Selezione di Abstracts sull'argomento

1: J Clin Endocrinol Metab 2000 Aug;85(8):2767-74

Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome.

Pasquali R, Gambineri A, Biscotti D, Vicennati V, Gagliardi L, Colitta D, Fiorini S, Cognigni GE, Filicori M, Morselli-Labate AM

Department of Internal Medicine and Gastroenterology, S Orsola-Malpighi Hospital, Bologna, Italy. rpasqual@almadns.unibo.it

[Medline record in process]

Abdominal obesity and hyperinsulinemia play a key role in the development of the polycystic ovary syndrome (PCOS). Dietary-induced weight loss and the administration of insulin-lowering drugs, such as metformin, are usually followed by improved hyperandrogenism and related clinical abnormalities. This study was carried out to evaluate the effects of combined hypocaloric diet and metformin on body weight, fat distribution, the glucose-insulin system, and hormones in a group of 20 obese PCOS women [body mass index (BMI) > 28 kg/m2] with the abdominal phenotype (waist to hip ratio >0.80), and an appropriate control group of 20 obese women who were comparable for age and pattern of body fat distribution but without PCOS. At baseline, we measured sex hormone, sex hormone-binding globulin (SHBG), and leptin blood concentrations and performed an oral glucose tolerance test and computerized tomography (CT) at the L4-L5 level, to measure sc adipose tissue area (SAT) and visceral adipose tissue area. All women were then given a low-calorie diet (1,200-1,400 kcal/day) alone for one month, after which anthropometric parameters and CT scan were newly measured. While continuing dietary treatment, PCOS women and obese controls were subsequently placed, in a random order, on metformin (850 mg/os, twice daily) (12 and 8, respectively) or placebo (8 and 12, respectively), according to a double-blind design, for the following 6 months. Blood tests and

the CT scan were performed in each woman at the end of the study while they were still on treatment. During the treatment period, 3 women of the control group (all treated with placebo) were excluded because of noncompliance; and 2 PCOS women, both treated with metformin, were also excluded because they became pregnant. Therefore, the women cohort available for final statistical analysis included 18 PCOS (10 treated with metformin and 8 with placebo) and 17 control women (8 treated with metformin and 9 with placebo). The treatment was well tolerated. In the PCOS group, metformin therapy improved hirsutism and menstrual cycles significantly more than placebo. Baseline anthropometric and CT parameters were similar in all groups. Hypocaloric dieting for 1 month similarly reduced BMI values and the waist circumference in both PCOS and control groups, without any significant effect on CT scan parameters. In both PCOS and control women, however, metformin treatment reduced body weight and BMI significantly more than placebo. Changes in the waist-to-hip ratio values were similar in PCOS women and controls, regardless of pharmacological treatment. Metformin treatment significantly decreased SAT values in both PCOS and control groups, although only in the latter group were SAT changes significantly greater than those observed during the placebo treatment. On the contrary, visceral adipose tissue area values significantly decreased during metformin treatment in both PCOS and control groups, but only in the former was the effect of metformin treatment significantly higher than that of placebo. Fasting insulin significantly decreased in both PCOS women and controls, regardless of treatment, whereas glucose-stimulated insulin significantly decreased only in PCOS women and controls treated with metformin. Neither metformin or placebo significantly modified the levels of LH, FSH, dehydroepiandrosterone sulphate, and progesterone in any group, whereas testosterone concentrations decreased only in PCOS women treated with metformin. SHBG concentrations remained unchanged in all PCOS women; whereas in the control group, they significantly increased after both metformin and placebo. Leptin levels decreased only during metformin treatment in both PCOS and control groups.

PMID: 10946879, UI: 20401703

2: Fertil Steril 2000 Aug;74(2):394-7

Polycystic ovary syndrome, infertility, familial thrombophilia, familial hypofibrinolysis, recurrent loss of in vitro fertilized embryos, and miscarriage.

Glueck CJ, Awadalla SG, Phillips H, Cameron D, Wang P, Fontaine RN

Cholesterol Center, Jewish Hospital, Cincinnati, Ohio, USA.

[Medline record in process]

Objective: To study reversible determinants of infertility and recurrent loss of transferred embryos after failure of 7 of 10 embryo transfers, 1 live birth, and 2 miscarriages.Design: Measures of thrombophilia, hypofibrinolysis, reproductive hormones, and androgenic steroids before and after metformin therapy.Setting: Outpatient clinical research center.Patient(s): A 32-year-old amenorrheic, infertile woman with polycystic ovary syndrome (PCOS) who had 7 of 10 embryo transfers fail, 1 premature live birth, and 2 miscarriages at 8 and 17 weeks.Intervention(s): Metformin (2.55 g/d) was given to ameliorate the endocrinopathy of PCOS.Main Outcome Measure(s): Coagulation, insulin, reproductive hormones, and androgenic steroids.Result(s): The propositus had thrombophilia (familial protein S deficiency [free protein S 32%; normal >/=65%]). She also had familial hypofibrinolysis with 4G4G polymorphism of the plasminogen activator inhibitor (PAI-1) gene and high PAI-1 activity (PAI-Fx), 42.5 U/mL, normal 15 mm, number of hyperstimulation, and the number of cycles with hCG withheld. RESULT(S): The number of follicles > 15 mm in diameter on the day of hCG administration was significantly lower in cycles performed after metformin treatment. The percentage of cycles with hCG withheld because of excessive follicular development was significantly lower in cycles treated with metformin. Plasma levels of E2 were significantly higher in cycles treated with FSH alone than in those treated with FSH and metformin. CONCLUSION(S): By reducing hyperinsulinism, metformin determines a reduction in intraovarian androgens. This leads to a reduction in E2 levels and favors orderly follicular growth in response to exogenous gonadotropins.

Publication Types:
Clinical trial
Randomized controlled trial

PMID: 10438996, UI: 99367851

18: Endocrinol Metab Clin North Am 1999 Jun;28(2):423-38, viii

Insulin-lowering therapeutic modalities for polycystic ovary syndrome.

Ehrmann DA

Department of Medicine, Pritzker School of Medicine, University of Chicago, Illinois, USA.

This article summarizes the relationship between insulin and androgen excess, with a focus on what is known regarding two related issues in polycystic ovary syndrome: (1) defects in insulin secretion in PCOS and their role in the development of glucose intolerance in this population; and (2) pharmacologic interventions designed to attenuate hyperinsulinemia and its sequelae in PCOS.

Publication Types:
Review
Review, tutorial

PMID: 10352927, UI: 99281193

19: Endocrinol Metab Clin North Am 1999 Jun;28(2):361-78

Insulin action in the normal and polycystic ovary.

Franks S, Gilling-Smith C, Watson H, Willis D

Department of Reproductive Science and Medicine, Imperial College School of Medicine, St. Mary's Hospital, London, United Kingdom. s.franks@ic.ac.uk

Insulin has a stimulatory effect on steroidogenesis by granulosa cells of normal and polycystic ovaries and interacts with gonadotropins in an additive or, as in the case of LH, a synergistic manner. These actions seem to be mediated specifically by the insulin receptor rather than by cross-reaction with the type I IGF receptor, even in tissue obtained from women with PCOS with biochemical evidence of insulin resistance. The authors suggest that hyperinsulinemia makes a significant contribution to premature arrest of follicle growth, which is characteristic of anovulation in women with PCOS, and that the interaction of insulin with LH is a key element in this process. Insulin may also have a role in amplifying LH-induced androgen production by theca cells, which may help explain the prominence of symptoms of hyperandrogenism in obese subjects with PCOS. The results of recent clinical studies of insulin-sensitizing agents such as metformin and the thiazoladinedione troglitazone in PCOS have provided encouragement that improvement of insulin sensitivity and consequent lowering of circulating insulin levels by these agents may be of therapeutic value in the management of both anovulation and hirsutism.

Publication Types:
Review
Review, tutorial

PMID: 10352923, UI: 99281189

20: Diabet Med 1999 Mar;16(3):179-92

Thiazolidinediones: a new class of antidiabetic drugs.

Day C

Diabetes Research Group, Life and Health Sciences, Aston University, Birmingham, UK.

Thiazolidinediones (TZDs) are a new class of oral antidiabetic agents. They selectively enhance or partially mimic certain actions of insulin, causing a slowly generated antihyperglycaemic effect in Type 2 (noninsulin dependent) diabetic patients. This is often accompanied by a reduction in circulating concentrations of insulin, triglycerides and nonesterified fatty acids. TZDs act additively with other types of oral antidiabetic agents (suphonylureas, metformin and acarbose) and reduce the insulin dosage required in insulin-treated patients. The glucose-lowering effect of TZDs is attributed to increased peripheral glucose disposal and decreased hepatic glucose output. This is achieved substantively by the activation of a specific nuclear receptor - the peroxisome proliferator-activated receptor-gamma (PPARgamma), which increases transcription of certain insulin-sensitive genes. To date one TZD, troglitazone, has been introduced into clinical use (in Japan, USA and UK in 1997). This was suspended after 2 months in the UK pending further investigation of adverse effects on liver function. TZDs have been shown to improve insulin sensitivity in a range of insulin-resistant states including obesity, impaired glucose tolerance (IGT) and polycystic ovary syndrome (PCOS). In Type 2 diabetes, the TZDs offer a new type of oral therapy to reduce insulin resistance and assist glycaemic control.

Publication Types:
Review
Review, academic

PMID: 10227562, UI: 99242101

21: Metabolism 1999 Apr;48(4):511-9

Metformin-induced resumption of normal menses in 39 of 43 (91%) previously amenorrheic women with the polycystic ovary syndrome.

Glueck CJ, Wang P, Fontaine R, Tracy T, Sieve-Smith L

The Cholesterol Center, Jewish Hospital, Cincinnati, OH 45229, USA.

In 43 amenorrheic women with polycystic ovary syndrome (PCOS), 31 (74%) with fasting hyperinsulinemia (> or =20 microU/mL), our aim was to determine whether Metformin (Bristol-Myers Squibb, Princeton, NJ), which reduces hyperinsulinemia, would reverse the endocrinopathy of PCOS, allowing resumption of regular normal menses. A second aim was to assess the effects of weight loss versus other Metformin-induced effects on ovarian function, and to determine if there were different responses to Metformin between those who lost weight and those who did not. A third aim was to assess associations between PCOS, 4G/5G polymorphism in the promoter sequence of the plasminogen activator inhibitor-1 gene (PAI-1 gene), and PAI activity (PAI-Fx). Of the 43

women, 40 (93%) had normal fasting blood glucose and 37 had normal hemoglobin A1C (HgA1C); onlythree (7%) had type 2 diabetes mellitus. Metformin (1.5 to 2.25 g/d) was given for 6.1+/-5.1 months (range, 1.5 to 24), to 16 patients for less than 3 months, to 12 for 3 to 6 months, and to 15 for at least 6 months. On Metformin, 39 of 43 patients (91%) resumed normal menses. The percentage of women resuming normal menses did not differ among treatment duration groups (P.1). The body mass index (BMI) decreased from 36.4 + 7 Kg/m2 at study entry to 35.1+/-6.7 on Metformin (P=.0008). Of 43 patients, 28 (67%) lost weight (1 to 69 pounds), with nine (21%) losing at least 12 pounds. On Metformin, the median fasting serum insulin decreased from 26 microU/mL to 22 (P=.019), testosterone decreased from 61 ng/dL to 47 (P=.003), and estradiol increased from 41 pg/mL to 71 (P=.0001). Metformin-induced improvements in ovarian function were independent of weight loss (testosterone decrease, P or = 1 previous pregnancy while they were not receiving metformin. INTERVENTION(S): Metformin, 1.5-2.55 g/day, throughout pregnancy. MAIN OUTCOME MEASURE(S): Rates of first-trimester spontaneous abortion and teratogenicity. RESULT(S): Before metformin, 10 women had 22 previous pregnancies with 16 first-trimester spontaneous abortions (73%). While receiving metformin, these 10 women had 6 normal live births (60%), 1 spontaneous abortion (10%), and 3 normal ongoing pregnancies (30%) (all > or = 13 weeks; median gestation, 23 weeks). Among women receiving metformin, including those with live births and normal pregnancy for at least the first trimester, 1 of 10 (10%) had first-trimester spontaneous abortion compared with 73% in 22 previous pregnancies without metformin (P/=65%]). She also had familial hypofibrinolysis with 4G4G polymorphism of the plasminogen activator inhibitor (PAI-1) gene and high PAI-1 activity (PAI-Fx), 42.5 U/mL, normal