
PKOS GUNCEL DURUM UZUN DONEM KOMPLIKASYONLAR YONETIMI

PROF DR ONUR KARABACAK
GAZI UNIVERSITESI TIP FAKULTESI ANKARA

LONG TERM PROBLEMS FOLLOWS SHORT TERMS

- Obesity
 - Hypertension
 - Diabetes
 - Infertility associated conditions > Nulliparity > NO Brest Ca
 - Endometrial Cancer NO Over Ca
 - Pcos / Endometriosis / Myomas
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SHORT TERM

LONG TERM

- Obesity
 - Infertility
 - Irregular Menses
 - Abnormal lipid levels
 - Hirsutism / Acne / Androgenic alopecia
 - Glucose intolerance / acanthosis nigricans
- Diabetes Mellitus
 - Cardiovascular Disease
 - Endometrial Cancer
 - Obstructive Sleep Apnea
-


ASSESSMENT AND TX

- Cardiovascular
 - TA, Lipids, cigarette
 - Obesity, AbOGTT
 - Metabolic Syndr
 - Fam Hx CVD
 - LifeChange
 - HypoCaloric diet,
 - Physical Exercise
 - No Smoking
 - Anti hypertesives
 - Statins to lower LDL C levels
-

ASSESSMENT AND TX

Metabolics: Diabetes 75gm OGTT Screening for T2DM Dx
- Metformin

- Age >40, BMI>30, PCOS phenotype, Acanth Nigri, Fam Hx of T2DM,
- BMI and Waist circum>80cm every visit, Abdomin Circum

- LifeChange HypoCaloric diet, Physical Exercise
 - Metformine as OGTT gets abnormal? and adjunct to LifeChange
 - ThiaZolidineDione TZD Lipid & TA (D-Chiro-Inositol, Pioglitazon, Rosiglitazon Avandia tr, Troglitazon) hepatox, Weight incr w/ Sulfonil ure.
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ASSESSMENT AND TX

PCOS FUTURE IS METABOLIC SYNDROME

Metabolic Risk Factors

three metabolic risk factors to be diagnosed with metabolic syndrome.

- A large waistline. Abdominal obesity or "having an apple shape."
 - A high triglyceride level (or you're on medicine to treat high triglycerides). Fat found in the blood.
 - A low HDL cholesterol level (or you're on medicine to treat low HDL cholesterol). A low HDL cholesterol level raises your risk for heart disease.
 - [High blood pressure](#) (or you're on medicine to treat high blood pressure). It can damage your heart and lead to plaque buildup.
 - High fasting blood sugar (or you're on medicine to treat high blood sugar). Mildly high blood sugar may be an early sign of diabetes.
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A COCHRANE REVIEW INSULIN-SENSITISING DRUGS

- metformin reduces serum testosterone levels and
- fasting insulin concentrations to a significant extent only among non obese women.
- Metformin do prevent diabetes, but is good if weight is lost?
- Metformin more effective ? if given before meal for weight loss

METFORMIN / BIGUANIDE CLASS

- First line treatment type 2 diabetes
- True if patient is overweight and/or PCOS
- Limited data prevention of CV outcomes and cancer of diabetes
- Side effects diarrhea, abdominal pain, nausea
- Safe to use in pregnancy
- Decreases glucose production at liver and increase use by tissues with unknown mechanism
- Has limited data effect on weight loss in non diabetic obese, comparing sulfonyl urea results weight gain.
- Modestly reduce LDL and triglyceride levels
- Prevents developing T2D under risk, comparable to life style modification and exercise = Pre Dm TX



METFORMIN IN PCOS

- First suggested use in PCOS in 1980
 - First report of use in PCOS 1994 from Venezuela
 - First use in PCOS, an ovulation, BMI over 25 in UK 2008 as second line drug after clomiphene.
 - First line drug PCOS with insuline resistance, hirsutism, obesity
 - Prolong use may cause Vit B12 deficiency and
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ASSESSMENT AND TX



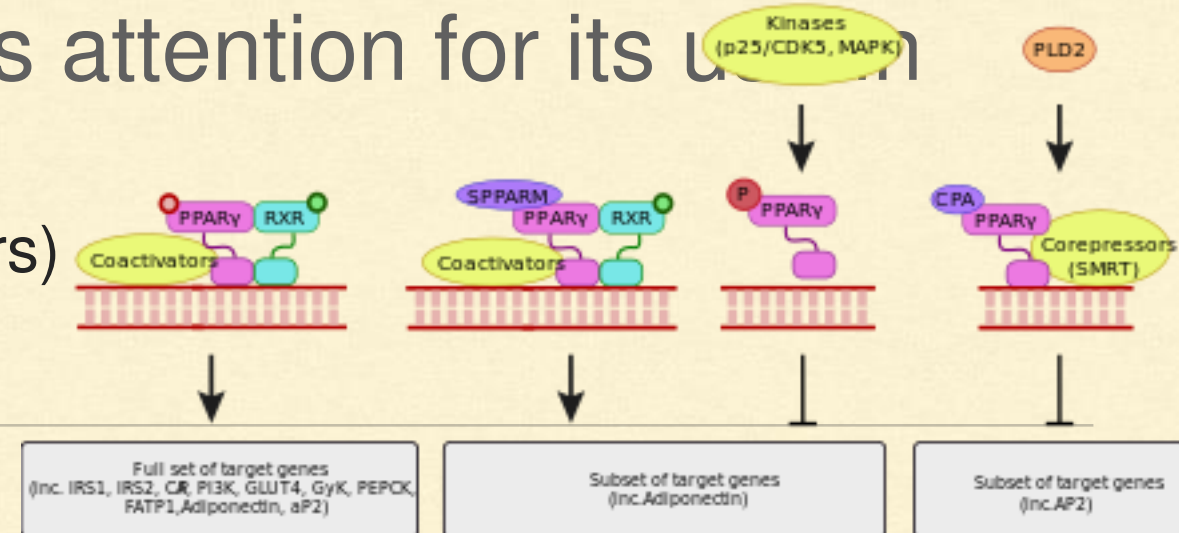
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Thiazolidinedione TZD group needs attention for its use in PCOS

PPARs (peroxisome proliferator-activated receptors)



- Gliatazone introduced 1990
- Increase storage of fatty acids in adipocytes, decreasing the amount of fatty acids present in circulation. cells become more dependent oxidation of carbohydrates, / glucose, yield energy.
- Insulin resistance is decreased
- Adipocyte differentiation is modified
- VEGF-induced angiogenesis is inhibited
- Leptin levels decrease (leading to an increased appetite)
- Levels of certain interleukins (e.g. IL-6) fall
- Antiproliferative action
- Adiponectin levels rise
- Pioglitazone (Actos), France and Germany small the risk of bladder cancer.
- Rosiglitazone (Avandia), US and increased CV events suspended in Europe, re marketed in US and EU with caution.

Ferwana M, Firwana B, Hasan R, Al-Mallah MH, Kim S, Montori VM, Murad MH (September 2013). "Pioglitazone and risk of bladder cancer: a meta-analysis of controlled studies". *Diabetes medicine: a journal of the British Diabetes Association* **30** (9): 1026–32.

LET`S LEARN TO HANDLE PIAGLITAZON

Ten trials were included.

TZDs were superior to metformin in reducing serum levels of free testosterone ($P = 0.03$) and dehydroepiandrosterone sulfate (DHEA) ($P = 0.002$) after 3 months. Decreases in triglyceride levels were more pronounced with metformin after 6 months ($P < 0.0001$).

Decreases in body mass index (BMI) were greater with metformin treatment as assessed at 3 and 6 months ($P < 0.00001$).

There were no significant between-group differences concerning improvements in ovulation, pregnancy rate, menstrual patterns or insulin sensitivity, or changes in serum levels of androstenedione, luteinizing hormone, follicle-stimulating hormone, total cholesterol, low-density lipoprotein C or insulin.

Metformin caused a significantly higher incidence of side effects such as nausea, diarrhoea and abdominal cramping ($P < 0.00001$). Significant between-study heterogeneity was detected for several variables assessed.

[Clinical Endocrinology](#)

Metformin vs Thiazolidinediones for Treatment of Clinical, Hormonal and Metabolic Characteristics of Polycystic Ovary Syndrome: A Meta-analysis

X-J. Li; Y-X. Yu; C-Q. Liu; W. Zhang; H-J. Zhang; B. Yan; L-Y. Wang; S-Y. Yang; S-H. Zhang

[Disclosures](#)

Clin Endocrinol. 2011;74(3):332-339.

LET`S LEARN TO HANDLE PIAGLITAZON

Insulin resistance is a key pathogenic defect of (PCOS).

Metformin is an insulin sensitizer acting in the liver and the peripheral tissues that ameliorates the metabolic and reproductive defects in PCOS.

Pioglitazone is an insulin sensitizer used in diabetes mellitus type 2 (T2DM), improving insulin resistance (IR) in adipose tissue and muscles. In T2DM, Combined treatment due to their "add-on effect" on insulin resistance.

Potentially promising role for combined pioglitazone/metformin treatment in the management of PCOS in metformin-resistant patients

Hormones (Athens). 2013 Jul-Sep;12(3):363-78.

Metabolic and other effects of pioglitazone as an add-on therapy to metformin in the treatment of polycystic ovary syndrome (PCOS).

[Valsamakis G](#)¹, [Lois K](#), [Kumar S](#), [Mastorakos G](#).

PIOGLITAZONE IN TR MARKET

- [DIALIC 15 MG 90 EFERVESAN TABLET](#) 89,82TL [VITALIS](#)
 - [DIALIC 30 MG 90 EFERVESAN TABLET](#) 122,84TL [VITALIS](#)
 - [DIALIC 45 MG 90 EFERVESAN TABLET](#) 197,94TL [VITALIS](#)
 - [DROPIA 45 MG 90 TABLET](#) 197,94TL [SANOVEL](#)
 - [DYNDION 45 MG 90 TABLET](#) 145,62TL [MUSTAFA NEVZAT](#)
 - [GLIFIX 45 MG 90 TABLET](#) 197,94TL [BILIM](#)
 - [PIOFORCE 45 MG 90 TABLET](#) 169,19TL [BIOFARMA](#)
 - [PIOGTAN 45 MG 90 TABLET](#) 176,95TL [ZENTIVA](#)
 - [PIONDIA 45 MG 90 FİLM TABLET](#) 188,72TL [SANDOZ](#)
 - [PIXART 45 MG 90 TABLET](#) 185,24TL [ABDI IBRAHIM](#)
- SGK reimbursed and Rxed only by endocrinologist



COMBO METFORMIN ROSIGLITAZONE = AVANDAMET



Glifix Plus 15 mg/1000 mg 30 tablet
çıktı!

OPTIMUM
komBiNasyon



- A combination of metformin and [rosiglitazone](#) was released in 2002 and sold as Avandamet by [GlaxoSmithKline](#).^[11]
9]

By 2009 it had become the most popular metformin combination
Withdrawn from market because of Good Manufacturing Practices

2011 - 2013 the [FDA](#) did not allow rosiglitazone or metformin/rosiglitazone to be sold without a prescription
/Through internet ordering

Combo is now available in US and Europe market freely since than.

AVANDAMET 2 mg rosiglitazon / 500 mg metformin 56 Film Tablet PO use in TR

2 tb a day one in the morning / one in the evening > 2*1 ACTION IN TWP WEEKS

Hepato and reno toxic / Do not use in Congestive Hearth diseased PCOS or T2DM or in prevention

**ROSI CAUSE WEIGHT GAIN, METF CAUSE WEIGHT LOSS SO NO EXPECTED
CAREFUL FOR CV INSUFICIENCY**

50 TI and SGK has limited reimbursement and can be Rxed by endocrinologist.



NEAR FUTURE DRUGS

KEEP AN EYE ON LIRAGLUTIDE



- Liraglutide (NN2211) is a long-acting glucagon-like peptide-1 receptor agonist, binding to the same receptors as does the endogenous metabolic hormone GLP-1 that stimulates insulin secretion. Help the pancreas make more insulin after eating a meal.
 - Marketed under the brand name **Victoza**, it is an injectable drug developed by Novo Nordisk for the treatment of type 2 diabetes.
 - Parenteral drug available in Tr as Victoza 6mg/ml 3ml parenteral. Maybe combined metformine 288 TL. 30 dose (0.6 mg, 3 ml.) Increase dose weekly up to 3mg/day is the max dose. No SGK coverage
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NEAR FUTURE DRUGS KEEP AN EYE ON LIRAGLUTIDE



- In overweight or obese women with PCOS treated with liraglutide for a minimum of 4 weeks,
- A mean weight loss of 9.0 kg (95% CI: 7.8–10.1, $p < 0.0001$) and
- A mean decrease in BMI of 3.2 kg/m² (95% CI: 2.8–3.6, $p < 0.0001$) were found.
- A weight loss of more than 5 and 10% of baseline weight was seen in 81.7 and 32.9% of patients, respectively.
- The mean duration of treatment with liraglutide was 27.8 weeks (SD 19.2).

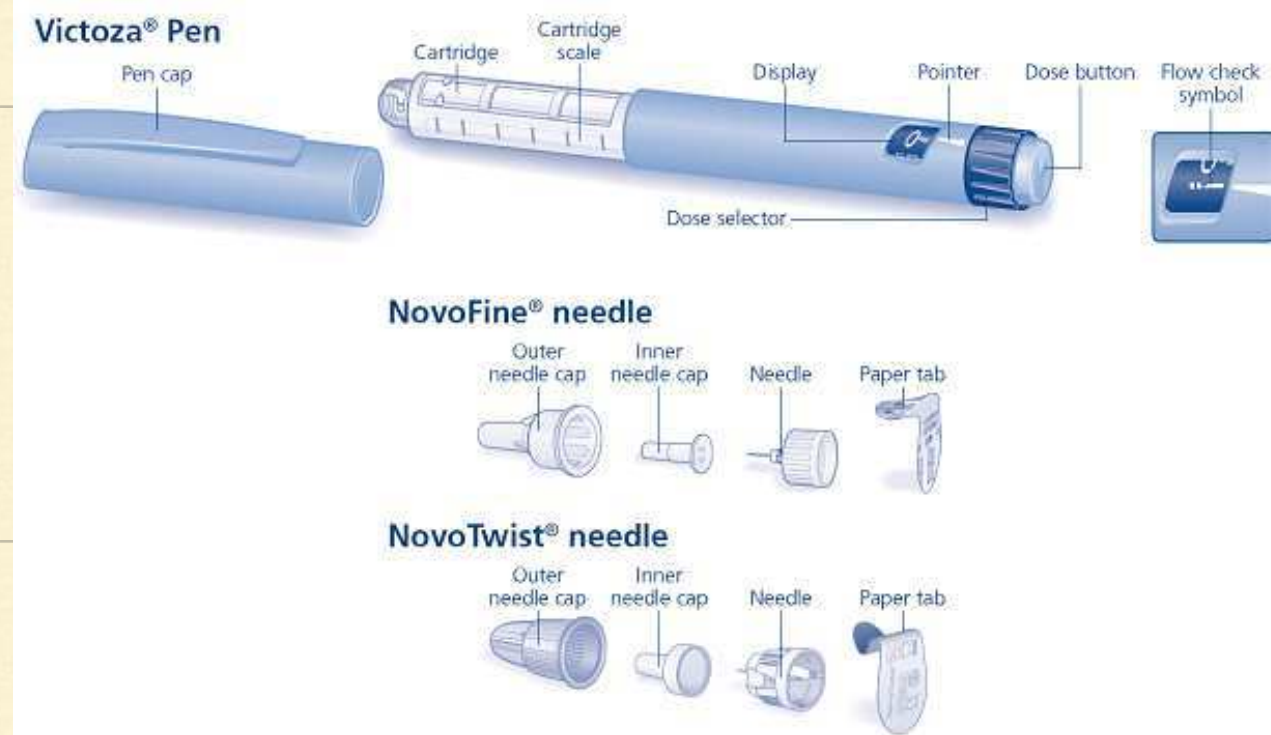
Front Endocrinol (Lausanne). 2014; 5: 140., 2014 Aug 27.

The Effect of Liraglutide on Weight Loss in Women with Polycystic Ovary Syndrome: An Observational Study

[Christina B. Rasmussen](#)^{1,*} and [Svend Lindenberg](#)¹

¹Copenhagen Fertility Center, Copenhagen, Denmark

NEAR FUTURE DRUGS KEEP AN EYE ON LIRAGLUTIDE



- 40 obese women with PCOS,
 - pretreated with metformin for at least 6 months,
 - participated in a 12-week open-label, prospective study.
 - randomized to one of three treatment arms: metformin (MET) arm 1000 mg BID, liraglutide (LIRA) arm 1.2 mg QD s.c., or combined MET 1000 mg BID and LIRA (COMBI) 1.2 mg QD s.c.
 - Lifestyle intervention was not actively promoted. The primary outcome body weight.
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- COMBI therapy was superior to LIRA and MET monotherapy in reducing weight, BMI, and waist circumference.
 - COMBI lost on average 6.5 ± 2.8 kg compared with a 3.8 ± 3.7 kg loss in the LIRA group and a 1.2 ± 1.4 kg loss in the MET group ($P < 0.001$).
 - Waist circumference also decreased by 5.5 ± 3.8 cm in the COMBI arm compared with 3.2 ± 2.9 cm in LIRA and 1.6 ± 2.9 cm in the MET arm ($P = 0.029$).
 - Subjects treated with liraglutide experienced more nausea than those treated with metformin, but severity of nausea decreased over time and did not correlate with weight loss.

• Eur J Endocrinol. 2014 Feb 7;170(3):451-9. doi: 10.1530/EJE-13-0797. Print 2014 Mar.

Short-term combined treatment with liraglutide and metformin leads to significant weight loss in obese women with polycystic ovary syndrome and previous poor response to metformin.

[Jensterle Sever M](#)¹, [Kocjan T](#), [Pfeifer M](#), [Kravos NA](#), [Janez A](#).

¹Department of Endocrinology, Diabetes and Metabolic Diseases, University Medical Center Ljubljana, Zaloska 7, 1525 Ljubljana, Slovenia.

ENDOMETRIOSIS AND PCOS

- Oligo ovulatory
 - Early low BMI
 - Endometriosis flourish and evolve,
 - Late endo behaves mild over 35 years of age, but if BMI is over 30
 - Some E1 and some fat derived estrogens contribute end
 - We institute Tx as progesterone in premenopause, lowering BMI in menopause
 - Cyst prevention in premenopause, Ca 125 values to understand active endo
-

HAVE MANY OLDER PCOS PATIENTS NOW !!!!!

TOO MANY SAFE OPTIONS >>>>>>>>>>>>>>>TO GO

