0021-972X/07/$15.00/0
*Printed in U.S.A.*

The Journal of Clinical Endocrinology & Metabolism 92(4):1209–1216

doi: 10.1210/jc.2006-2641

# CLINICAL REVIEW: Hyperandrogenism and Polycystic Ovary Syndrome in Women with Type 1 Diabetes Mellitus

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**Context:** At present, women with type 1 diabetes (DM1) are being treated with supraphysiological doses of exogenous insulin with the aim of providing a strict metabolic control, thereby avoiding the long-term complications of this disease. We hypothesized that PCOS would be especially prevalent in DM1, as might happen in any condition in which the ovary and the adrenals are exposed to excessive insulin concentrations. As will be seen in the present review, androgen excess and PCOS are very frequent complaints in women with DM1, yet nowadays hyperandrogenism is seldom diagnosed in these patients.

**Evidence Acquisition:** We conducted a systematic review of all the published studies addressing hyperandrogenic symptoms in women with DM1, identified through the Entrez-PubMed search engine, followed by a comprehensive review of the pathophysiology and clinical and laboratory features of PCOS in women with DM1.

**Evidence Synthesis:** The prevalence of PCOS in adult women with DM1 is 12–18, 40, and 31% using National Institute for Child Health and Human Development, Rotterdam, and Androgen Excess Society criteria, respectively. Mild hirsutism and biochemical hyperandrogenism are present in 30 and 20% of the patients, respectively. In addition, menstrual abnormalities are observed in 20% of adult women with DM1, and a prevalence of 50% of polycystic ovarian morphology is reported.

**Conclusions:** Physicians treating women with DM1 should be aware of the risk of hyperandrogenism in them and should include evaluation of hirsutism, menstrual abnormalities, and biochemical hyperandrogenism in their routine examinations. Future studies are needed to determine the best preventive and therapeutic options for the hyperandrogenism of these patients. **(*J Clin Endocrinol Metab* 92: 1209–1216, 2007)**

POLYCYSTIC OVARY SYNDROME (PCOS) is the most common endocrine disorder in premenopausal women, with a 6–7% prevalence worldwide. PCOS is a heterogeneous disorder characterized by chronic ovulatory dysfunction and hyperandrogenism (1–3). Androgen excess is the central defect in PCOS patients (3), yet it is triggered by other factors, obesity and insulin resistance being frequently involved (2).

Because the hyperinsulinemia resulting from insulin resistance stimulates androgen secretion at the adrenal gland and the ovary, the association between PCOS and type 2 diabetes has been recognized for a long time. However, at present, women with type 1 diabetes (DM1) are being treated with supraphysiological doses of exogenous insulin with the aim of providing a strict metabolic control, thereby avoiding the long-term complications of this disease. Accordingly, several years ago, we hypothesized that PCOS would be especially prevalent in DM1, as might happen in any condition in which the ovary and the adrenals are exposed to excessive insulin concentrations. The present review summarizes the results of the two published studies previously reported by the authors that addressed the prevalence of hyperandrogenic disorders in women with DM1—no other original studies on the issue were identified through the Entrez-PubMed search engine—as well as several other manuscripts that provided insight into the mechanisms explaining this association. The description of these studies is followed by a comprehensive review of the pathophysiology and clinical and laboratory features of PCOS in women with DM1. As will be seen, androgen excess and PCOS are very frequent complaints in women with DM1, yet nowadays hyperandrogenism is seldom diagnosed in these patients.

**First Published Online February 6, 2007**

Abbreviations: AES: Androgen Excess Society; DHEAS, dehydroepiandrosterone sulfate; DM1, type 1 diabetes mellitus; GnRH-a, GnRH agonist; PCOS, polycystic ovary syndrome.

**JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**

## Diagnostic Criteria for PCOS (Table 1)

The definition of PCOS has been matter of intense debate since its recognition 70 yr ago. During the past two decades, the syndromic nature of the disorder has been widely recognized along with the need of using diagnostic criteria both for clinical and research purposes. Especially important was the establishment of research criteria derived from the National Institute for Child Health and Human Development (NICHD) 1990 conference (1).

Most researchers attending this conference agreed that a diagnosis of PCOS could be sustained when a woman presented with clinical and/or biochemical hyperandrogenism in association with menstrual dysfunction, provided that a specific etiology was ruled out (1).

The NICHD criteria were rapidly adopted by researchers and clinicians in the United States and some European coun-

**TABLE 1.** Diagnostic criteria for PCOS according to different published definitions

| Definition/ year (Ref.) | Diagnostic criteria | Possible phenotypes | Exclusion criteria | Clinical hyperandrogenism | Biochemical hyperandrogenism | PCOM (PCOS) |
|---|---|---|---|---|---|---|
| NICHD/ 1990 (1) | Requires the simultaneous presence of 1) clinical and/or biochemical hyperandrogenism and 2) menstrual dysfunction | Clinical and/or biochemical hyperandrogenism plus menstrual dysfunction | Congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, and hyperprolactinemia | Hirsutism, alopecia, and acne | 1) Total testosterone, 2) free testosterone, 3) androstenedione, and 4) DHEAS | Not included |
| Rotterdam/ 2003 (2) | Requires the presence of at least two criteria: 1) clinical and/or biochemical hyperandrogenism, 2) ovulatory dysfunction, and 3) PCOM | 1) Clinical and/or biochemical hyperandrogenism plus ovulatory dysfunction; 2) clinical and/or biochemical hyperandrogenism plus ovulatory dysfunction plus PCOM; 3) clinical and/or biochemical hyperandrogenism plus PCOM; 4) PCOM plus ovulatory dysfunction | Congenital adrenal hyperplasia, androgen-secreting tumors, and Cushing's syndrome | Hirsutism, acne, and androgenic alopecia? | 1) Free androgen index or free testosterone, 2) total testosterone, and 3) DHEAS | At least one ovary showing either: 1) 12 or more follicles (2–9 mm in diameter) or 2) ovarian volume > 10 ml |
| AAES/2006 (3) | Requires the presence of hyperandrogenism, clinical or biochemical, and either 1) oligo-anovulation or 2) PCOM | 1) Clinical and/or biochemical hyperandrogenism plus oligo-anovulation; 2) clinical and/ or biochemical hyperandrogenism plus oligo-anovulation plus PCOM; 3) clinical and/or biochemical hyperandrogenism plus PCOM | Congenital adrenal hyperplasia, androgen-secreting neoplasms, androgenic/anabolic drug use or abuse, Cushing's syndrome, syndromes of severe insulin resistance, thyroid dysfunction, and hyperprolactinemia | Hirsutism | 1) Free androgen index or free testosterone, 2) total testosterone, 3) DHEAS, and 4) androstenedione | At least one ovary showing either 1) 12 or more follicles (2–9 mm in diameter) or 2) ovarian volume > 10 ml |

PCOM, Polycystic ovarian morphology.

tries, but because ovarian morphology was not considered for PCOS diagnosis, these criteria were seldom used by researchers from Commonwealth and Northern European countries.

In 2003, the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine organized a consensus workshop that was held in Rotterdam, The Netherlands. The resulting definition requires the presence of two of the three following criteria: clinical and/or biochemical hyperandrogenism, chronic oligoovulation, and polycystic ovaries in ultrasound (2). Of note, the latter requires the presence of an ovarian volume above 10 ml or the presence of 12 or more follicles of 2–9 mm diameter in at least one ovary (2).

It should be highlighted that Rotterdam criteria include those patients diagnosed by NICHD criteria but add two new phenotypes: hyperandrogenism with polycystic ovarian morphology and oligoovulation with polycystic ovarian morphology but with no evidence for clinical or biochemical hyperandrogenism (2).

The issue of whether or not a diagnosis of PCOS could be sustained in women with no evidence of hyperandrogenism again raised an intense debate among certain researchers from both sides of the Atlantic ocean (4, 5). Considering also that both the conclusions of NICHD and Rotterdam conferences were authority-based definitions and resulted from the views and opinions of those researchers invited to participate, the Androgen Excess Society (AES; http://www.androgenexcesssociety.org) recently charged a Task Force to review all available data and recommend an evidence-based definition for PCOS, whether already in use or not, to guide clinical diagnosis and future research (3).

A systematic review of the published peer-reviewed medical literature was conducted, by querying MEDLINE databases, to identify studies evaluating the epidemiology or phenotypic aspects of PCOS. The initial Task Force report was followed by a consensus process in which minority opinions were noted. The 2006 AES evidence-based definition sustains a diagnosis of PCOS in the presence of clinical and/or biochemical hyperandrogenism in association with either oligoovulation and/or polycystic ovarian morphology (3). Essentially, these criteria are those of the Rotterdam definition, yet the phenotype consisting of oligoovulation and polycystic ovarian morphology was not included, because only a minority considered the possibility that there may be forms of PCOS without overt evidence of hyperandrogenism and recognized that more data are required before validating this supposition.

## Pathophysiology of PCOS: The Role of Insulin Resistance and Hyperinsulinism

### *Androgen excess is the central defect in PCOS*

As stated above, the most recent views consider PCOS as a disorder of androgen excess or hyperandrogenism (3).

An abnormal steroidogenic activity has been observed in the gonads of PCOS patients, resulting in elevated androgen levels in the ovary that, by contributing to arrested follicle maturation, collaborates in the development of anovulation (6). Ovarian theca cells obtained from PCOS women main-

tained increased steroidogenic activity *in vitro* compared with those of controls secreting greater amounts of androgens, even after these cells are propagated in culture several times, thereby ruling out an external influence (7). The increased androgen secretion is accompanied by increased activities of the enzymes involved in the synthesis of testosterone, such as 3$\beta$-hydroxysteroid dehydrogenase, CYP17, and CYP11A (7).

Furthermore, adrenal hyperandrogenism is also common in PCOS patients, yet because adrenal tissue cannot be obtained for research purposes because of the risk of serious complications, the contribution of the adrenals to the androgen excess of PCOS has not been confirmed at the molecular level (7).

### *The role of insulin resistance and hyperinsulinism as triggers of the primary defect*

Even if the primary defect in PCOS is exaggerated androgen synthesis and secretion, hyperinsulinemia, either of endogenous or exogenous origin, is a well-known triggering factor.

*Effects of insulin on steroidogenesis. In vitro* studies have shown that insulin acts synergistically with LH to stimulate the synthesis of testosterone by ovarian theca cells (8). This effect of insulin involves the binding of insulin to insulin, IGF-I, and hybrid receptors in the ovary (8) and also the up-regulation of type 1 IGF receptors, reduction of IGF-binding protein-1, and activation of the IGF-I system (9).

This way insulin may act in concert with gonadotropins on the ovary, enhancing ovarian LH-induced androgen synthesis and secretion (8). In addition, hyperinsulinemia may stimulate the development of antral follicles, increasing the sensitivity of granulosa cells to FSH, thus increasing the number and growth of follicular cysts and the ovarian volume in animals and humans (10–12). A similar mechanism of insulin facilitation of the ACTH-stimulated adrenal androgen secretion has been proposed to underlie the adrenal androgen excess frequently found in PCOS patients (8).

*Endogenous hyperinsulinism.* Because insulin may facilitate androgen synthesis in the ovary and the adrenal gland, it would not be actually unexpected that any clinical situation in which circulating insulin levels are increased is associated with an increased prevalence of functional hyperandrogenism, including PCOS. Many studies have shown a positive correlation between fasting insulin and androgen plasma levels, suggesting that insulin resistance is common in PCOS patients (8). However, the finding of hyperinsulinemia in these patients raised the question of whether hyperandrogenism led to insulin resistance and hyperinsulinemia, or hyperinsulinemia was responsible for hyperandrogenism.

Clinical evidence suggests that elevated insulin levels cause hyperandrogenism, and not the other way, as shown by the decrease in serum androgen levels observed when circulating insulin concentrations are lowered by the administration of insulin-sensitizing drugs (13) or drugs that inhibit insulin secretion such as diazoxide (14) or somatostatin analogs (15).

On the contrary, decreasing serum androgen levels even with extreme measures such as bilateral oophorectomy (16) or administration of GnRH agonists (GnRH-a) (17) has not shown any significant short-term effects on circulating insulin levels. However, androgen excess during fetal life, infancy, and adolescence may favor a predominantly abdominal and visceral deposition of body fat favoring the occurrence, later in life, of insulin resistance and hyperinsulinemia (18). The facilitation of insulin resistance by androgen excess through the induction of abdominal adiposity would close the vicious circle of insulin resistance, hyperinsulinism, and further hyperandrogenism in PCOS patients.

The importance of hyperinsulinemia in the pathogenesis of PCOS is also illustrated by the occurrence of a PCOS-like syndrome in clinical situations characterized by insulin resistance and hyperinsulinemia, such as the syndromes of extreme insulin resistance resulting from mutations in the insulin receptor gene (19) or from autoantibodies against the insulin receptor (20) or in adolescents with congenital portosystemic shunt (21). Moreover, PCOS may also develop in situations in which endogenous hyperinsulinemia develops even in the absence of insulin resistance, including women with insulinoma in whom PCOS resolved after surgical resection of the tumor (22).

*Exogenous hyperinsulinism.* Although the acute administration of insulin during a euglycemic hyperinsulinemic clamp to healthy women does not increase their circulating androgen levels (23), it is possible that chronic administration of supraphysiological insulin doses might stimulate androgen secretion and excess in predisposed women.

At present, patients with DM1 are frequently treated with intensive insulin therapy to achieve a strict metabolic control with the aim of preventing the long-term complications of maintained hyperglycemia. This practice usually requires the administration of supraphysiological doses of insulin delivered through a nonphysiological sc route. This facilitates that the doses of sc insulin needed to reach portal insulin concentrations sufficient to suppress glucose generation at the liver also result in supraphysiological insulin levels in the systemic circulation. These increased insulin levels could theoretically lead to an increased exposure of the ovary to insulin (24), potentially facilitating the androgen synthesis by the ovaries (25).

But in addition to exogenous hyperinsulinism, insulin resistance is also possible in women with DM1 (26) due to decreased glucose uptake by the muscle (26). The insulin resistance observed in DM1 may be related to hyperglycemia, and in such a case it can be reversed by improved metabolic control (27). This phenomenon, termed glucose toxicity, occurs because increased glucose levels lead to insulin resistance in the muscle and adipose tissue by down-regulating glucose transporter-4 receptors, diminishing glucose uptake by target cells (27).

Yet also, insulin resistance might develop during adolescence in girls with DM1 as a result of abnormal fat mass gain during puberty (28) and of the absence of a decrease in the waist-to-hip ratio observed in nondiabetic girls (29). Therefore, both exogenous hyperinsulinism and insulin resistance might collaborate in the development of androgen excess in

predisposed DM1 women and, as will be seen below, may contribute to explain the increased prevalence of hyperandrogenic disorders found in these patients.

## Hyperandrogenism and PCOS in Women with DM1

Traditionally, before the advent of successful insulin treatment, reproductive abnormalities in women with DM1, including arrest of pubertal development, oligoovulation, and infertility, were explained by their poor glycemic control and general health (30).

However, after insulin treatment became widely available, it became apparent that menstrual disturbances were common in DM1 women irrespective of their better or poorer metabolic control (31) and that the increased serum androgen levels found in some of these women could play a role in these abnormalities (32). Nevertheless, only in the past years has certain scientific evidence supporting a role for hyperandrogenism in the reproductive abnormalities of women with DM1 accumulated.

### *Ovarian hyperandrogenism is common in adolescent girls with DM1*

In 1997, Virdis *et al.* (33) reported that ovarian hyperandrogenism, as defined by an exaggerated serum 17-hydroxyprogesterone response to a single dose of a GnRH-a (34), was present in about four of nine adolescent girls with DM1 who reported oligomenorrhea, but in none of seven eumenorrheic DM1 girls. Furthermore, when considered as a group, oligomenorrheic DM1 girls presented with increased serum 17-hydroxyprogesterone levels after stimulation with GnRH-a compared with those observed in an age-matched control group composed of 13 nondiabetic healthy girls (34). A similar response has been recently confirmed in 56 Chilean pubertal girls with DM1, Tanner stages 2–5, who presented with increased 17-hydroxyprogesterone and testosterone responses to leuprolide throughout puberty when compared with a control group of 64 nondiabetic healthy girls matched for age, body mass index, and stage of pubertal development (35).

### *PCOS and hyperandrogenic disorders in DM1*

*Prevalence (Table 2).* Clinical hyperandrogenism is found in approximately 40% of diabetic women (36, 37). The most frequent hyperandrogenic symptom in these women is hirsutism, present in as many as 30% of adult women with DM1 (36, 37). This prevalence is much higher than in the Spanish and Chilean general populations (7.1 and 3.0%, respectively) (38, 39).

The frequencies of other clinical signs of hyperandrogenism, such as moderate or severe acne or alopecia, may be slightly increased, but the studies have lacked the power to definitely demonstrate this fact. However, a tendency toward a greater frequency of acne was observed in DM1 Chilean patients compared with nondiabetic controls (37).

Chronic oligomenorrhea has been reported in approximately 20% of women with DM1 (36, 37, 40, 41), a figure that is considerably higher than the 8% prevalence observed in large populations of nondiabetic women (42). In conceptual agreement, Strotmeyer *et al.* (41) evaluated the length of the menstrual cycle using a questionnaire and reported that 22% of 143 DM1 women had menstrual periods longer than 31 d in duration, a frequency that was higher than that observed in their nondiabetic sisters or in unrelated control women. Menstrual irregularities in women with DM1 are especially prevalent in women younger than 30 yr (41) and may appear in association with other reproductive disorders, including an earlier menopause, delayed menarche, increased number of stillbirths, and fewer pregnancies (29, 41, 43, 44).

The prevalence of PCOS in women with DM1 varies depending on the diagnostic criteria employed and on the ethnicity of the population studied. Using the NICHD criteria, an 18.8% prevalence of PCOS was observed in DM1 women from Spain, a figure that is much higher than the 6.5% prevalence of PCOS observed by the same authors in the Spanish general population (38).

The prevalence of PCOS in Chilean DM1 women was 12% using NICHD criteria (37), yet this figure boosted up to 40.5% when applying Rotterdam criteria, because the combination of hyperandrogenism and polycystic ovarian morphology is especially common in these women (37). Finally, applying the most recent AES criteria, the prevalence of PCOS is 31% in Chilean DM1 women (unpublished data).

*Clinical and hormonal characteristics.* Characteristically, hirsutism appears to be less severe in women with DM1 compared with nondiabetic hirsute women. Roldan *et al.* (45) found an average modified Ferriman-Gallwey score of 11 in hyperandrogenic DM1 women, compared with an average hirsutism score of 15 in nondiabetic hyperandrogenic women (Fig. 1). Similarly, the hirsute DM1 women in the Chilean study had an average modified Ferriman-Gallwey score of 10. The fact

**TABLE 2.** Proportion of adult women with DM1 exhibiting hyperandrogenism, clinical or biochemical, PCOS, and polycystic ovarian morphology

| | Escobar-Morreale *et al.* (36), Spain, 2000 | Codner *et al.* (37), Chile, 2006 |
|---|---|---|
| Hirsutism | 30.6 | 28.6 |
| Clinical hyperandrogenism | 38.8 | 38.1 |
| Biochemical hyperandrogenism | 19.1 | 23.8 |
| Menstrual dysfunction | 25.9 | 19.0 |
| Polycystic ovary morphology | NR | 54.8 |
| PCOS by NICHD criteria | 18.8 | 11.9 |
| PCOS by Rotterdam criteria | NR | 40.5 |
| PCOS by AES criteria | NR | 31.0 |

Data are percentages. NR, Not reported.

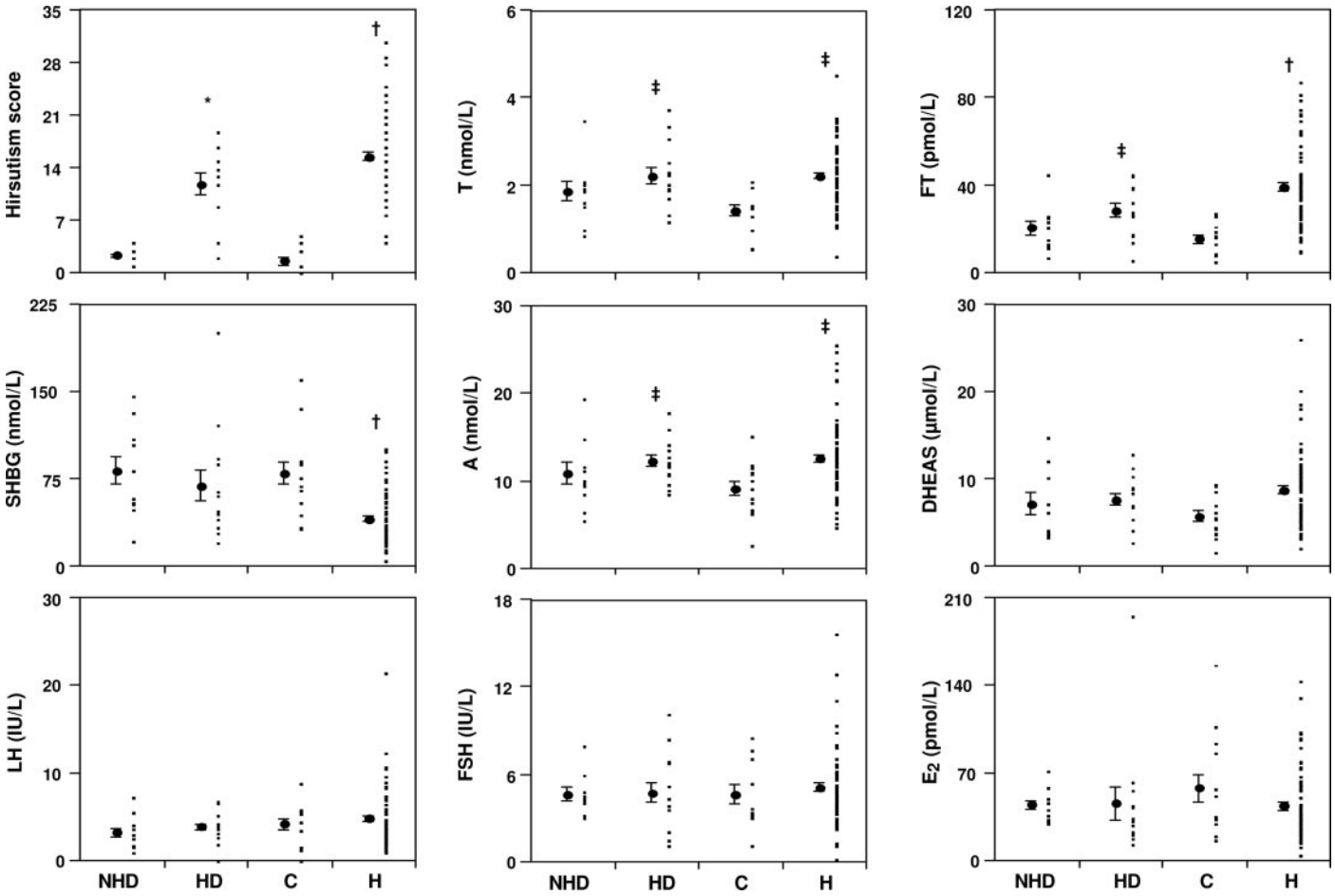


FIG. 1. Comparison of the serum androgen and gonadotropin levels among non-hyperandrogenic DM1 women (NHD, n = 10), hyperandrogenic DM1 patients (HD, n = 14), healthy control subjects (C, n = 13), and nondiabetic hyperandrogenic women (H, n = 73). Data are represented as means ± SEM, and the dot scattergram shows the individual data. The mean values of all groups were compared by one-way ANOVA followed by the least-significant difference test for multiple comparisons. Hirsutism score is the modified Ferriman-Gallwey score. A, Basal androstenedione; $E_2$, estradiol; FT, calculated free testosterone; T, total testosterone. *, $P < 0.05$ *vs.* non-hyperandrogenic DM1 women and healthy control subjects; †, $P < 0.05$ *vs.* hyperandrogenic and non-hyperandrogenic DM1 patients and healthy control subjects; ‡, $P < 0.05$ *vs.* healthy control subjects. [Reproduced with permission from B. Roldan *et al.*: *Diabetes Care* 24:1297, 2001(45). © American Diabetes Association.]

that hirsutism is usually mild in DM1 women might explain why this sign is frequently overseen by clinicians taking care of diabetic women (37). As occurs in nondiabetic women, the severity of hirsutism appears to increase with age after puberty (35, 37). Acne and alopecia are not particularly prevalent in these women (36, 37).

The hormone profiles of DM1 patients presenting with PCOS are somehow different from those observed in nondiabetic hyperandrogenic women. In the former, although both serum testosterone and androstenedione levels are increased (37, 45), circulating SHBG, gonadotropin, estradiol, and dehydroepiandrosterone sulfate (DHEAS) concentrations are characteristically within the normal range (Fig. 1), and androgen excess appears to be mostly of ovarian origin given that the adrenal androgen-precursor responses to cosyntropin are similar to those of healthy women (45). The ovarian origin of the androgen excess in hyperandrogenic DM1 women is also supported by the finding of increased 17-hydroxyprogesterone responses to GnRH-a in a significant proportion of DM1 girls (33, 35).

The particular behavior of SHBG levels in women with DM1 may be related to the fact that insulin concentrations at the portal vein are the main regulators of SHBG (46), and in women with DM1, the hormone is administered sc to the systemic circulation and may not attain increased portal levels of insulin even when supraphysiological doses are given.

On the contrary, insulin-resistant women with PCOS without DM1 have high portal vein concentrations of insulin that decrease SHBG synthesis and secretion. The normal levels of SHBG in DM1 women explain why the most sensitive serum marker of hyperandrogenism in these patients is total testosterone levels and not free testosterone concentrations or the free androgen index as occurs in nondiabetic PCOS patients (3). Furthermore, the normal SHBG levels characteristic of hyperandrogenic DM1 patients may contribute, at least partly, to their milder hyperandrogenic symptoms because the binding of serum androgens to these normal levels of SHBG reduces their bioavailability to target tissues.

*Ultrasonographic polycystic ovaries in women with DM1.* Early studies reported ultrasonographic polycystic ovaries in as many as 80% of adolescents with DM1 (47). However, when

more strict criteria such as those of the Rotterdam definition were applied, approximately 50% of adult DM1 women, as compared with only 13% of age-matched nondiabetic controls, have polycystic ovaries in ultrasound examination, associated with increased ovarian volume and follicle counts per ovary when compared with a control group of healthy women (Fig. 2) (35, 37). Therefore, ultrasonographic polycystic ovaries appear to be quite common in women with DM1 and are accompanied by other criteria for PCOS in most cases.

*Predisposing factors for PCOS in DM1.* The rationale to suspect a high prevalence of ovarian hyperandrogenism and PCOS in women with DM1 was that exogenous systemic hyperinsulinism might occur as a result of treatment with supraphysiological doses of sc insulin.

In conceptual agreement, intensive conventional insulin therapy, as defined by administration of three or more daily insulin injections, is associated with PCOS in these women. Codner *et al.* (37) recently reported that 75% of DM1 women on intensive insulin therapy had either PCOS or asymptomatic polycystic ovarian morphology on ultrasound scans, as compared with only 33% of the patients on a more conservative conventional therapy using two daily insulin injections. Of note, the study by Escobar-Morreale *et al.* (36) included very few patients on conventional therapy and was underpowered for such a comparison.

However, both in the Chilean and Spanish studies no differences were observed in the mean daily insulin doses received, diabetes duration, or degree of metabolic control in non-hyperandrogenic DM1 women and those presenting with PCOS (36, 37) or isolated polycystic ovarian morphology (37). Furthermore, there were also no differences between these groups in the degree of metabolic control estimated by glycosylated hemoglobin levels (36, 37), suggesting that the menstrual disturbances observed in these studies were actually related to hyperandrogenism and not to poor metabolic control (40).

Puberty is a critical period for women with DM1 and is also involved in the pathogenesis of hyperandrogenism. Escobar-Morreale *et al.* (36) evaluated the factors that could be associated with PCOS in DM1 women receiving mostly intensive insulin therapy and found that the only factor that could be associated with the development of PCOS was the onset of DM1 before menarche.

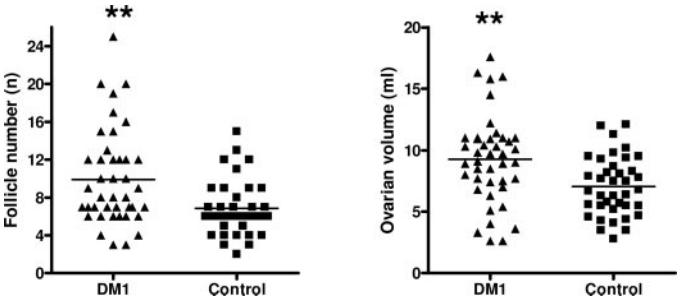


FIG. 2. Ultrasonographic findings in adult women with DM1 and nondiabetic controls, including follicle number (the ovary with the greatest number of follicles is shown) and ovarian volume (the ovary with the greatest volume is shown). The *horizontal lines* are the mean values of each group. **, $P < 0.01$ for the comparison of the mean values in women with DM1 compared with nondiabetic controls by Student's *t* test.

In agreement, other studies have shown that premenarcheal onset of DM1 is also related to menstrual irregularities later in life (41, 48). Furthermore, the levels of sexual steroids or gonadotropins in girls with DM1 do not show significant abnormalities at the beginning of puberty, yet after its completion, several abnormalities such as increasing levels of total and free testosterone, increased LH to FSH ratios, larger ovarian volumes, and abnormalities in ovarian morphology may be present (35, 47, 49). Therefore, we might hypothesize that exogenous hyperinsulinism at the onset of ovarian function during puberty reprograms ovarian function toward increased androgen secretion, leading to hyperandrogenism and PCOS later in life.

Finally, it must be highlighted that insulin resistance, weight gain, increased fat mass, and abnormalities in the GH/IGF axis, characteristic of nondiabetic PCOS patients (50, 51), also occur in DM1 women during adolescence (28, 47, 52–55) and might influence the development of hyperandrogenism in some of them.

*Consequences of PCOS for the health of women with DM1 and strategies for the detection and treatment of this condition.* The consequences of having PCOS in a woman with DM1 are simply unknown at present, because no studies have been conducted to address this issue. However, there is no reason to suspect that the consequences of PCOS would be different from those expected in nondiabetic women, and therefore PCOS may also put these DM1 women at risk for additional impairment in quality of life, infertility, endometrial hyperplasia or carcinoma resulting from oligomenorrhea, metabolic dysfunction, hypertension, and perhaps cardiovascular disease (56).

In fact, there are data suggesting that androgen excess might also occur in association with renal microvascular complications of diabetes. Although the presence of hyperandrogenic disorders such as PCOS was not recorded, Amin *et al.* (53) showed that adolescent girls who developed microalbuminaria after a follow-up of 9 yr exhibited higher free testosterone levels than those not presenting this complication, even for the same glycosylated hemoglobin level. Similar results had been reported previously by Rudberg and Persson (57), who found a relationship between low SHBG concentrations, increased free androgen index, and microalbuminuria in DM1 patients.

Therefore, every effort must be made for the early detection and treatment of hyperandrogenic disorders in these women. Because of the large prevalence of PCOS in adolescent and adult DM1 women, this disorder must be routinely ruled out in all of them, at least by including in their usual evaluation a detailed menstrual history, a hirsutism score, and possibly an ovarian ultrasound scan. In those women with hyperandrogenic symptoms and/or signs, an androgen profile including total testosterone and prospective evaluation of ovulation are also warranted.

Treatment should be considered for DM1 women presenting with hyperandrogenic disorders. Although it must be highlighted that there are no specific studies addressing treatment of hyperandrogenism in diabetic patients, there is

no actual reason for avoiding the use of therapeutic strategies that have proven success in hyperandrogenic nondiabetic patients. If present, the correction of unhealthy lifestyle habits such as overweight, obesity, sedentary, and smoking should be stressed.

Pharmacological therapy should also be offered with the aim of improving symptoms. Considering that exogenous hyperinsulinism might play a major triggering role in the development of PCOS in DM1 women (36, 37), treatment with an insulin sensitizer such as metformin or a thiazolidinedione might be considered. In fact, the use of metformin in combination with insulin in lean, overweight, and obese DM1 patients permits a significant reduction in the insulin dose administered while providing an improvement in metabolic control (58, 59). However, the potential side effects of these drugs, especially the low risk of developing lactic acidosis if diabetic ketoacidosis develops in a patient taking metformin and the possibility of congestive heart failure when combining insulin administration with a thiazolidinedione, should be also taken into consideration.

Because of its already demonstrated beneficial effects on two of the putative mechanisms underlying hyperandrogenism in DM1 (exogenous hyperinsulinism and insulin resistance) and its demonstrated efficacy for the treatment of PCOS in nondiabetic women (60), metformin appears as a very promising drug for the management of hyperandrogenism and PCOS in DM1 patients. Furthermore, combined treatment with oral contraceptives, antiandrogens, and metformin has proven successful in the treatment of nondiabetic hyperandrogenic patients (61), and a similar success is to be expected in DM1 women according to the recent results obtained in a very small pilot study in hyperandrogenic DM1 adolescents using a combination of metformin and the antiandrogen flutamide (62).

For women not desiring conception, a low-dose oral contraceptive containing a nonandrogenic progestin with or without an antiandrogen could be recommended to correct menstrual dysfunction, prevent endometrial hyperplasia, and ameliorate cutaneous hyperandrogenic symptoms without fearing a worsening in metabolic control (63).

Nevertheless, future studies comparing the different therapeutic options for PCOS and hyperandrogenism specifically in DM1 women are needed, because the present recommendations are not supported by actual scientific evidence obtained specifically in diabetic women.

## Concluding Remarks

Ovarian hyperandrogenism and PCOS are very prevalent in adolescent and adult women with DM1 and are possibly related to the clinical practice of treating this condition with supraphysiological doses of sc insulin with the aim of providing a strict metabolic control. Considering that hyperandrogenic disorders are present in as many as 40% of premenopausal DM1 women, routine screening for these conditions and subsequent treatment is warranted to avoid the undesirable consequences of hyperandrogenism for the health of these women. Although theoretically, the addition to insulin treatment of low-dose nonandrogenic oral contraceptives, metformin, or both should improve hyperandrogenic symptoms and signs in these women, the best therapeutic strategy is yet to be established because studies addressing this issue in DM1 women have not been conducted to date.

## Acknowledgments

We thank our colleagues in our respective centers who contributed to the studies in women with type 1 diabetes described here.

Received November 30, 2006. Accepted January 26, 2007.

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This work was partially supported by Grant 1050452 from the Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT) of Chile (to E.C.) and by Grants PI050341 and REDIMET RD06/0015/0007 from the Instituto de Salud Carlos III, Spanish Ministry of Health and Consumer Affairs (to H.F.E.-M.).

Disclosure Statement: The authors have nothing to declare.

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