS: National Institutes of Health (NIH) [5], the 2003 Rotterdam [6, 7], and the Androgen Excess Society (AES) [8]. The NIH criteria suggest the mandatory presence of 1st and 3rd phenotypic features, the Rotterdam criteria suggest the presence of any two, and the AES criteria suggests the mandatory presence of the 3rd plus optional presence of any of the 1st and 2nd phenotypic features for the confirmed diagnosis of PCOS.

Insulin resistance (IR) is known to be an important covariate in PCOS both as an intermediate risk factor as well as an outcome of HA. The prevalence of IR in PCOS patients has been reported to vary from 44 to 70% [9, 10]. This wide range may be due to several factors, including the heterogeneity of the diagnostic criteria for PCOS employed in these studies [10], the genetic background among the assessed population [11] and differences in the methods used for defining IR [10, 11]. Compared to European and European-American subjects, Asian PCOS women have been shown to be more prone to become insulin-resistant [12, 13].

Although the pathophysiological mechanism of IR in PCOS is fairly well understood, its etiological role as well as covariates are still not fully clear. There is ongoing debate as to whether IR is intrinsic to PCOS, related to obesity alone, or related to both factors. Several studies have indicated the presence of insulin resistance and compensatory hyperinsulinemia in approximately 80% of obese women with PCOS, and in 30–40% of lean women [14]. On the other hand, there is an increased prevalence of obesity and abdominal obesity in PCOS [15, 16] which may potentially worsen the IR-associated clinical features [17, 18]. It has been hypothesized that lean women with PCOS have PCOS-specific IR or intrinsic IR, which is augmented by the presence of obesity-specific IR [19]. Other authors have also suggested IR as inherent in PCOS which, consequently, decreases hepatic sex hormone-binding globulin (SHBG production) and increases total as well as free androgens and LH secretion [20].

Women with PCOS are known to have a 5- to 8-fold increased risk of type 2 diabetes mellitus (T2DM) compared with age- and weight-matched controls [21]. The pathogenesis of T2DM is critically affected by IR as well as pancreatic B-cell dysfunction [22–24]; however, studies exploring insulin secretory defect in specific PCOS populations are relatively scarce. One study [24] has shown the presence of B-cell dysfunction among PCOS subjects. Polymorphism in the insulin secretory gene has also been implicated in the etiopathogenesis of the disorder [24]. Further insight, however, is still required on the interaction of IR, insulin secretory dysfunction and other relevant confounders (like obesity and dyslipidemia) in PCOS among ethnicity-specific groups and subgroups of subjects.

Bangalees are the 8th largest ethnic group in the world. The prevalence as well as clinical, metabolic and endocrine aspects of PCOS in this population have not yet been well studied in this population. From facility-based data the presence of IR has been reported to vary widely from 16 to 77% [25–32]; however, the methodology and cut-off values of the IR assessment were not detailed in most of the studies. Also, the functional capacity of the pancreatic B-cells and their covariates were not assessed in these studies. Under this context, we have now studied IR and insulin secretory capacity, as well as their covariates, among a group of relatively younger PCOS subjects with their matching non-PCOS counterparts.

Materials and methods

The present observational analytic study, with a case-control design, included 285 reproductive-aged (15–34 years) participants recruited, through purposive sampling, from the primary responders to a social media call. Informed consents were obtained from each participant or the parent/ legal guardian of the participant aged below 16 years. The origin of the responders included residential halls of the universities/ colleges, outpatient units of tertiary care hospitals, and urban families in Dhaka city. The participants were classified into the case group (PCOS) and the control group (non-PCOS). The case group comprised 158 PCOS subjects diagnosed according to the Modified Rotterdam Criteria 2003 [6] following which the presence of at least two of the following three findings was ensured: (i) menstrual abnormalities (AO/OM), (ii) clinical and biochemical hyperandrogenism (HA), and (iii) the ultrasound looks of polycystic ovaries (POM). In the non-PCOS group, there were 127 non-hirsute women (without clinical evidence of hyperandrogenism) with regular menstrual cycles (without anovulation); they did not show the required hormonal and sonographic features of PCOS. Women with pregnancy, lactation, hyperprolactinemia, Cushing syndrome, thyroid dysfunction, congenital adrenal hyperplasia, and androgen-secreting tumors were excluded from the study. Use of insulin-sensitizing or glucose-reducing agents, hormonal treatments, oral contraceptive pills, antihypertensives, lipid-lowering drugs, or corticosteroids three months before the study were considered as criteria for exclusion from the study.

Using an interviewer-administered pretested Questionnaire cum Data Collection Form (DCF) which was developed for this study around Rotterdam criteria, all the relevant information was collected. Personal and medical history were taken, anthropometric measurements were done and blood pressure was measured following standard techniques. Anthropometric measurements included body weight, height, and waist circumference. Height and weight were scaled with the subjects in light

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clothes and without shoes. Waist circumference was evaluated using a flexible tape at the midline between the lower rib border and the curved superior border of the ilium (at the level of the umbilicus); with participants in the standing position, the measurement was done at the end of a normal exhalation. Following World Health Organization (WHO) guidelines, BMI was computed, and the categorization of the study participants was done as per guidelines for Asian women [33]. Using a mercury sphygmomanometer, blood pressure (BP) was measured in the right arm after a 10-min rest period; with the subjects at non-fasting state, wearing loose sleeves, having depleted bladders, and avoiding eating, drinking (except water) or smoking for at least one hour before the test. Metabolic Syndrome (MetS) was defined following API criteria.

The participants were questioned about the regulation of their menstrual cycle and they were subjected to clinical examination to evaluate hirsutism based on the Ferriman-Gallwey score (FG-score), with a value≥ 8 being considered as clinical HA [34]. Lack of menstrual cycle for >3 months or a cycle duration of >35 days was considered as ovulation disorder, denoted by the term oligomenorrhea/anovulation (AO) [35]. A subject was preliminarily placed in the control group when one or both of these factors were normal; once the subsequent results of ultrasound and serum hormonal tests were also not characteristics of PCOS, she was confirmed as a non-PCOS subject in the study. Acanthosis Nigricans was evaluated by the presence of black velvety patches in body folds and creases; it was used as a surrogate marker for insulin resistance. For each participant, lower abdominal ultrasonography (Voluson E6, USA), with folliculometry, was done by a trained professional; ovaries containing 12 or more follicles measuring 2–9 mm in diameter and/or enlarged ovarian volume (>10 mm^3) were considered to have a positive polycystic sonographic view [6].

Following an overnight fast (10–12 h.), each subject underwent a standard 75-g oral glucose tolerance test (OGTT); 0 h. (fasting serum glucose, FSG) and 2 h (postprandial serum glucose, PPG) serum samples were preserved at relevant freezers for future glucose and lipid profile estimation as well as for hormonal analyses. Serum glucose was measured by Glucose Oxidase and serum lipids [total cholesterol (TChol), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)] were estimated by enzymatic methods using an automated chemistry analyzer (Abbott, USA). Serum C-peptide was assayed by a Chemiluminescent ELISA technique (Abbott, USA). Based on homeostatic model assessment (HOMA) IR was calculated by using the C-peptide-modified formulae given by Li et al. [36]. The modified formula was HOMA1-IR$=1.5+$FPG $\times$ FCP / 2800. HOMA%B

was calculated by $0.27 \times$ FCP / (FPG-3.5)$+50$. HOMA of insulin sensitivity (HOMA%S) index was calculated by (1/HOMA-IR)$\times 100\%$. A HOMA-IR value>2.4 was considered to represent insulin resistance which is the 75th percentile value of control women and the closest indicator value (≥ 2.5) of IR in Indian adults [37].

Statistical analysis

Normal and non-normal quantitative variables were reported as Mean (SD) and Median (Min-Max), respectively. Qualitative variables were presented as numbers (percentages). The comparison of the groups was performed using the Mann-Whitney's U test (MW). Qualitative variables were compared by Chi-square test. The multiple linear regression analysis with the stepwise method was applied to evaluate the association between androgenic components (TT, FAI, and SHBG) as the independent variables and IR as the dependent variable in each group. Statistical significance was set at $p<0.05$. Data were analyzed using the SPSS software (Statistical Package for the Social Sciences, SPSS Inc, Chicago, IL, USA), version 26.0.

Results

The PCOS subjects were found to have more insulin resistance (median HOMA-IR, 2.48 vs. 2.22; $p=0.001$) and less insulin sensitivity (median HOMA%S, 45.00 vs. 40.37, $p=0.001$) as compared to their non-PCOS counterparts (Table 1). The insulin secretory capacity of the PCOS subjects was also found to be higher (median HOMA%B, 143 vs. 111, $p=0.001$). Table 1 also shows the anthropometric, clinical, biochemical and ultrasonography comparisons between the two groups. PCOS women were slightly lower aged (median age 24 years and 23 years, respectively); however, their WHR, 2hABG, TChol, and C-peptide values were significantly higher (p, 0.045–0.001) as compared to the non-PCOS counterparts. As expected, total Testosterone and FAI levels of the PCOS subjects were also significantly higher.

On considering the 75th percentile value of the non-PCOS subjects as the cut-off value of HOMA-IR (which is close to the cut-off value of 2.5 in Indian subjects [13]) the proportion of insulin-resistant subjects was found to be 52% in the PCOS group (Fig. 1); however, even the non-PCOS group showed 28% of its subjects as insulin resistant.

The association of IR among subjects with individual characteristic phenotypic features of PCOS was analyzed (Table 2). The median value of HOMA-IR was significantly higher in subjects with HA positive compared to their normal counterparts ($p<0.001$); in contrast, the median HOMA-IR values did not show any difference between AO/OM and POM absent and present groups. On separate analyses in the two study groups (Table 3),

Table 1 Anthropometric, clinical, biochemical and ovarian ultrasonography characteristics of PCOS among Non-PCOS and PCOS groups

Variables	Non-PCOS Median (IQR)	PCOS Median (IQR)	p
Age (Years)	24 (19–34)	23 (15–34)	0.008
BMI	23.4 (15.9–37.4)	23.98 (15.4–37.7)	0.074
Underweight, n (%)	10(8)	6(4)	0.214
Normal weight, n (%)	50(40)	52(33)	
Overweight n (%)	25(20)	35(22)	
Obese n (%)	40(32)	63(40)	
Waist Hip Ratio(WHR)	0.92 (0.76–1.03)	0.94 (0.71–1.61)	0.019
FBG	5.20 (4.0-8.20)	5.10 (4.0-7.40)	0.280
2ABG	5.70 (4.2–16.0)	6.0 (4.8–12.9)	0.004
Total Cholesterol	156.0 (105–240)	161.0 (105–275)	0.045
TG	84.0 (43–470)	102.0 (26–313)	0.002
LDL	95.0 (52–157)	101.0 (40–217)	0.082
HDL	40.0 (20–126)	38.50 (23–246)	0.335
Total Testosterone	1.130 (0.45–2.91)	1.450 (0.47–5.20)	<0.001
FAI	4.34 (1.42–21.56)	9.7 (0.62–486.00)	<0.001
S C-peptide	380 (83-1123)	523 (133-12666)	<0.001
HOMA%S	45 (22–60)	40.37 (3.00-0.58)	<0.001
HOMA-IR	2.22 (1.66–4.22)	2.48 (1.48–29.10)	<0.001
HOMA%B	111 (61–304)	143 (74-6368)	<0.001

Data are presented as Numbers (percentages) or Median (IQR). Difference between the Groups was calculated by Chi-Square or Mann-Whitney Test, as appropriate

Table 2 HOMA-IR values in the PCOS group in the absence and presence of characteristic phenotypic features of PCOS (n=143)

Phenotypic characteristics	Absent Median (IQR)	Present Median (IQR)	U	p
AO/OM	2.6 (1.9–29.1)	2.4 (1.7–27.7)	1165	0.404
POM	2.6 (1.8–27.7)	2.5 (1.7–29.1)	1442	0.293
HA	2.2 (1.7–3.2)	2.7 (1.9–29.1)	4483	**<0.001**
Hirsutism	2.7 (1.9–29.1)	2.4 (1.7–18.2)	2365	0.252

Data were expressed as Median (Range) and comparison between two groups were done by Mann-Whitney U test. AO/OM, anovulation/Oligomenorrhea; POM, Polycystic Ovarian Morphology; HA, Hyperandrogenism

The association of the individual characteristic phenotypic features of PCOS with HOMA%B were also analyzed in the PCOS group considering the 75th percentile value (140.78) of the non-PCOS subjects as the cut-off point (Table 4). Anovulation/ Oligomenorrhea was found to be present in 95% compromised B-Cell function subjects as compared to 82% of their normal counterparts (p=0.014). In contrast, hyperandrogenism was present in higher proportion (73%) of normal insulin secretory subjects in contrast to their compromised counterparts (55%) (p=0.021).

In addition to having association with anovulation/ oligomenorrhea and hyperandrogenism, HOMA%B was also found to have association with some other covariates in PCOS (Table 5). 2hPPG and HOMA%S were significantly lower (p=0.014 to 0.001) among insulin secretory compromised subjects as compared to their normal counterparts; in contrast, their FBG, FAI and HOMA-IR values were significantly higher (p=0.001).

On Spearman correlation analysis among subjects of the PCOS group, BMI, FBG, 2hPPG, TG, and FAI were found to be positively correlated with HOMA-IR (p=0.036 to 0.001) (Table 6). HOMA%B was also found

only subjects with HA showed significantly higher proportions of insulin-resistant subjects as compared to their normal counterparts (36% in non-PCOS and 83% PCOS groups, p=0.02 and 0.001, respectively).
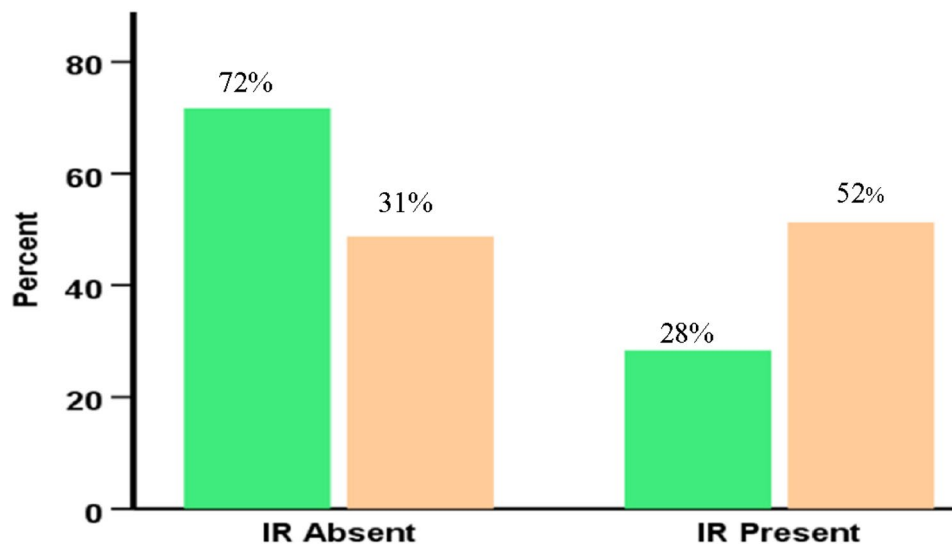

Fig. 1 Proportion of IR among Non-PCOS and PCOS Groups

Table 3 Proportion of insulin-resistant subjects in the Non-PCOS and PCOS groups in the presence of different diagnostic phenotypic features of PCOS

Variables	Non-PCOS (n = 127)			PCOS (n = 158)		
	IR Absent, n (%)	IR Present, n (%)	p-value	IR Absent, n (%)	IR Present, n (%)	p-Value
AO/OM	4 (4)	2 (5.6)	0.78	68 (88)	71 (88)	0.89
POM	1 (1)	1 (3)	0.49	65 (84)	68 (84)	0.94
HA	16 (18)	13 (36)	0.02	35 (46)	67 (83)	< 0.001
Hirsutism	14 (15)	4 (11)	0.57	56 (73)	53 (65)	0.32

Data were expressed as number (percentage) and comparison between two groups were done by Chi-Square test. AO/OM, anovulation/Oligomenorrhea; POM, Polycystic Ovarian Morphology; HA, Hyperandrogenism

Table 4 Characteristic phenotypic features among PCOS subjects with below and above 75th percentile HOMA% B (140.78) derived from Control subjects (n=158)

Variables	HOMA%B <75th Percentile n (%)	HOMA%B >75th Percentile n (%)	p
Anovulation Absent	4 (5)	15 (18)	0.014
Anovulation Present	72 (95)	67 (82)	
POM Absent	14 (18)	11 (13)	0.513
POM Present	62 (82)	71 (87)	
Hyperandrogenism Absent	34 (45)	22 (27)	0.021
Hyperandrogenism Present	42 (55)	60 (73)	
Hirsutism Absent	28 (37)	21 (26)	0.168
Hirsutism Present	48 (63)	61 (74)	

Table 5 Covariates among PCOS subjects with below and above 75th percentile HOMA% B (140.78) derived from Control subjects (n = 158)

Variables	HOMA%B < 75th Percentile Median (IQR)	HOMA%B > 75th Percentile Median (IQR)	Standardized test statistic/p-value
FBG, mmol/l	5.20 (4.00-8.20)	5.10 (4.00-7.40)	-4.04/<0.001
2hABG, mmol/l	5.70 (4.20–16.00)	6.00 (4.80–12.90)	-2.88/0.014
sTChol, mg/dl	156 (105–240)	161 (105–275)	-0.73/0.468
sTG, mg/dl	84 (43–470)	102 (26–313)	-0.59/0.558
sLDL, mg/dl	95 (52–157)	101 (40–217)	-1.84/0.066
sHDL, mg/dl	40 (20–126)	39 (23–246)	0.47/0.667
FAI	4.33 (1.42–21.56)	9.72 (0.62–485.7)	3.82/<0.001
HOMA-IR	2.22 (1.66–4.62)	2.48 (1.74–29.10)	6.53/<0.001

Table 6 Correlation of HOMA-IR and HOMA%B with various covariates in the PCOS group

Variables	HOMA-IR		HOMA%B	
	r	p-value	r	p-value
Age (yrs)	0.133	0.083	-0.179	0.019
BMI	0.286	**< 0.001**	0.107	0.165
WHR	0.017	0.823	0.019	0.803
2hABG	0.345	**< 0.001**	0.065	**0.012**
TChol	0.281	**< 0.001**	0.117	0.127
TG	0.239	**0.002**	0.165	**0.031**
LDL-Chol	0.230	**0.003**	0.072	0.352
HDL-Chol	0.033	0.668	-0.039	0.615
FAI	0.355	**< 0.001**	0.185	**0.016**
HOMA_IR	-	1.00	0.605	**< 0.001**

to be positively correlated with 2hPPG ($p = 0.012$), TG ($p = 0.031$), FAI ($p = 0.016$) and HOMA-IR ($p < 0.001$).

Since a fairly high proportion (48%) of the PCOS women showed compromised B-cell function and this, in turn, is a major defect in the diabetes mellitus, the association of 2hPPG with HOMA%B was further explored by adjusting the effects of the confounding variables. On binary logistic analysis (Table 7) 2hPPG was found to have a highly significant negative association with HOMA%B ($p < 0.001$) even when the effects of age, BMI, WHR, FAI and HOMA-IR were adjusted.

On multiple regression analysis (Table 8), HOMA-IR showed an independent association with age, BMI and TG in the Non-PCOS group ($p = 0.006$ to < 0.001) and it did not show any association with FAI on adjustment of the effects of confounding variables. In contrast to the non-PCOS group, HOMA-IR showed a highly significant

Table 7 Binary logistic regression analysis in the PCOS Group with IR and ISD as the dependent variables

Variables	IR		Compromised HOMA%B	
	β value	*p*-value	β value	*p*-value
Age	-0.093	0.138	-0.006	0.925
BMI	0.276	**<0.001**	0.246	**<0.001**
WHR	0.162	0.935	-3.188	0.160
2hABG	0.107	0.105	-0.444	**0.002**
TG	0.007	0.199	0.001	0.773
FAI	0.035	**0.001**	0.032	**0.003**

positive association (*p*<0.001) with FAI and no other covariates were found to have any significant association with HOMA-IR. With the same analysis, with the inclusion of the relevant confounders of insulin secretion, HOMA%B showed a significant positive association with age (*p*=0.016) and HOMA-IR (p=<0.001) and it also showed a highly significant negative association with post-stimulated blood glucose (p=<0.001). In contrast to the non-PCOS subjects, HOMA%B showed a highly positive correlation only with HOMA-IR (p=<0.001) and there was a strong tendency to be correlated with FAI (*p*=0.093).

Discussion

The present data show that insulin resistance is present among more than half of the young adult to early middle-aged PCOS women belonging to the Bangalee ethnic group. Insulin resistance has been reported to be more common among people of Indian subcontinent origin [13]. Data in the present study are generally in line with these previous findings since the proportion of insulin-resistant subjects and median value of HOMA-IR in the PCOS group are significantly higher as compared to those in the non-PCOS group. Compared to the median value of 2.48% HOMA-IR among the PCOS subjects, the corresponding value of HOMA-IR was 2.22% among the non-PCOS counterparts (*p*<0.001, Table 1). These values, in controls as well as in patients, are nearly parallel

to those reported for the South Indian population [38]. In Bangladesh, the values of HOMA-IR have been variably reported, and the assessment techniques used have not always been mentioned [25]. Shah et al. [27] reported a mean HOMA-IR of 1.40% among control and 4.44% among PCOS subjects with a similar age range. The WHR of their subjects was lower than the present one (mean values of 0.83 among PCOS and 0.80 among controls in contrast to median values of 0.94 and 0.92 among their counterparts in the present study). The median values of 3.98 and 3.34 have been reported by Banu et al. [29] among hyperandrogenemic and normoandrogenemic subjects, respectively. Zamila et al. [30] reported the median values of HOMA-IR% as 4.38, 3.70, and 3.05 among amenorrheic, oligomenorrheic, and eumenorrheic subjects, respectively; in the control group, they found a median value of 1.64. Differences in age, BMI, WHR and variation in laboratory techniques seem to explain these HOMA-IR values among various studies.

The proportion of insulin-resistant subjects among the PCOS population has been shown to vary from 44 to 70% [9, 10]. In Indian subjects, the proportion has been claimed to be higher [24]. The cut-off value of HOMA-IR% for IR positivity (to define an insulin-resistant subject) in this study (2.4%) was derived from the 75th percentile value of the parameter among the control (Non-PCOS group). The value is very close to the cut-off value used for the Indian population [38], which was derived through a different technique. Using this criterion, a 52% value for IR positivity among PCOS subjects was obtained in the present study (Fig. 1), which was somewhat lower than that reported by other Bangladeshi Authors [25].

In Bangladesh, from facility-based data, the presence of IR has been reported to vary widely from 16 to 77% among PCOS subjects [25]; however, the methodology and cut-off values of the IR assessment were not detailed in most of the studies [25]. Methods, as well as HOMA%IR cut-off value similar to the methods of the present study, were followed in three studies. In the study

Table 8 Multiple linear regression analysis of explanatory variables considering IR as the dependent variable

Variables	HOMA-IR Non-PCOS		HOMA_IR PCOS		HOMA%B Non-PCOS		HOMA%B PCOS	
	Standardized coefficients (β)	*p*-value	Standardized coefficients (β)	*p*-value	Standardized coefficients (β)	*p*-value	Standardized coefficients (β)	*p*-value
Age	0.311	**<0.001**	0.011	0.831	-0.186	0.016	0.043	0.480
BMI	0.296	**<0.001**	0.011	0.851	0.100	0.216	0.008	0.900
WHR	-0.100	0.201	0.008	0.882	-0.90	0.206	0.014	0.816
TG	0.217	**0.006**	-0.033	0.551	-	-	-	-
FAI	0.099	0.210	14.441	**<0.001**	-0.073	0.403	0.157	0.093
2ABG	-	-	-	-	-0.370	**<0.001**	-0.122	0.53
SHBG	-	-	-	--	0.024	0.797	-0.007	0.910
HOMA_IR	-	-	-	-	0.695	**<0.001**	0.563	**<0.001**

of Shah et al. [27], 65% of the PCOS subjects were insulin resistant using a cut-off value of HOMA-IR as 2.6%. Using the same cut-off value of HOMA%IR, Banu et al. [29] reported a 70% prevalence of IR among Bangladeshi women. Zamila et al. [30] have reported that IR is present among 78% eumenorrheic, 72% oligomenorrheic, and 63% amenorrheic subjects. In all these studies, the PCOS subjects had higher degrees of overweight/obesity than their counterparts in the present study. This, along with differences in subject characteristics and laboratory techniques, may partly explain the lower proportion (52%) of insulin resistance among the present group of PCOS women. Since the cut-off value of HOMA%IR in the present study was 2.4, this value, by itself, cannot explain the variations; instead, it can be postulated that the present proportion would be a little lower if the cut-off value of 2.6 was used. Despite these differences, it is apparent that insulin resistance is present among more than 50% of young PCOS women of Bangalee ethnicity. Thus, in general, the current data demonstrate the existence of a high burden of IR among Bangalee PCOS women.

The existence of insulin resistance among more than a quarter (28%, Fig. 1) of Non-PCOS subjects needs to be specially noted as the finding has significant public health importance. Only one study [27] from Bangladesh has reported the proportion of HOMA%IR among Non-PCOS control subjects, and it is substantially lower [only 5%] in comparison to that in the present one (28%). As mentioned previously, the cut-off value of HOMA%IR in that study was closely similar to that of the present one. The reasons for the difference in proportions of insulin-resistant non-PCOS subjects in the two studies are unclear. However, the sample size in the earlier study was very small (only 40) in contrast to the present study, where data from 126 subjects have been analyzed. This, and variations in patient characteristics and laboratory techniques, may partly explain the difference in proportions.

The finding of IR among more than one-fourth of the non-PCOS women raises a public health concern as the condition is known to create substantial risk for PCOS itself as well as a number of chronic cardiometabolic disorders and other NCDs like T2DM, hypertension, chronic liver diseases (CLDs) and chronic obstructive pulmonary diseases (COPD). It needs to be noted that the non-PCOS subjects in the present study are relatively young (age range 19–34 years, 96% within 21–30 years, Table 1), and public health interventions targeted to dietary practices, physical exercise, and other lifestyle-related issues can help them to avoid the potentially serious consequences of IR.

As shown in Tables 3 and 18% without IR and 36% with IR were found to have hyperandrogenemia among the non-PCOS subjects. Since other well-known causes of

PCOS were excluded, it is probably a phenotypic feature indicating an initial stage of the evolving PCOS whose clinical diagnosis needs at least one more phenotypic feature (anovulation or POM). On chi-square analysis, IR was found to be strongly associated with biochemical hyperandrogenism among PCOS subjects ($p < 0.001$), and it also had some significance in the non-PCOS group ($p = 0.02$, Table 3). On the other hand, there was no significant association with anovulation, PCOM, and hirsutism in either of the subject groups. On correlation analysis, the association differed between the two study groups, with BMI, FAI, and 2hPPG being the common covariates in both groups, age being significant only in the non-PCOS group and TG being significant only in the PCOS group (Table 5). On binary logistic regression analysis (Table 6), age and FAI showed significant ($p = 0.001$) association with IR, and in the non-PCOS group, a different set of variables, namely age ($p = 0.002$), WHR ($p = 0.04$) and TG ($p = 0.03$) showed significant association with IR. The pattern of association remained almost the same on multiple regression analysis (Table 7), and 2hPPG was found to be independently associated with IR ($p = 0.001$). In this analysis, BMI and TG were found to be to be independently associated with IR. These findings indicate that age, obesity, and dyslipidemia are important covariates of insulin resistance among the young and early middle-aged Bangalee women with variable degrees of involvement among Non-PCOS and PCOS subjects. The importance of these factors in the development and severity of insulin resistance is well known [2] and, again, these findings have significant clinical and public health importance as the conditions can be managed or even prevented through appropriate lifestyle and/or minimum public health interventions.

As compared to insulin resistance, insulin secretory defect has been relatively less studied in PCOS. The compensatory hypersecretion of insulin by the pancreatic B-cell in response to insulin resistance is a well-known phenomenon [22] and it is also evident in the present study with higher level of serum C-peptide and HOMA%B (Table 1) in the PCOS group as compared to the non-PCOS counterparts. The HOMA%B has also shown a strong independent positive association with HOMA-IR indicating a positive feedback cycle between the two variables (Table 7). In contrast to insulin resistance, the insulin secretory capacity has not been found to be associated with obesity or lipid levels in any of the study groups. However, even after adjustment of the confounding variables, pancreatic B-cell function shows a significant negative association with postprandial hyperglycemia both in Non-PCOS (Table 7) and PCOS groups (Table 6) indicating a central role of the secretory capacity in the development of prediabetes and diabetes among these women. The importance of B-cell secretory

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dysfunction in the pathogenesis of diabetes is well established. In the present study, the independent role of the B-cell defect regarding abnormal glycemia in PCOS becomes more evident with the finding that, in addition to its association with hyperandrogenemia, compromised HOMA%B is significantly associated with anovulation/oligomenorrhea (Table 4). The postprandial hyperglycemia among PCOS subjects is also associated independently with B-cell secretory capacity. Accordingly, it seems that a group of women with susceptibility to PCOS through insulin resistance or other pathways may also have intrinsic dysfunction in pancreatic B-cell function and these subjects need special attention for the prevention of prediabetes and diabetes. As evident from multivariate analysis in this study (Table 7), management and prevention of obesity, postprandial hyperglycemia and hyperandrogenism would play a major role in preserving B-cell functional capacity and, consequently, in the development of prediabetes and diabetes among these groups of women. Assessment of insulin secretory capacity during the routine investigation may also have a screening role in identifying vulnerable women.

In conclusion, the present data suggest that insulin resistance is a major risk factor for PCOS among Bangalee women with obesity and hyperandrogenemia as its major covariates. The findings also indicate that the presence of insulin secretory defect is a major determinant of hyperglycemia among young-aged PCOS subjects among Bangalee population and, consequently, PCOS leads to a higher risk of prediabetes and diabetes among young women in this population through the failure of compensatory enhancement in pancreatic B-cell function.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-024-01720-3.

> Supplementary Material 1.

Authors' contributions
Jannatul Nayeem was involved in the planning and conduction of the study, data analysis and drafting of the manuscript. MM Towhidul Islam contributed to the planning and conduction of the study, data interpretation and review of the manuscript. Farzana Deeba was involved in the conduction of the study and review of the manuscript. Shahjada Selim contributed to the conceptualization and planning of the study and review of the manuscript. Liaquat Ali and Yearul Kabir were involved in the conceptualization and conduction of the study, data interpretation and finalization of the manuscript. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Declarations

Ethics approval and consent to participate
The Research Ethics Committee of the Department of Biochemistry and Molecular Biology, University of Dhaka, Dhaka, Bangladesh, reviewed and approved the study protocol (BMBDU-ERC/EC/09/20). All women were informed in the local language about the project and fulfilled the written informed consent before participating in the study. In cases of women below the age of 16 years, informed consent to participate was obtained from the parents/ legal guardians of the participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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