The Prevalence of Hirsutism and Polycystic Ovary Syndrome in Women with Type 1 Diabetes Mellitus

Rucsandra Dănciulescu Miulescu[1], MD, Mădălina Muşat[1], MD, Denisa Margină[1], MD, Cătălina Poiană[1], MD, PhD, Suzana Dănoiu[2], MD

1. „Carol Davila" University of Medicine and Pharmacy, Bucharest
2. University of Medicine and Pharmacy, Craiova

Correspondence:
Rucsandra Dănciulescu
e-mail: rucsandra_m@yahoo.com

Abstract

The polycystic ovary syndrome (PCOS) was defined by the presence of chronic anovulation, clinical and/or biochemical evidence of hyperandrogenism, in the presence of polycystic ovaries in the absence of other causes.
***Objective:** The aim of the study is to estimate the prevalence of hirsutism and polycystic ovary syndrome (PCOS) in women with type 1 diabetes mellitus.*
***Method:** 24 women with type 1 diabetes were recruited for this study. A detailed clinical history was obtained, including age at the time of the study, type of insulin treatment employed (conventional vs. intensive), mean insulin doses. Blood samples were drawn the morning after an overnight fast, during the early follicular phase of the menstrual cycle or during amenorrhea. Real-time ultrasonography was done with a 7.5 MHz vaginal transducer.*
***Results:** 14 type 1 diabetic women (58.33%) presented hirsutism with or without increased serum androgens. The prevalence of PCOS in women with type 1 diabetes mellitus was 16.66% (4 patients). The groups of type 1 diabetic women with PCOS were on long-term intensive insulin treatment at the time of the study, receiving three or four daily doses. The mean daily insulin dose was 62U/day.*
***Conclusion:** Women with type 1 diabetes mellitus have a high prevalence of PCOS.*
***Keywords:** type 1 diabetes mellitus, hirsutism, polycystic ovary syndrome.*

Introduction

The polycystic ovary syndrome is one of the most frequent endocrine disorders, affecting approximately 5% of fertile female population[1]. It usually has a peripubertal onset, mainly being characterized by chronic anovulation and hyperandrogenism, menstrual cycle disorders, and infertility. The special importance of PCOS in medical practice is justified by it representing the main reason of the woman infertility due to anovulation, and of hirsutism, but at the same time a risk factor for other diseases, namely diabetes, hyperlipidemia, cardiovascular disorders, endometrial and ovary cancer.

Today it is considered that the polycystic ovary syndrome is a heterogeneous disorder that includes more subpopulations of women in whom ovary etiopathogenic elements induce hormonal disturbances that perpetuate them in the same vicious circle, causing chronic anovulation and hyperandrogenism. The hyperinsulinism plays an important role in PCOS pathogenesis, representing, at a considerable proportion of patients, the primitive disorder. The hyperinsulinism and insulin resistance are associated with altered functions of the endothelium[2] and different types of hyperandrogenism.

The medical research has pointed out a tight correlation between the hyperinsulinism and hyperandrogenism which characterizes the polycystic ovary syndrome:

1. The insulin receptors are present in the granulosa cells and the insulin stimulates the steroidogenesis in these cells; the interaction of the insulin with the gonadotrophic hormones may be an additive way or regarding the LH in a synergic way. This action seems to be mediated by the insulin receptor or better by the cross-reaction with the IGF-I receptor[3];

2. The insulin intensifies the productivity of the androgens, induced by LH, at the level of thecal cells which probably are intrinsically programmed to synthetize androstenedione and testosterone excessively[4];

3. The insulin can activate the IGF-I receptor and, consequently, to increase the synthesis of androgens in thecal cells as an answer to LH stimulation. Studies on the isolated thecal cells have shown the IGF-I is equipotent regarding the stimulation of androstenedione synthesis comparatively with the insulin[4];

4. The effect of insulin on cellular proliferation seems to play an important part in stromal hyperplasia characteristic to PCOS; the mitogenical effects of the insulin on the ovarian stromal cells have been compared to IGF ones and the studies have proved that insulin is much more potent comparatively with IGF-I in stimulation of the proliferation of the stromal cells[5];

5. The insulin increases the pituitary secretion of lutein hormone (LH), stimulating the increase of the synthesis of androgens[5];

6. Hyperinsulinism induces inhibition of hepatic synthesis of the sex-hormone binding globulin (SHBG) resulting in growth of the free fraction of the androgens and estrogen hormones. Insulin also impaires the hepatic production of insulin-like growth factor binding protein-1-(IGFBP-1) thus increasing the circulating level of IGF-I and the IGF-I and/or IGF-II (insulin-like growth factor I II) activity at the ovarian site[6].

In women diagnosed with type 1 diabetes mellitus the current recommendations regarding the severe metabolic control imposes the administering of overphysiological insulin doses that can generate the stimulation of androgens.

The study intends to point out the prevalence of the hirsutism and of the polycystic ovary syndrome in women with type 1 diabetes mellitus.

Material and method

Twenty-four women diagnosed with type 1 diabetes mellitus have been included in this study. The diagnosis of polycystic ovarian syndrome has been based on the excess of androgens, ovulary dysfunction, excluding other causes that can stimulate excess of androgens, respectively congenital adrenal hyperplasia, Cushing syndrome, hyperthyroidism, hyperprolactinemia, ovary or adrenal tumors. The study assessed the clinical parameters, the hormonal profile as well as the ovaries aspect. The general clinical checkup assessed: Body Mass Index (BMI) that represents the report between the weight and the height square, expressed in kg/m^2, the evidence of the hyperandrogenism (hirsutism, acnea, seborrhea). The hirsutism was assessed by Ferriman-Gallway score, a simple and semiquantitative method of estimation of the pilosity distribution and intensity[7]. The following areas are explored: the superior lip, the menton, the undermentonic region, the anterior thorax (the presternal and periareolar region), the posterior thorax (the shoulders and interscapula-vertebral region), the abdominal region, the lumbar-sacral region (Michaelis' rhombus), the arms and the ante-internal face of thighs. The maximum Ferriman-Gallway's score is 36. The women with the score >7 were considered hirsute ones. A score of 8-12 is characteristic of the mild hirsutism, a score of 13-14 is characteristic to the moderate hirsutism, but a score over 19 was viewed as a severe one.

The endocrine profile: plasma hormonal values during early follicular phase (the 3^{rd}-5^{th} days) were determined in women with regular menstrual cycle or after progesterone induced menses or randomly in the case of women with secondary amenorrhea or oligomenorrhea. The blood samples for total and free testosterone, androstendione were drawn between 8 and 9 a.m. Androstendione was determined by an automatic system of chemiluminescence ACS 180 Bayer Diagnostic Ltd. This incorporates a samples conveyer and an automatic system of injection of the samples and reagents, all integrated by a software system. Total and free testosterone was determined with on a TECAN ELISA system. The hormonal typings were done in accordance with the directions of the diagnosis systems' laboratories, Webster, Texas.

Ovarian ultrasonographycal examination. The uterus and the ovaries were explored by endovaginal (transvaginal) ultrasonography, on a Toshiba Casasee ecograph endowed with endovaginal probe of 7.5 Mhz.

Table 1

The endocrine features of the women with type 1 diabetes mellitus and polycystic ovary syndrome.

	Median value	Average	Minim value	Maxim value
Total testosterone (ng/dl)	121.05	123.10	93.08	157.22
Free testosterone (pg/ml)	4.00	4.11	3.41	5.02
Androstendione (ng/ml)	3.87	3.88	2.90	4.90

Table 2

The endocrine features of the women with type 1 diabetes mellitus without polycystic ovary syndrome.

	Median value	Average	Minim value	Maxim value
Total testosterone (ng/dl)	45.01	45.60	37.86	55.74
Free testosterone (pg/ml)	1.96	1.90	1.11	2.40
Androstendione (ng/ml)	2.97	2.71	1.49	3.45

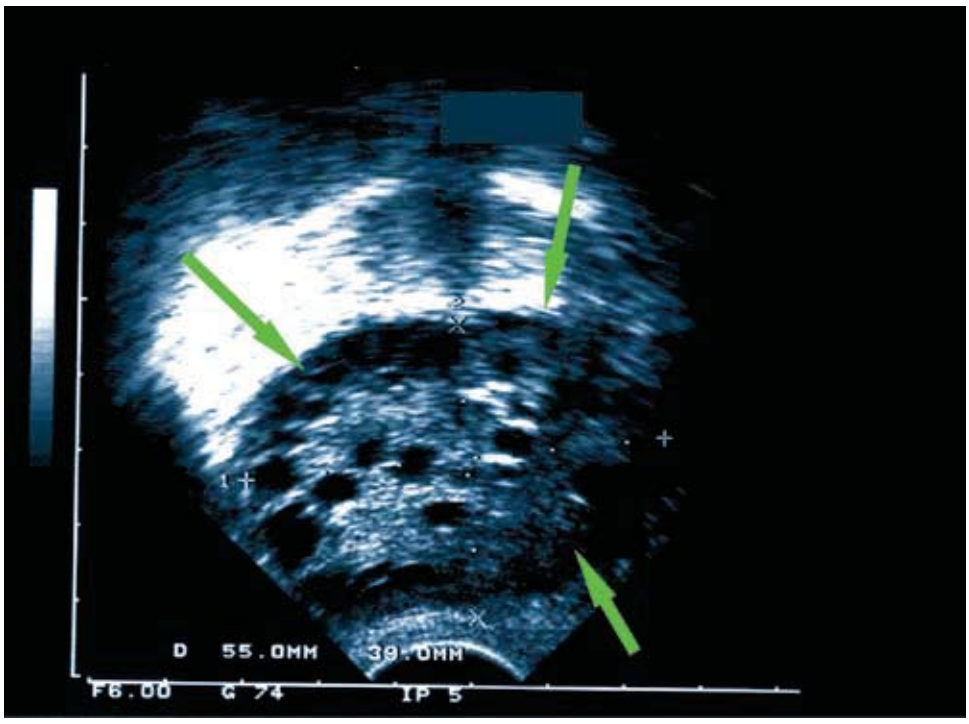

Figure 1. The ultrasonographic aspect of micropolycystic ovary

According to Rotterdam consensus the ultrasonographycal criteria of polycystic ovary includes the presence of 12 or more small (under 10 mm) peripheral distributed cysts. Ovaries dimensions can raise due these cysts 1.5 to 3 fold[8].

Results

The prevalence of the polycystic ovary syndrome in women with type 1 diabetes mellitus included in this study was of 16.66% (4 women). The relatively small number of patients in the study represented a limitation and did not allow a complete statistical analysis of the data. The women diagnosed with polycystic ovary syndrome presented increased values of total and free testosterone and of androstendione compared to those without PCOS. The endocrine features of the women with type 1 diabetes mellitus and/without polycystic ovary syndrome are presented in table 1 and 2.

There were no considerable differences in the number of women with polycystic ovary syndrome and those without it, regarding the age and the Body Mass Index. The women diagnosed with polycystic ovary syndrome were on intensive insulin treatment at the time of the study (4 injections daily), the mean daily insulin dose being 62±12U/day.

The echographic evaluation of the ovaries sustained the ultrasonographic polycystic ovary diagnosis according to the criteria from the Consensus elaborated by the Rotterdam work group[8].

Discussions

The hirsutism was detected in 14 patients (58.33%). The Ferriman-Gallwey's score varied in these women between 8-17, with an average of 12.6. In the absence of the polycystic ovary syndrome and of other causes of increased androgens production (adrenal hyperplasia by 21-hydroxilase deficiency, Cushing's syndrome, the hypothyroidism, the hyperprolactinemia, the ovary and adrenal tumors), the hirsutism has been considered idiopathic. The idiopathic or constitutional hirsutism is defined by excessive pilosity in women with regular and ovulatory menses without excessive androgenous hormones. This phenomenon is encountered especially in certain ethnical groups, particularly in Mediterranean women. The idiopathic hirsutism is likely to be produced by increased activity of the 5 alpha reductase in dermic fibroblasts[9].

The prevalence of the polycystic ovary syndrome in women with type 1 diabetes mellitus included in our study was 16.66% (4 women), a higher prevalence in comparison with the female population during the fertile period (5%).

The women with polycystic ovary syndrome have increased values of total and free testosterone and of androstendione compared to those without PCOS. The level of total plasma testosterone was 2.68 fold higher in women with polycystic ovary syndrome (median value of 121.05 ng/dl, range between 93.08 ng/dl and 157.22 ng/dl) than in the group of women lacking this dysfunction (median value of 45.01 ng/dl, range betwe-

en 37.86 ng/dl and 55.74 ng/dl). The free testosterone level in the group of women with PCOS (median value 4.00 pg/ml, range between 3.41 pg/ml and 5.02 pg/ml) was 2.04 fold hinger than the level in the group of women with only type 1 diabetes mellitus (median value 1.96 pg/ml, range between 1.11 pg/ml and 2.40 pg/ml).The plasma androstendione, an androgen synthesized both by the ovary and the adrenals, had a higher level in women with polycystic ovary syndrome (median value 3,87 ng/dl, range between 2.90 ng/dl and 4.90 ng/dl), compared to that of the women diagnosticated only with type 1 diabetes mellitus (median value 2,97 ng/dl, range between 1.49 ng/dl and 3.45 ng/dl). There are no consistent data in the literature with respect to plasmat levels of the androstendione and insulin in PCOS[10,11].

The ultrasonographic aspect of micropolycystic ovary has been shown in 2 women with type 1 diabetes mellitus (10%) and in 3 women with polycystic ovary syndrome (75%). The data from the current study is in agreement with those in the literature stating that 8-25% of normal women present ovaries with polycystic ultrasonographic aspect[9]. In the case of nondiabetic persons, the insulin released by pancreatic beta cells arrives at liver level through port circulation. More than 50% of the insulin secreted by pancreas is taken by the liver so that in peripheral circulation is much lower than at the portal level. The current recommendations regarding the severe metabolic control imposes the administering of overphysiological doses of insulin to the patients with diabetes mellitus that can generate, in the case of women, the stimulation of the synthesis of androgens. Moreover the studies proved that the hyperinsulinism and the resistance to insulin occur approximately to almost 50% of the patients with type 1 diabetes mellitus[12,13].

The women diagnosed with polycystic ovary syndrome were on long-term intensive insulin therapy at the time of the study (4 daily doses), on a mean daily insulin dose of 62 U/day, which was about 2 times (1.87 fold) higher in comparison with those in women without polycystic ovary syndrome (33 U/day).

Conclusions

The prevalence of the polycystic ovary syndrome in women with type 1 diabetes mellitus recruited for the study was 16.66% (4 patients), a increased prevalence in comparison with the prevalence reported (5%) in other studies for the fertile age female population[1].

The women diagnosticated with polycystic ovary syndrome were on intensive insulin therapy at the time of the inclusion in the study (4 doses per a day), the mean daily insulin dose being 62 ± 12 U/day, which was higher in comparison with those women without polycystic ovary syndrome (33 ± 5U/day).

The hirsutism was observed in 14 women with type 1 diabetes mellitus (58.33%). ■

References

1. Solomon CG (1999). "The epidemiology of polycystic ovary syndrome. Prevalence and associated disease risks". Endocrinol. Metab. Clin. North Am. 28 (2): 247-63.
2. Denisa Margină, Andreea Marin, Niculina Mitrea, Maria Vlădică, Rucsandra Dănciulescu, Daniela Grădinaru (2006) - Evaluation of the intercellular adhesion molecule 1 (ICAM-1) as marker of the endothelial dysfunction, Farmacia, nr 3, vol LIV, 18-24.
3. Willis D., Mason H., Gilling - Smith C., Franks S., (1996), Modulation by insulin of follicle - stimulating hormone and luteinizing hormone actions in human granulosa cells of normal and polycystic ovaries. J Clin Endocrinol Metab 81: 302.
4. Nestler J.E., Jakubowicz D.J., de Vargas A.F., et al, (1988), Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndroome by activating its own receptor and using inositolglycan mediators as the signal transduction system. J Clin Endocrinol Metab 83: 2001.
5. Nestler J.E., (1997), Role of hyperinsulinemia in the pathogenesis of the polycystic ovary syndrome and its clinical implications. Seminars reprod Endocrinol 15: 111.
6. Buyalos R.P., (1995), The relationship between circulating androgens, obesity and hyperinsulinemia in serum insulin - like growth factor binding protein - 1 in the polycystic ovary syndrome. Am J Obstet Gynecol 172: 932.
7. Ferriman D., Gallwey Y.D., (1961), Clinical assesement of body hair growth in women, J Clin Endocrinol Metab. 21: 1440-7.
8. Ricardo Azziz (2006) Diagnosis of Polycystic Ovarian Syndrome: The Rotterdam Criteria Journal of Clinical Endocrinology&Metabolism,No.3781-785.
9. Bulun S.E., Adashi E.Y., (2003)., The Physiology and Pathology of the Female Reproductive Axis în Wilson & Foster, Williams Textbook of Endocrinolology, 10th edition, cap. 16 p. 587-650.
10. Kiddy D.S., Sharp P.S., White D.M., et al, (1990), Differences in clinical and endocrine features between obese and non-obese subjects with polycystic ovarian syndrome: an analisys of 263 consecutive cases. Clin Endocrinol (Oxf), 32:213-220.
11. Sutterlin M., Steck T., (1995), Sensitivity of plasma insulin levels in obese and non-obese women with functional hyperandrogenism. Gynecol Endocrinol, 9: 37-44.
12. Yki-Jarvinen H, Koivisto VA (1986). Natural course of insulin resistance in type 1 diabetes. N Engl J Med 315:224-230.
13. DeFronzo RA, Hendler R, Simonson D (1982): Insulin resistance is a prominent feature of insulin-dependent diabetes. Diabetes 31:795-801.