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Comparative analysis of clinical symptoms and biochemical alterations in women with polycystic ovary syndrome: assessing the impact of type 1 diabetes versus non-diabetic controls

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Abstract

Background Women with type 1 diabetes depend on insulin injections throughout their life. However, the recommendation for strict metabolic control of diabetes requires the administration of supra-physiological doses of insulin, which might result in insulin-mediated stimulation of androgen synthesis. Hyperandrogenism in women with type 1 diabetes may be associated with polycystic ovary syndrome (PCOS). This study was performed to investigate PCOS and its associated clinical symptoms and biochemical alterations in women with type 1 diabetes in the Palestinian Territories. This retrospective cohort study consists of 50 women with type 1 diabetes and 50 apparently healthy non-diabetic controls. Questionnaire interviews were conducted. The diagnosis of PCOS was based on chronic anovulation and biochemical evidence of hyperandrogenism. Serum total testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and insulin were measured by ELISA.

Results The mean waist-to-hip ratio and age at menarche were significantly higher in diabetic women than in non-diabetic controls (81.9 ± 7.9 and 13.9 ± 1.6 years vs. 78.8 ± 5.7 and 13.2 ± 1.2 years, and $P = 0.045$, $P = 0.020$, respectively). Oligomenorrhea, acanthosis nigricans, seborrhea, and hirsutism were more frequent in diabetics. The levels of total testosterone and insulin were significantly higher in diabetics (0.58 ± 0.11 ng/ml and 15.8 ± 12.4 mlU/ml vs. 0.44 ± 0.11 ng/ml and 10.8 ± 4.5 mlU/ml, $P < 0.001$ and $P = 0.010$, respectively). PCOS was present in 11 (22.0%) of diabetic women compared to 3 (6.0%) in non-diabetics ($P = 0.044$). Diabetic women with PCOS received higher doses of insulin than non-PCOS women (72.7 ± 23.9 vs. 55.0 ± 19.8 UI.cc/ml/day, $P = 0.023$). PCOS women showed more frequent oligomenorrhea (100% vs. 15.4%, $P < 0.001$) and higher levels of total testosterone and insulin (0.64 ± 0.09 and 23.1 ± 13.0 vs. 0.53 ± 0.11 and 14.1 ± 11.8, $P = 0.023$ and $P = 0.041$, respectively). PCOS cases were significantly more frequent in diabetic women receiving intensive insulin therapy than their counterparts with non-intensive insulin therapy (40.9% vs. 7.1%, $P = 0.012$).

Conclusion Intensive insulin treatment in type 1 diabetes potentiates the development of PCOS and its related clinical and biochemical features particularly oligomenorrhea, hyperinsulinemia, and hyperandrogenemia.

Keywords Hyperandrogenemia, Hyperinsulinemia, Palestinian Territories, Polycystic ovary syndrome, Type 1 diabetes

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Background

Type 1 diabetes is a common autoimmune chronic disease caused by the destruction of pancreatic endocrine β-cells resulting in insulin deficiency and hyperglycemia. In type 1 diabetic patients, insulin injections remain the "one-size-fits-all" daily therapeutic practice throughout their life. However, this option is not very effective and many patients may face a risk of some complications, as well as an overall decreased life expectancy [1, 2]. Therefore, type 1 diabetes is more likely to be a personalized, monitored, and controlled condition. The current recommendation for strict metabolic control of type 1 diabetes requires the administration of supra-physiological doses of exogenous insulin, which might result in insulin-mediated stimulation of androgen synthesis, as occurs in insulin-resistant states [3]. Elevated levels of androgens in women with type 1 diabetes may be associated with polycystic ovarian changes, including PCOS [4].

PCOS is the most common endocrine disorder in premenopausal women, with a prevalence rate of approximately 5–20% based on the National Institute of Health (NIH) and Rotterdam criteria [5–7]. Women with PCOS are characterized by chronic ovulatory dysfunction, hyperandrogenemia, hyperinsulinemia, hypothalamic-pituitary-ovarian axis dysfunction, menstrual irregularities, deranged adipokine secretion from the adipose tissue, and/or small cysts on one or both ovaries [8, 9]. These specific alterations interact in different tissues, such as fat, liver, muscle, and ovaries, resulting in a variety of phenotypes of the syndrome [10], and it is probably the most frequent cause of hirsutism and infertility [11–13].

The definition of PCOS requires the presence of two of three of the following criteria: clinical and/or biochemical hyperandrogenism, oligo-anovulation, and polycystic ovaries in ultrasound; ≥ 12 follicles measuring 2–9 mm in diameter, and/or an ovarian volume > 10 mL in at least one ovary [14]. Hyperandrogenism is a cardinal clinical and biochemical characteristic of PCOS and is a central component in both the androgen excess and PCOS (AE-PCOS) Society and earlier NIH diagnostic criteria [15]. In adult women affected by type 1 diabetes, the global prevalence of PCOS is relatively high to be about 24% [4]. Although PCOS is extensively studied worldwide in patients with type 2 diabetes, limited data are available on such condition in type 1 diabetes. In the Palestinian Territories, Gaza Strip, the present study is the first to assess PCOS in women with type 1 diabetes. The present investigation is designed (I) to study socio-demographic and clinical data, anthropometric parameters, menstrual status, and apparent symptoms in type 1 diabetic compared to non-diabetic women; (II) to determine hormonal levels of total testosterone, FSH, LH, and insulin in both diabetic and non-diabetic women; (III) to find out the distribution of PCOS among diabetic and non-diabetic women; (IV) to compare clinical and biochemical features of diabetic women with and without PCOS; and (V) to assess the relation of insulin therapy with PCOS and apparent symptoms in diabetic patients.

Methods

Study population and ethical considerations

This is a retrospective cohort study comprising 50 type 1 diabetic and 50 non-diabetic females matched for age and body mass index (BMI). A non-probability accidental sample of type 1 diabetic women, previously diagnosed according to the World Health Organization diagnostic criteria for diabetes [16], was selected from the Medical Relief Center in Gaza Governorate. The sample size calculations were based on the formula for case–control studies. EPI-INFO statistical package version 3.5.1 was used with 95% Cl, 80% power, 50% proportion as conservative, and OR > 2. The sample size in the case of a 1:1 ratio of case–control was found to be 47:47. For a no-response expectation, the sample size was increased to 50 women with type 1 diabetes. The control also consisted of 50 non-diabetic women [17]. Women with type 2 diabetes or other forms of diabetes, pregnant or lactating women, women who used sex steroids, women with androgenic ovarian or adrenal tumors or other endocrinopathies, women who had abnormal thyroid function, and women who have had recent ovarian surgery were excluded from this study. On the other hand, the inclusion criteria were women aged between 15 and 38 years and women suffering from PCOS based on chronic anovulation (oligomenorrhea: < 8 cycles/year) and biochemical evidence of hyperandrogenism [18, 19].

Questionnaire interviews

All interviews were conducted face-to-face by the researcher herself with both diabetic and non-diabetic women. The questionnaire was based on the questions of a previous study with some modifications [20]. Most questions were yes/no questions, which offer a dichotomous choice [21]. The questionnaire was validated and then piloted with eight patients who were not included in the study. The questionnaire included questions on sociodemographic and clinical data, the status of the menstrual cycle, apparent symptoms, and insulin therapy.

Body mass index, waist-to-hip ratio, oligomenorrhea and hirsutism assessment

The BMI measurements were taken for both diabetic and non-diabetic women, and the BMI was calculated as kilogram (kg) body weight/height in meters squared [22]. The body weight and height were measured using a

carefully calibrated balance (Detecto, CAP-180 kg, USA) and a vertical measuring rod, respectively. The waist circumference was measured to the nearest 0.5 cm using a flexible measuring tape at the narrowest circumference between the lower costal margin and the iliac crest in the standing position. The hip circumference measurement was obtained at the maximum perimeter at the level of the femoral trochanters. The waist-to-hip ratio was calculated as the ratio of these two circumferences [23]. Oligomenorrhea was defined as less than 8 menstrual cycles per year [24]. Hirsutism was assessed by determining the presence of terminal hair using the modified Ferriman-Gallway score [25].

Blood sample collection, processing and hormonal assay

A fasting overnight venous blood sample (5 mL) was collected by a well-trained medical technologist from each participant on days 3–5 of their menstrual cycle into a plain vacutainer tube without anticoagulant, under quality control and safety procedures. The tubes were allowed to stand for 20 min at room temperature, and then the serum was separated for hormonal determination by centrifugation at 3000 rpm for 10 min using a Rotina 46 Hettich Centrifuge, Japan. Serum total testosterone, FSH, and LH levels were measured following the previously described methods [26–28], respectively, using enzyme-linked immunosorbent assay (ELISA) TECO kits. Serum insulin was also determined by ELISA using the DRG kit, Germany [29].

Data analysis

The IBM SPSS program for Windows (Statistical Package for the Social Sciences Inc., Chicago, Illinois, USA), version 22.0, was used for data analysis in this study. The frequency of the study variables and the cross-tabulation were presented. The chi-square (χ^2) test was used to identify the significance of the relations, associations, and interactions among various variables. Yates's continuity correction test, $\chi^2_{(corrected)}$, was used when not more than 20% of the cells had an expected frequency of less than 5. The independent sample *t*-test procedure was used to compare the means of the quantitative variables in the separated cases into two qualitative groups, such as the relationship between hormones in diabetic and non-diabetic women. In all the abovementioned tests, *P*-values less than 0.05 were regarded as the statistically significant limit. A range of minimum and maximum values was used. The percentage difference was calculated according to the formula: The percentage difference equals the absolute value of the change in value divided by the average of the 2 numbers, all multiplied by 100. Percent difference = $(|(V1-V2)|/((V1+V2)/2)) \times 100$.

Results

Sociodemographic and clinical data of the study population

Table 1 shows no significant difference between the mean ages of non-diabetic controls and diabetic patients

Table 1 Sociodemographic and clinical data of the study population

Variable	Non-diabetic controls (No. = 50)	Diabetic patients (No. = 50)	Test		*P*-value
Age (years)					
Mean ± SD	23.8 ± 5.2	23.3 ± 5.7	*T*	0.401	0.689
Range (min–max)	16–37	15–38			
Marital status, No. (%)					
Single	35 (70.0)	30 (60.0)	χ^2	1.099	0.294
Married	15 (30.0)	20 (40.0)			
Have children					
Yes	10 (66.7)	11 (55.0)		0.486	0.486
No	5 (33.3)	9 (45.0)			
First delivery after marriage (years)					
Mean ± SD	1.2 ± 0.5	2.5 ± 1.9	χ^2	2.197	0.049
Education, No. (%)					
University	35 (70.0)	19 (38.0)	χ^2	9.698	0.021*
Secondary	12 (24.0)	20 (40.0)			
Preparatory	1 (2.0)	8 (16.0)			
Primary	2 (4.0)	3 (6.0)			
Employment, No. (%)					
Yes	17 (34.0)	6 (12.0)	χ^2	6.832	0.009
No	33 (66.0)	44 (88.0)			
Family history of diabetes, No. (%)					
Yes	12 (24.0)	25 (50.0)	χ^2	7.250	0.007
No	38 (76.0)	25 (50.0)			
Duration of diabetes (years)					
< 7	-	27 (54.0)	-	-	-
7–14		13 (26.0)			
> 14		10 (20.0)			
Mean ± SD		7.8 ± 5.9			
Range (min–max)		1–22			
Retinopathy, No. (%)					
Yes	9 (18.0)	10 (20.0)	χ^2	0.065	0.799
No	41 (82.0)	40 (80.0)			
CVD, No. (%)					
Yes	1 (2.0)	3 (6.0)	χ^2	0.260	0.610*
No	49 (98.0)	47 (94.0)			
Neuropathy, No. (%)					
Yes	4 (8.0)	7 (14.0)	χ^2	0.409	0.522*
No	46 (92.0)	43 (86.0)			

CVD cardiovascular disease, *No.* number, *SD* standard deviation. *P-value of $\chi^2_{(corrected)}$ test, $P < 0.05$: significant, $P > 0.05$: not significant

(23.8 ± 5.2 vs. 23.3 ± 5.7 years, $P = 0.689$). More than half of married women have children. However, the mean period of first delivery after marriage was significantly longer in diabetic women compared to non-diabetic women (2.5 ± 1.9 vs. 1.2 ± 0.5 years, $P = 0.049$). Analysis of the educational status showed that the difference between various educational levels of diabetic and non-diabetic women was significant ($\chi^2_{(corrected)} = 9.698$, $P = 0.021$). Regarding employment, the difference between the two groups was significant ($\chi^2 = 6.832$, $P = 0.009$), with an increase in diabetes among unemployed women. Half of diabetic women had a family history of diabetes, compared to almost a quarter of non-diabetic women ($\chi^2 = 7.250$, $P = 0.007$). The mean diabetic duration was 7.8 ± 5.9 years, with a range of 1–22 years. Self-reported complications, including retinopathy, cardiovascular disease, and neuropathy, were higher among diabetic women compared to non-diabetic women, but the differences were not significant ($P > 0.05$).

Anthropometric measurements of the study population

As indicated in Table 2, there was no significant difference between diabetic and non-diabetic women for BMI. Waist-to-hip ratio was significantly higher in diabetic compared to non-diabetic controls (81.9 ± 7.9 vs. 78.8 ± 5.7, $P = 0.045$). Although the number of diabetics who have an android body type was higher than that of non-diabetics, no significant difference was detected ($\chi^2 = 1.961$, $P = 0.161$).

Status of menstrual cycle, apparent symptoms and insulin therapy

Table 3 reveals that the mean age at menarche was significantly higher in diabetic women compared to non-diabetic women (13.9 ± 1.6 vs. 13.2 ± 1.2 years, $P = 0.020$). Seventeen (34.0%) of diabetics reported oligomenorrhea versus 9 (18.0%) of non-diabetics ($\chi^2 = 3.326$, $P = 0.068$). Acanthosis nigricans was present only in the diabetic group ($\chi^2_{(corrected)} = 4.433$, $P = 0.035$). Seborrhea was significantly higher in diabetics ($\chi^2_{(corrected)} = 4.640$, $P = 0.031$). Hirsutism was also more frequent in diabetics, but the difference was not significant ($\chi^2_{(corrected)} = 2.367$, $P = 0.124$). Concerning insulin therapy, Table 4 points out that 28 (56.0%) diabetic patients received < 3 insulin injections/day (conventional or non-intensive treatment), whereas 22 (44.0%) received ≥ 3 insulin injections/day (intensive

Table 3 Status of menstrual cycle and apparent symptoms among the study population

Variable	Non-diabetic controls (No. = 50)	Diabetic patients (No. = 50)	Test		*P*-value
Age at menarche (years)					
Mean ± SD	13.2 ± 1.2	13.9 ± 1.6	*t*	2.368	0.020
Range (min–max)	11–16	11–18			
Oligomenorrhea, No. (%)					
Yes	9 (18.0)	17 (34.0)	χ^2	3.326	0.068
No	41 (82.0)	33 (66.0)			
Acanthosis nigricans, No. (%)					
Yes	0 (0.0)	6 (12.0)	χ^2	4.433	0.035*
No	50 (100)	44 (88.0)			
Seborrhea, No. (%)					
Yes	2 (4.0)	10 (20.0)	χ^2	4.640	0.031*
No	48 (96.0)	40 (80.0)			
Hirsutism, No. (%)					
Yes	3 (6.0)	9 (18.0)	χ^2	2.367	0.124*
No	47 (94.0)	41 (82.0)			

No. number, *SD* standard deviation; **P*-value of $\chi^2_{(corrected)}$ test, $P < 0.05$: significant, $P > 0.05$: not significant

Table 2 Anthropometric measurements of the study population

Anthropometric parameter	Non-diabetic controls (No. = 50)	Diabetic patients (No. = 50)	Test		*P*-value
BMI					
Mean ± SD	25.1 ± 4.9	26.1 ± 4.5	*T*	0.973	0.333
Range (min–max)	16–37	18–36			
Waist-to-hip ratio					
Mean ± SD)	78.8 ± 5.7	81.9 ± 7.9	*T*	2.033	0.045
Range (min–max)	67–95	70–113			
Android body type, No. (%)					
Yes	5 (10.0)	10 (20.0)	χ^2	1.961	0.161
No	45 (90.0)	40 (80.0)			

BMI body mass index; people with BMI = 18.5–24.9 were considered to have normal weight and people with BMI = 25.0–29.9 were considered overweight (WHO, 2014), Android body type: Apple shape; *No.* number, *SD* standard deviation; $P < 0.05$: significant, $P > 0.05$: not significant

Table 4 Insulin therapy among diabetic patients

Treatment	Diabetic patients (No. = 50)
Insulin injection frequency/day No. (%)	
< 3	28 (56.0)
≥ 3	22 (44.0)
Dose (UI.cc/ml/day)	
Mean ± SD	57.8 ± 22.9
Range (min–max)	17–130
Other treatment No. (%)	
Yes	6 (12.0)
No	44 (88.0)

Insulin injection frequency/day: < 3: conventional or non-intensive treatment, ≥ 3: intensive treatment, other treatment included glucophage; *No.*, number; *SD*, standard deviation

treatment). The mean insulin dose/day was 57.8 ± 22.9 UI.cc/ml, with a range of 17–130 UI.cc/ml.

Hormonal levels of the study population

The mean levels of hormones in both diabetic and non-diabetic women are presented in Table 5. The total testosterone and insulin hormones were significantly higher in diabetic women with respect to non-diabetic women (0.58 ± 0.11 ng/ml and 15.8 ± 12.4 mlU/ml vs. 0.44 ± 0.11 ng/ml and 10.8 ± 4.5 mlU/ml, $P < 0.001$ and $P = 0.010$, respectively). On the other hand, FSH and LH levels showed no significant differences between diabetic and non-diabetic groups.

Distribution of PCOS, and clinical and biochemical features of diabetic women with and without PCOS

Table 6 shows that PCOS was present in 11 (22.0%) out of 50 diabetic women compared to 3 (6.0%) in non-diabetics ($\chi^2_{(corrected)} = 4.070$, $P = 0.044$). Clinical and biochemical features of diabetic women with and without PCOS are compared in Table 7. A significantly higher insulin dose was received by PCOS women than non-PCOS women (72.7 ± 23.9 vs. 55.0 ± 19.8 UI.cc/ml/day, $P = 0.023$). Oligomenorrhea was found in all PCOS women in 11 (100%) compared to 6 (15.4%) of non-PCOS women ($\chi^2_{(corrected)} = 23.735$, $P < 0.001$). Testosterone and insulin levels were significantly higher in women with PCOS compared to their counterparts without PCOS (0.64 ± 0.09 and 23.1 ± 13.0 vs. 0.53 ± 0.11 and 14.1 ± 11.8, $P = 0.023$ and 0.041, respectively).

Relation of insulin therapy with PCOS and apparent symptoms in diabetic women

In Table 8, a significant increase has been observed in PCOS frequency among women receiving intensive insulin therapy (9 out of 22 "40.9%") compared to 2

Table 5 Hormonal levels of the study population

Hormone	Non-diabetic controls (No. = 50)	Diabetic patients (No. = 50)	% difference	*t*	*P*-value
T testosterone (ng/ml)	0.44 ± 0.11	0.58 ± 0.11	26.3	6.112	< 0.001
Range (min–max)	0.2–0.7	0.39–0.80			
FSH (mlU/ml)	5.6 ± 1.9	6.6 ± 4.3	18.0	1.512	0.135
Range (min–max)	2.1–12.7	0.1–18.7			
LH (mlU/ml)	6.1 ± 2.9	6.9 ± 5.1	12.3	1.070	0.288
Range (min–max)	0.7–13.7	0.3–25.1			
Insulin (mlU/ml)	10.8 ± 4.5	15.8 ± 12.4	37.6	2.667	0.010
Range (min–max)	4.9–24.8	2.2–59.2			

T testosterone total testosterone, *FSH* follicle stimulating hormone, *LH* luteinizing hormone, *No.* number; all values are presented as mean ± SD; $P < 0.05$: significant, $P > 0.05$: not significant

Table 6 Distribution of polycystic ovary syndrome (PCOS) among the study population

PCOS	Non-diabetic controls (No. = 50)		Diabetic patients (No. = 50)		χ^2	*P*-value
	No.	%	No.	%		
Have PCOS (oligomenorrhea + hyperandrogenism)	3	6	11	22	4.070	0.044
Have no PCOS	47	94	39	78		

No. number; *P*-value of $\chi^2_{(corrected)}$ test, $P < 0.05$: significant

Table 7 Clinical and biochemical features of diabetic women with and without polycystic ovary syndrome (PCOS)

Variable	With PCOS (No. = 11)	Without PCOS (No. = 39)	Test		*P*-value
Waist-to-hip ratio					
Mean ± SD	84.0 ± 5.6	80.3 ± 5.4	*t*	1.736	0.091
Insulin dose (UI.cc/ml/day)					
Mean ± SD	72.7 ± 23.9	55.0 ± 19.8	*t*	2.350	0.023
Age at menarche (years)					
Mean ± SD	14.5 ± 1.9	13.6 ± 1.2	*t*	1.631	0.110
Oligomenorrhea, No. (%)					
Yes	11 (100)	6 (15.4)	χ^2	23.735	< 0.001*
No	0 (0.0)	33 (84.6)			
T testosterone (ng/ml)					
Mean ± SD	0.64 ± 0.09	0.53 ± 0.11	*t*	2.350	0.023
Insulin (mIU/ml)					
Mean ± SD	23.1 ± 13.0	14.1 ± 11.8	t	2.104	0.041

No. number; **P*-value of $\chi^2_{(corrected)}$ test, $P < 0.05$: significant, $P > 0.05$: not significant

Table 8 Relation of insulin therapy with polycystic ovary syndrome (PCOS) and apparent symptoms in diabetic patients

Variable	Non-intensive insulin therapy (No. = 28)	Intensive insulin therapy (No. = 22)	χ^2	*P*-value
Have PCOS, No. (%)				
Have	2 (7.1)	9 (40.9)	6.336	0.012
Have not	26 (92.9)	13 (59.1)		
Acanthosis nigricans, No. (%)				
Yes	2 (7.1)	4 (18.2)	0.568	0.451
No	26 (92.9)	18 (81.8)		
Seborrhea, No. (%)				
Yes	3 (10.7)	7 (31.8)	2.237	0.135
No	25 (89.3)	15 (68.2)		
Hirsutism, No. (%)				
Yes	2 (7.1)	6 (27.3)	2.368	0.124
No	26 (92.9)	16 (72.7)		

Non-intensive insulin treatment: < 3 insulin injections/day, intensive insulin treatment: ≥ 3 insulin injections/day; *No.*, number; *P*-value of $\chi^2_{(corrected)}$ test, $P < 0.05$: significant, $P > 0.05$: not significant

out of 28 (7.1%) women receiving non-intensive insulin therapy ($\chi^2_{(corrected)} = 6.336$, $P = 0.012$). Although acanthosis nigricans, seborrhea, and hirsutism were more prevalent among diabetic women receiving intensive insulin therapy, no significant differences were achieved between the two groups ($P > 0.05$).

Discussion

PCOS is the most common gynecological endocrinopathy. Despite the heavy burden and impact of PCOS on reproduction and public health, there are underdiagnosis and underreporting of the disease in the Palestinian Territories. Very few studies have targeted the prevalence and characteristics of metabolic syndrome in Palestinian women with PCOS [20]. However, to the best of our knowledge, there has been no previous study investigating PCOS in type 1 diabetic Palestinian women. The present study is a retrospective cohort design comprised of 50 type 1 diabetic women aged 23.3 ± 5.7 years and 50 healthy women aged 23.8 ± 5.2 years who served as controls. The mean period of first delivery after marriage was significantly longer in diabetic women compared to non-diabetics. This result coincides with previous studies reporting that type 1 diabetic women had higher levels of sexual dysfunction and distress compared with healthy control subjects [30, 31]. The negative impact of type 1 diabetes on pregnancy, particularly in women with poor glycemic control, was also documented [32, 33]. An analysis of the educational status indicated that type 1 diabetes is more prevalent among the less educated women. The incidence of type 1 diabetic complications was reported to be two to three times greater for type 1 diabetic individuals without a college degree compared to those with a college degree [34]. Type 1 diabetes was also found to be more frequent among unemployed women and women with a family history of the disease. Researchers provided evidence that diabetes affects patients, employers, and society not only by reducing employment but also by contributing to work loss and health-related work limitations for those who remain employed [35, 36]. Family history of type 1 diabetes not only contributes to the higher frequency of the disease but also is extended in children [37, 38].

In the present study, neither BMI nor body type showed a significant difference between diabetic and non-diabetic females. However, the waist-to-hip ratio was significantly higher in diabetics. This result is supported by the finding that the waist-to-hip ratio decreased during puberty in normal control girls but not in type 1 diabetic girls [39]. The waist-to-hip ratio was addressed as a predictor of incident diabetes in young adults [40].

The status of the menstrual cycle showed that diabetic females had a later onset of menarche and a more frequent oligomenorrhea than non-diabetics. Similar results were obtained by other authors [41, 42]. The concept that the younger the age at onset of diabetes, the higher the age at menarche coincides with our result that around half of patients had diabetes for more than 7 years [43]. The apparent symptoms of acanthosis nigricans, seborrhea, and hirsutism were more prevalent in diabetic

females compared to non-diabetics. Such symptoms were reported among women with type 1 diabetes [44, 45]. Intensive insulin therapy in type 1 diabetic women stimulates granulosa, theca, and stromal ovarian cells, leading to ovarian hyperandrogenism which is believed to increase the incidence of menstrual disturbance as well as the prevalence of acanthosis nigricans, seborrhea, and hirsutism; the main clinical manifestations of PCOS [46, 47]. This hypothesis is supported, in part, by the present result that 44.0% of diabetic women had received intensive insulin treatment. In this context, a high frequency of hyperandrogenism and PCOS in type 1 diabetic women was reviewed and found to be associated with intensive insulin treatment [48].

The tested hormones showed higher levels in diabetic women than in non-diabetic controls. However, this change was significant for total testosterone and insulin. These results are in agreement with those discussed by other researchers, who suggested that the ovary is more likely to be the main source of androgen excess in hyperandrogenic type 1 diabetic patients [49, 50]. Hyperinsulinemia derived from the supraphysiological doses of exogenous insulin needed to achieve adequate glycemic control in diabetic women confirms the idea that hyperinsulinism may facilitate LH-mediated androgen synthesis in the ovary [49].

PCOS was significantly more frequent among diabetic women compared to non-diabetic controls. Systematic reviews and meta-analyses showed that PCOS and its related traits are frequent findings in women with type 1 diabetes; approximately one in every four type 1 diabetic women has PCOS [16, 51]. The prevalence of PCOS in our population sample of women with type 1 diabetes was 22.0%, which is around to that reported by Spanish and Egyptian Scientists (24.0% and 28.0%, respectively) [4, 52], but lower than that mentioned by French authors (47.9%) [53]. This variation may be attributed to the use of different diagnostic criteria for PCOS and multiple genetic and environmental factors that may play an important role in the occurrence of PCOS. Additionally, the relatively small sample size used in this study may constitute a limitation. However, global research linking PCOS and type 1 diabetes is limited, and this is the first study to investigate PCOS in type 1 diabetic Palestinian women.

Clinical and biochemical features of diabetic women with PCOS showed a higher mean waist-to-hip ratio than diabetic women without PCOS. A significantly higher insulin dose was received by PCOS women. The age at menarche was delayed, and a significantly more frequent oligomenorrhea was found in PCOS women. The waist-to-hip ratio was addressed as an anatomical predictive marker of the risk of PCOS [54]. It is also accepted that the age at menarche is experienced later in type 1 diabetic women with PCOS [3]. Oligomenorrhea is also one of the essential diagnostic criteria for PCOS [55]. Therefore, it is not surprising to find a significantly higher frequency of oligomenorrhea in women with PCOS. Oligomenorrhea may be attributed in part to ovarian hyperandrogenemia resulting from higher doses of exogenous insulin received by PCOS women with the aim of metabolic control and preventing the long-term complications of maintained hyperglycemia. The higher levels of insulin and testosterone registered in PCOS women in the present study support this scenario. Hyperinsulinemia and hyperandrogenemia in PCOS women have been reported elsewhere in the literature [3, 51]. However, hormonal interplay in diabetic women with PCOS needs further investigation.

When related to insulin therapy, PCOS cases were significantly more frequent in diabetic women receiving intensive insulin therapy than their counterparts with non-intensive insulin therapy. Such a result is in line with that previously reported in adolescents [56]. Type 1 diabetic patients frequently treated with intensive insulin therapy usually develop supraphysiological insulin levels in the systemic circulation, which could potentially facilitate ovarian androgen synthesis and make them more likely to display PCOS-related symptoms. Again, such frequent insulin therapy-PCOS interaction reinforces the previous scenario and may explain the higher frequency of PCOS apparent symptoms among diabetic women receiving intensive insulin therapy. Finally, one can say that hyperandrogenism is the backbone of the development of PCOS and its related features in type 1 diabetic females treated with frequent insulin therapy.

Conclusions

Type 1 diabetic women showed a longer period of first delivery after marriage than non-diabetic controls. Type 1 diabetes was more prevalent among the less educated, the unemployed, and women with a family history of the disease. The waist-to-hip ratio and mean age at menarche were higher in diabetics. Oligomenorrhea, acanthosis nigricans, seborrhea, and hirsutism were more frequent in diabetics. The levels of total testosterone and insulin were higher in diabetics. Polycystic ovary syndrome was significantly more frequent among diabetic women compared to non-diabetic controls. Diabetic women with PCOS received higher doses of insulin than non-PCOS women. PCOS women showed more frequent oligomenorrhea and higher levels of testosterone and insulin. PCOS cases were significantly more frequent in diabetic women receiving intensive insulin therapy than their counterparts with non-intensive insulin therapy.

Abbreviations

PCOS	Polycystic ovary syndrome
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
NIH	National Institute of Health
BMI	Body mass index
ELISA	Enzyme-linked immunosorbent assay

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Authors' contributions
Maged M. Yassin performed the main effort in the data curation, methodology, and writing of the original draft. Mohammed Laqqan and Saleh Mwafy provided support in the methodology, review of the manuscript, and editing. Sana EL-Qreenawy performed the main effort in the sample collection and biochemical analysis.

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Availability of data and materials
The authors do not have the right to share any data information as per their institution's policies.

Declarations

Ethics approval and consent to participate
This study was approved by the Palestinian Health Research Council (Reference Number PHRC/HC/258/13), and the approval required was provided according to the Helsinki Declaration and approval letters signed by the institutional review board and the Palestinian Ministry of Health. Besides that, written informed consent was freely signed by each participant prior to inclusion in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. Wise J (2015) Type 1 diabetes still shortens life span Scottish study finds. BMJ 7:350
2. Rodrigues Oliveira SM, Rebocho A, Ahmadpour E, Nissapatorn V, de Lourdes PM (2023) Type 1 diabetes mellitus: a review on advances and challenges in creating insulin producing devices. Micromachines 14(1):151
3. Zachurzok A, Deja G, Gawlik A, Drosdzol-Cop A, Małecka-Tendera E (2013) Hyperandrogenism in adolescent girls with type 1 diabetes mellitus treated with intensive and continuous subcutaneous insulin therapy. Endokrynol Pol 64(2):121–128
4. Escobar-Morreale HF, Roldán-Martín MB (2016) Type 1 diabetes and polycystic ovary syndrome: systematic review and meta-analysis. Diabetes Care 39(4):639–648
5. Codner E, Escobar-Morreale HF (2007) Hyperandrogenism and polycystic ovary syndrome in women with type 1 diabetes mellitus. J Clin Endocrinol Metab 92(4):1209–1216
6. Yildiz BO, Bozdag G, Yapici Z, Esinler I, Yarali H (2012) Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. Hum Reprod 27(10):3067–3073
7. Conway G, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Franks S, Gambineri A, Kelestimur F, Macut D, Micic D, Pasquali R, Pfeifer M (2014) The polycystic ovary syndrome: a position statement from the European Society of Endocrinology. Eur J Endocrinol 171(4):1–29
8. Ndefo UA, Eaton A, Green MR (2013) Polycystic ovary syndrome: a review of treatment options with a focus on pharmacological approaches. Pharmacy Therapeut 38(6):336
9. Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM (2014) Pharmacotherapy: a pathophysiologic approach, ed. Connecticut: Appleton Lange 4:141–2
10. Livadas S, Diamanti-Kandarakis E (2013) Polycystic ovary syndrome: definitions, phenotypes and diagnostic approach. Polycyst Ovary Syndr 40:1–21
11. Ramanand SJ, Ghongane BB, Ramanand JB, Patwardhan MH, Ghanghas RR, Jain SS (2013) Clinical characteristics of polycystic ovary syndrome in Indian women. Indian J Endocrinol Metab 17(1):138
12. Zandi S, Farajzadeh S, Safari H (2010) Prevalence of polycystic ovary syndrome in women with acne: hormone profiles and clinical findings. J Pak Assoc Dermatol 20(4):194–198
13. Yasmin A, Roychoudhury S, Paul Choudhury A, Ahmed AF, Dutta S, Mottola F, Verma V, Kalita JC, Kumar D, Sengupta P, Kolesarova A (2022) Polycystic ovary syndrome: an updated overview foregrounding impacts of ethnicities and geographic variations. Life 12(12):1974.
14. Smet ME, McLennan A (2018) Rotterdam criteria, the end. Australas J Ultrasound Med 21(2):59–60
15. Cussen L, McDonnell T, Bennett G, Thompson CJ, Sherlock M, O'Reilly MW (2022) Approach to androgen excess in women: Clinical and biochemical insights. Clin Endocrinol 97(2):174–186
16. World Health Organization (2006) Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation
17. Dean AG, Arner TG, Sunki GG, Friedman R, Lantinga M, Sangam S, Zubieta JC, Sullivan KM, Brendel KA, Gao Z, Fontaine N (2011) Epi Info™, a database and statistics program for public health professionals. CDC, Atlanta, GA,USA. 2011;1
18. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 19(1):41–47
19. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE, Witchel SF (2006) Androgen Excess Society. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J Clin Endocrinol Metab 91(11):4237–45
20. Mousa WM (2009) Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome in Gaza Strip. M.Sc. Thesis, The Islamic University of Gaza, Gaza Strip, Palestinian Territories
21. Backestrom C, Hursh-Cesar G (2012) Survey research. Literary Licensing, LLC, Pennsylvania
22. World Health Organization (2014) Ten facts on obesity. Available on: http://www.who.int/features/factfiles/obesity/en/
23. Codner E, Soto N, Lopez P, Trejo L, Ávila A, Eyzaguirre FC, Íniguez G, Cassorla F (2006) Diagnostic criteria for polycystic ovary syndrome and ovarian morphology in women with type 1 diabetes mellitus. J Clin Endocrinol Metab 91(6):2250–2256
24. Diamanti-Kandarakis E, Dunaif A (2012) Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev 33(6):981–1030
25. Hatch R, Rosenfield RL, Kim MH, Tredway D (1981) Hirsutism: implications, etiology, and management. Am J Obstet Gynecol 140(7):815–830
26. Tietz NW, Andresen BD (1986) Textbook of clinical chemistry. WB Saunders Company, Philadelphia
27. Vitt UA, Kloosterboer HJ, Rose UM, Bete S, Nayudu PL (1998) Human follicle-stimulating hormone isoform fractions differentially affect both

the development of in vitro grown ovarian follicles and the subsequent maturation capacity of the oocytes. Biol Reprod 58(1):209
28. Lenton EA, Sulaiman R, Sobowale O, Cooke ID (1982) The human menstrual cycle: plasma concentrations of prolactin, LH, FSH, oestradiol and progesterone in conceiving and non-conceiving women. Reproduction 65(1):131–139
29. Engvall E (1980) Methods in Enzymology, Volume 70, VanVanukis, H. and Langone, JJ. (eds.), Academic Press, New York, p 419
30. Salonia A, Lanzi R, Scavini M, Pontillo M, Gatti E, Petrella G, Licata G, Nappi RE, Bosi E, Briganti A, Rigatti P (2006) Sexual function and endocrine profile in fertile women with type 1 diabetes. Diabetes Care 29(2):312–316
31. Zamponi V, Mazzilli R, Bitterman O, Olana S, Iorio C, Festa C, Giuliani C, Mazzilli F, Napoli A (2020) Association between type 1 diabetes and female sexual dysfunction. BMC Womens Health 20(1):1–7
32. Vargas R, Repke JT, Ural SH (2010) Type 1 diabetes mellitus and pregnancy. Rev Obstet Gynecol 3(3):92–100
33. Negrato CA, Mattar R, Gomes MB (2012) Adverse pregnancy outcomes in women with diabetes. Diabetol Metab Syndr 4(1):1–6
34. Secrest AM, Costacou T, Gutelius B, Miller RG, Songer TJ, Orchard TJ (2011) Associations between socioeconomic status and major complications in type 1 diabetes: the Pittsburgh epidemiology of diabetes complication (EDC) Study. Ann Epidemiol 21(5):374–381
35. Tunceli K, Bradley CJ, Nerenz D, Williams LK, Pladevall M, Elston Lafata J (2005) The impact of diabetes on employment and work productivity. Diabetes Care 28(11):2662–2667
36. Minor T (2013) An investigation into the effect of type I and type II diabetes duration on employment and wages. Econ Hum Biol 11(4):534–544
37. Yassin M, Alghora S, Elhamalawi IM, Yasin M (2020) Vitamin D and its relation to metabolic profile in type 1 diabetic patients from Gaza Strip. Integr Food Nutr Metab 7(3):1–7
38. Kuusela S, Keskinen P, Pokka T, Knip M, Ilonen J, Vähäsalo P, Veijola R (2020) Extended family history of type 1 diabetes in HLA-predisposed children with and without islet autoantibodies. Pediatr Diabetes 21(8):1447–1456
39. Codner E, Barrera A, Mook-Kanamori D, Bazaes RA, Unanue N, Gaete X, Avila A, Ugarte F, Torrealba I, Pérez V, Panteón E (2004) Ponderal gain, waist-to-hip ratio, and pubertal development in girls with type-1 diabetes mellitus. Pediatr Diabetes 5(4):182–189
40. Paras AP, Chanchal S (2022) Waist circumference and waist hip ratio as predictor of incident diabetes in young adults: A cross-sectional study. MedPulse Int J Physiol 21(1):05–08
41. Schweiger BM, Snell-Bergeon JK, Roman R, McFann K, Klingensmith GJ (2011) Menarche delay and menstrual irregularities persist in adolescents with type 1 diabetes. Reprod Biol Endocrinol 9:1–8
42. Nishikawa-Nakamura N, Kawamura T, Nakamichi T, Yuyama Y, Hotta Y, Hashimura K, Hashimoto T, Hirose M, Higashide T, Hamazaki T (2022) Age at menarche in Japanese patients with type 1 diabetes mellitus: a look at changes since 1960s. Endocr J 69(6):627–633
43. Harjutsalo V, Maric-Bilkan C, Forsblom C, Groop PH, FinnDiane Study Group (2016) Age at menarche and the risk of diabetic microvascular complications in patients with type 1 diabetes. Diabetologia 59:472–480
44. Calcaterra V, De Silvestri A, Schneider L, Acunzo M, Vittoni V, Meraviglia G, Bergamaschi F, Zuccotti G, Mameli C (2021) Acanthosis nigricans in children and adolescents with type 1 diabetes or obesity: The potential interplay role between insulin resistance and excess weight. Children 8(8):710
45. Güven M, Anık A, Ünüvar T, Şendur N (2021) Cutaneous manifestations in children patients with type 1 diabetes mellitus. Turkderm-Turk Arch Dermatol Venereol 55:22–26
46. Lentscher JA, Decherney AH (2021) Clinical presentation and diagnosis of polycystic ovarian syndrome. Clin Obstet Gynecol 64(1):3–11
47. Fahs D, Salloum D, Nasrallah M, Ghazeeri G (2023) Polycystic Ovary Syndrome: pathophysiology and controversies in diagnosis. Diagnostics 13(9):1559
48. Tibuni-Sanders S, Nader S (2012) PCOS and hyperandrogenism in type 1 diabetes. Open J Obstet Gynecol 2(1):76-80
49. Bizzarri C, Benevento D, Ravà L, Patera IP, Schiaffini R, Ciampalini P, Giannone G, Cappa M (2011) Ovarian hyperandrogenism in adolescents and young women with type I diabetes is primarily related to birth weight and body mass index. Fertil Steril 96(6):1497–1502
50. Coons A, Shubrook JH (2021) The interaction between the female reproductive system and type 1 diabetes. Ann Infertil Reprod Endocrinol 4(1):1026
51. Bayona A, Martínez-Vaello V, Zamora J, Nattero-Chávez L, Luque-Ramírez M, Escobar-Morreale HF (2022) Prevalence of PCOS and related hyperandrogenic traits in premenopausal women with type 1 diabetes: a systematic review and meta-analysis. Hum Reprod Update 28(4):501–517
52. Abd Elmonem DH, Hammad FK, Ghanem AI, Aly EM (2022) Prevalence, phenotypic distribution, and clinical characteristics of polycystic ovary syndrome in Egyptian women with type 1 diabetes mellitus. J Med Sci Res 5(1):51
53. Busiah K, Colmenares A, Bidet M, Tubiana-Rufi N, Levy-Marchal C, Delcroix C, Jacquin P, Martin D, Benadjaoud L, Jacqz-Aigrain E, Laborde K (2017) High prevalence of polycystic ovary syndrome in type 1 diabetes mellitus adolescents: is there a difference depending on the NIH and Rotterdam criteria? Hormone Res Paediatr 87(5):333–341
54. Yadav S, Tarware R (2019) Waist hip ratio: an anatomical predictive marker of risk of PCOS. Int J Reprod Contracept Obstet Gynecol 8(4):1630–1633
55. Villarroel C, López P, Merino PM, Iñiguez G, Sir-Petermann T, Codner E (2015) Hirsutism and oligomenorrhea are appropriate screening criteria for polycystic ovary syndrome in adolescents. Gynecol Endocrinol 31(8):625–629
56. Bernier A, Fung J, Ergun-Longmire B (2022) A narrative review: polycystic ovary syndrome (PCOS) and type 1 diabetes (T1D). Pediatr Med 5:1–7

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