



Tratamentul cu metformin in sindromul ovarelor micropolichistice

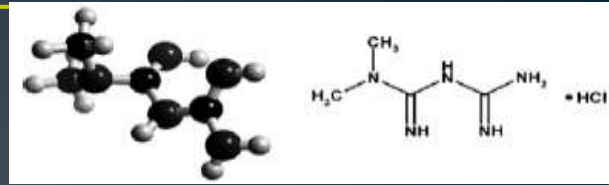
Cristina Preda, Letitia Leustean, Cristina Cristea, Voichita Mogos, Carmen
Vulpoi

Universitatea de Medicina si Farmacie "Gr. T. Popa" Iasi, Romania

- *Galega officinalis* (liliac francez)

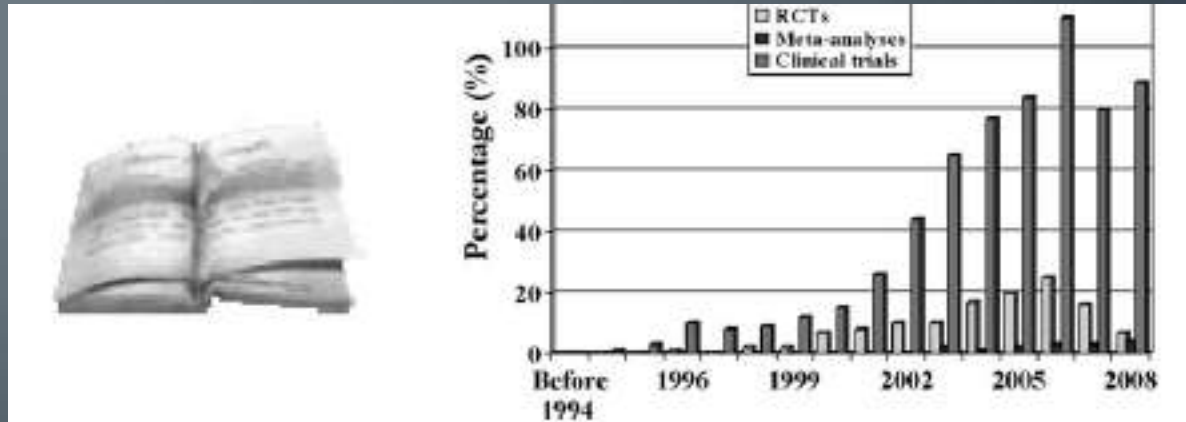
Derivat- METFORMIN

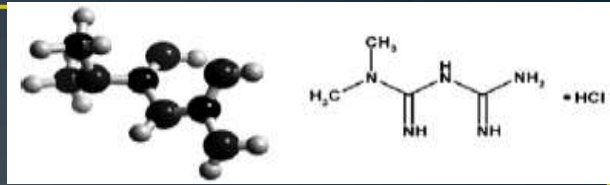




METFORMIN

- Anul aparitiei- 1957
- 1994 Velazquez si colab. au evaluat pentru prima data efectul tratamentului cu metformin la 26 paciente obeze cu PCOS in cursul investigarii rolului insulino-rezistentei in patogenia sindromului ovarelor polichistice.



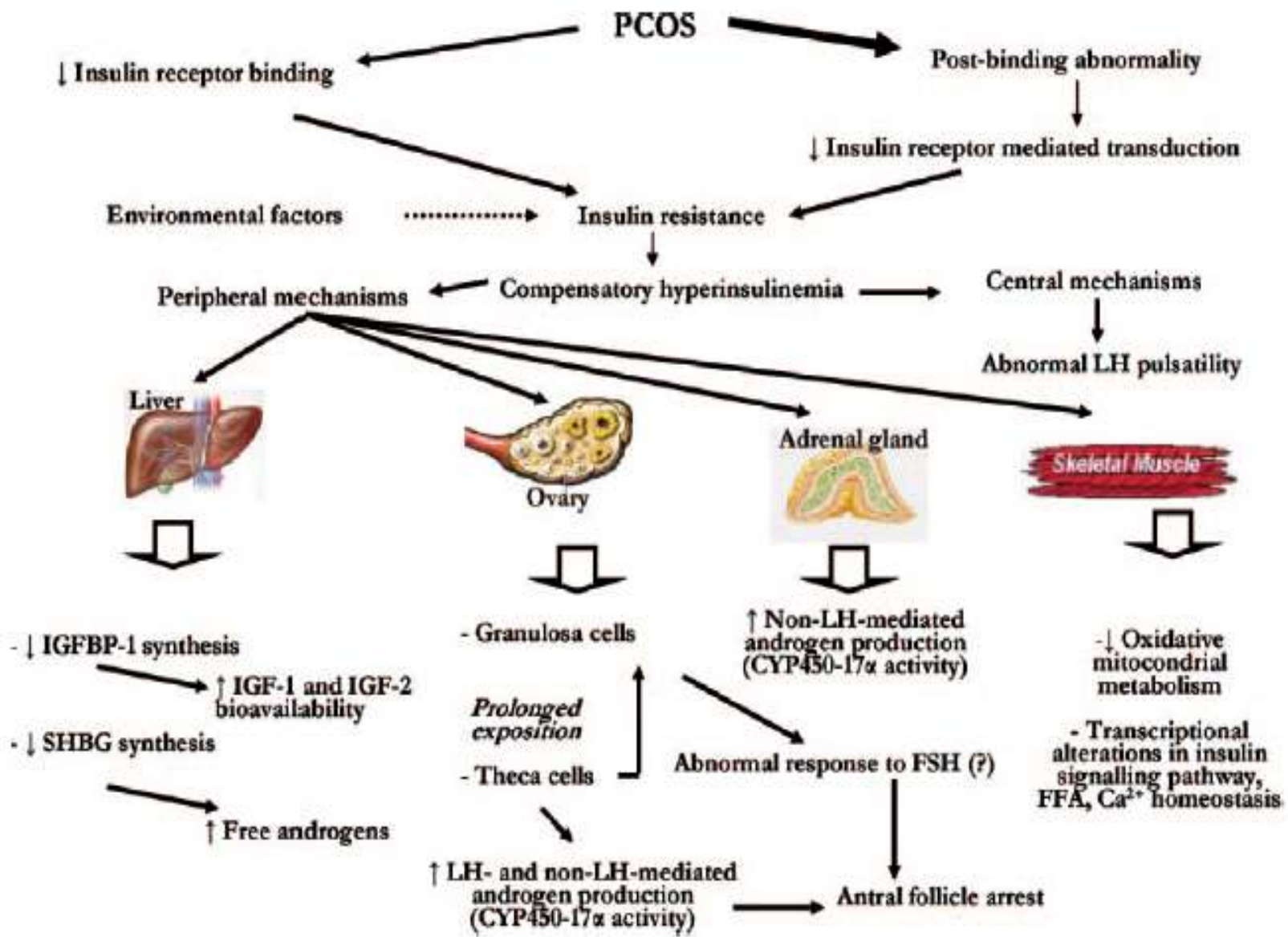


METFORMIN

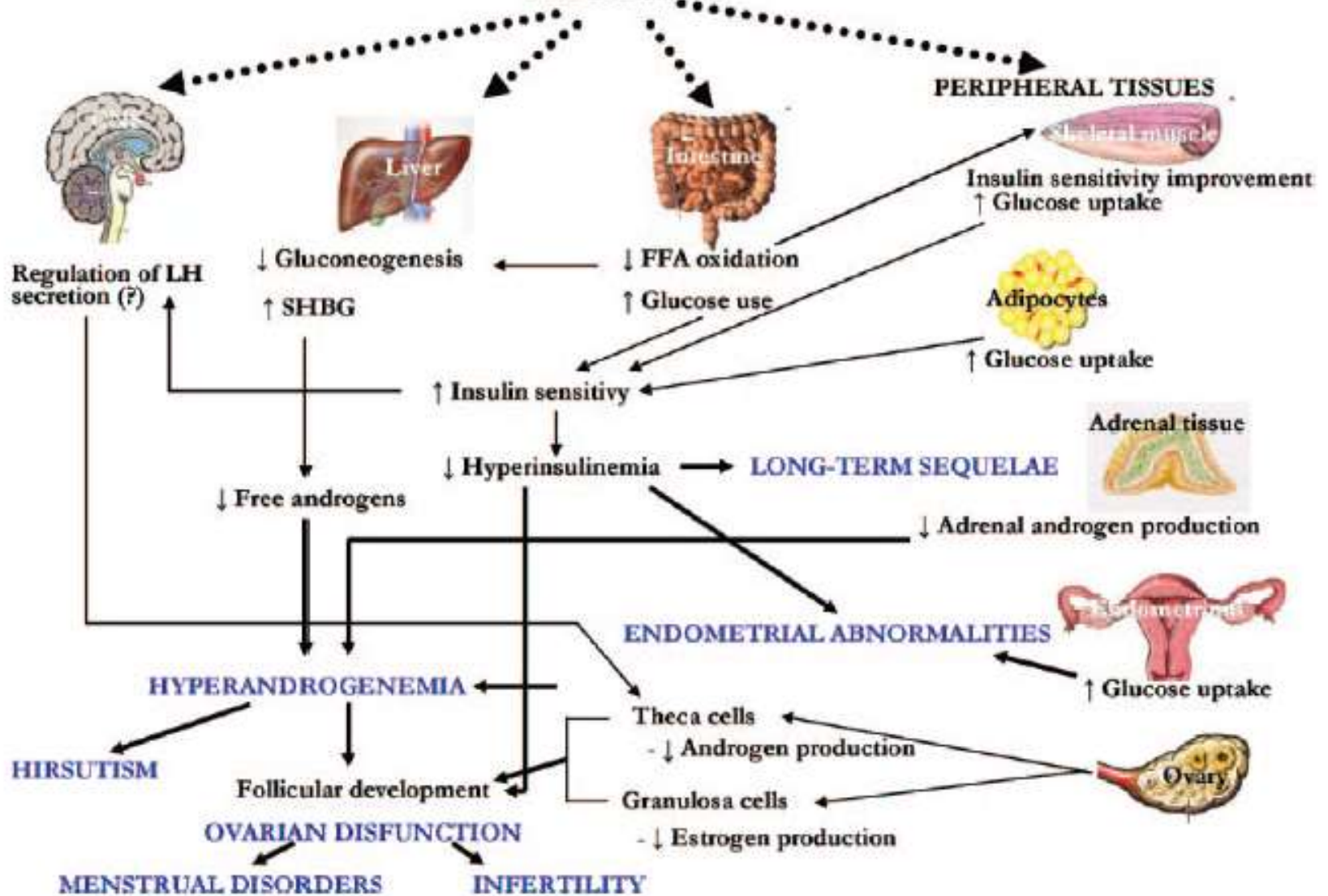
- Agent hipoglicemiant: scaderea productiei hepatice de glucoza
- Amelioreaza insulinoresistenta si steatoza hepatica
- Protejeaza impotriva complicatiilor diabetului
- Efect dual in PCOS (scaderea insulinoresistentei si efect direct ovarian).
- Efect de prevenire a diabetului
- Terapia cancerului

Valsamakis G et al., 2013

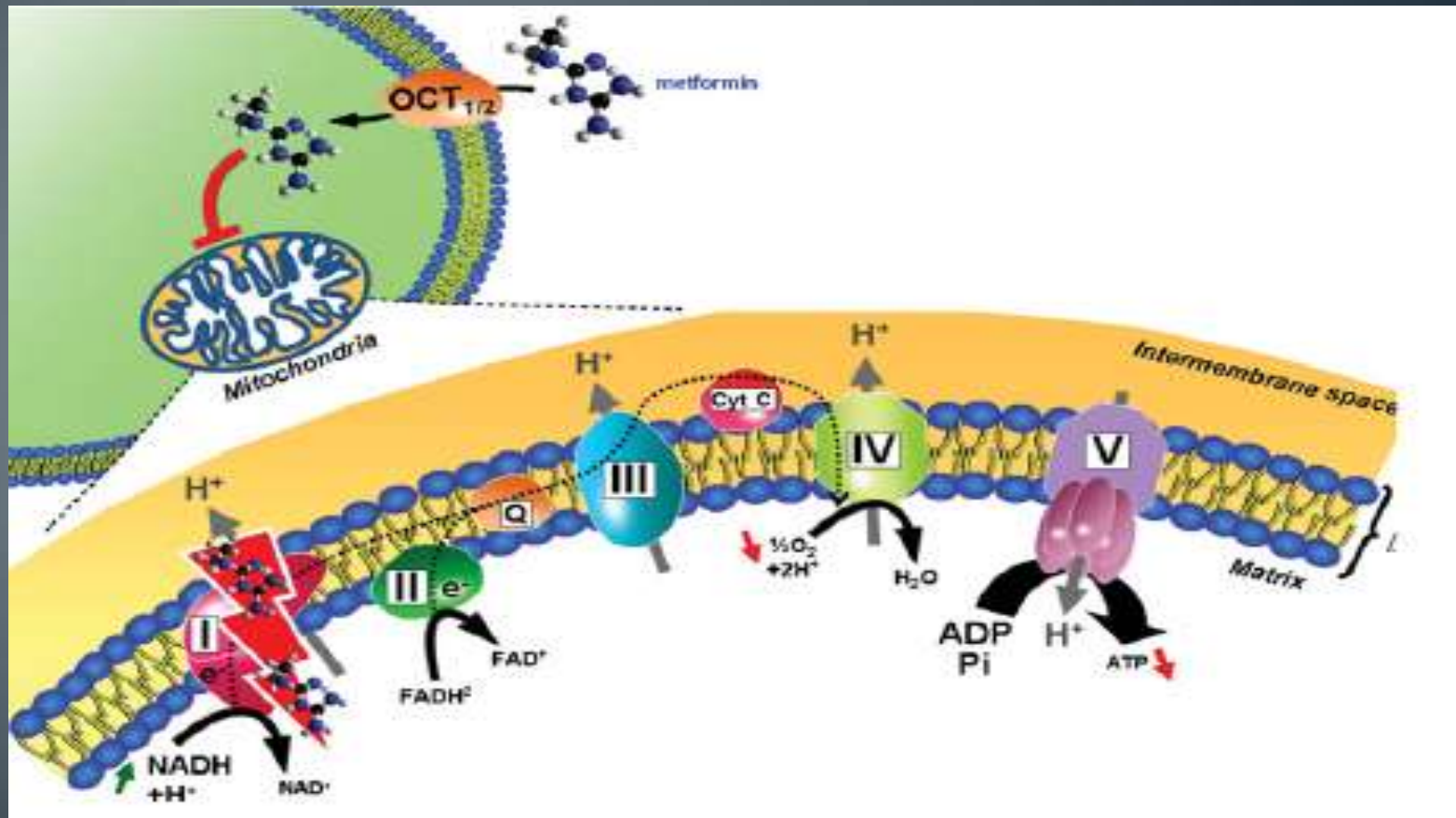
Benoit V et al., 2012



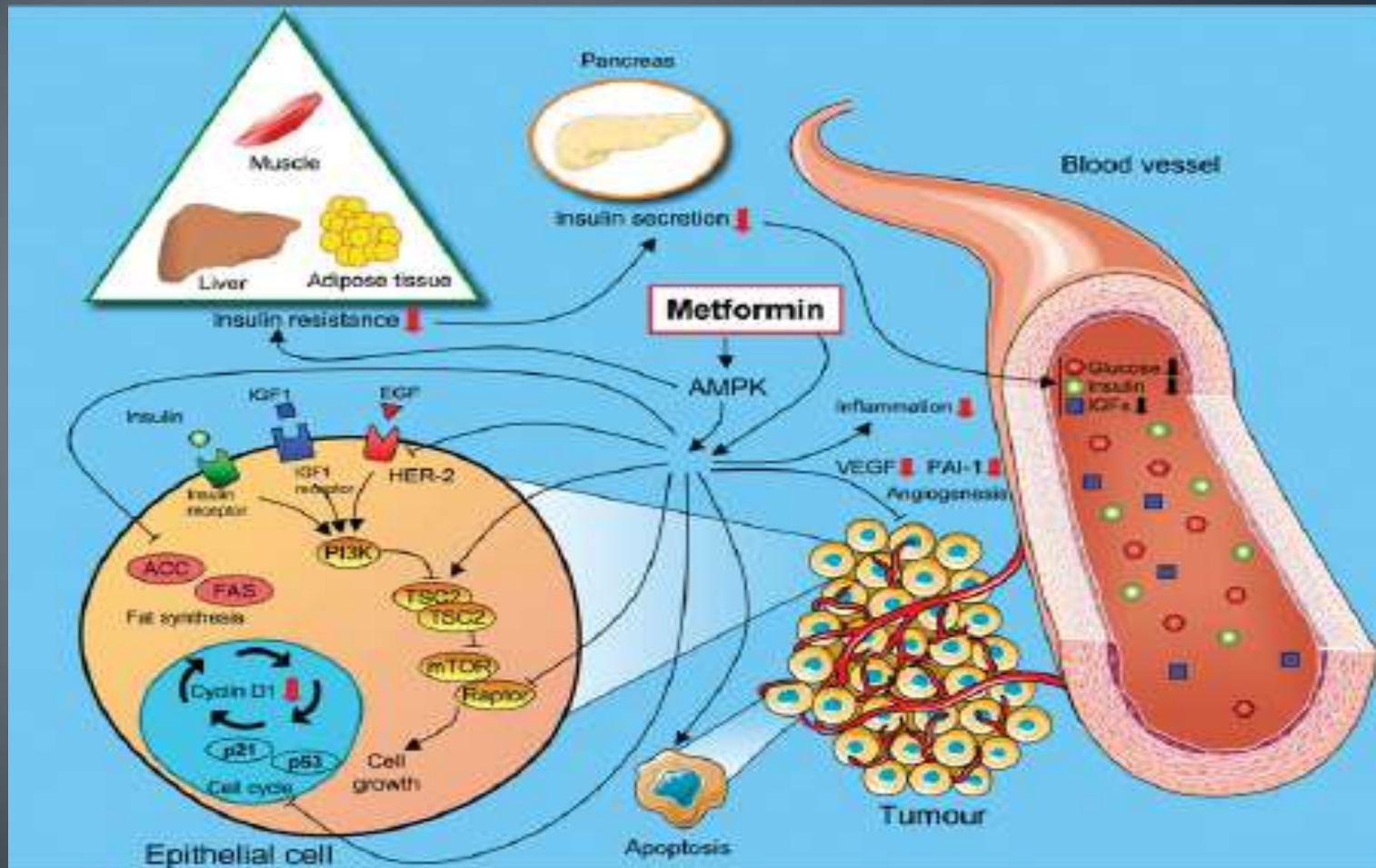
Metformin



EFFECTUL METFORMIN LA NIVEL MITOCONDRIAL



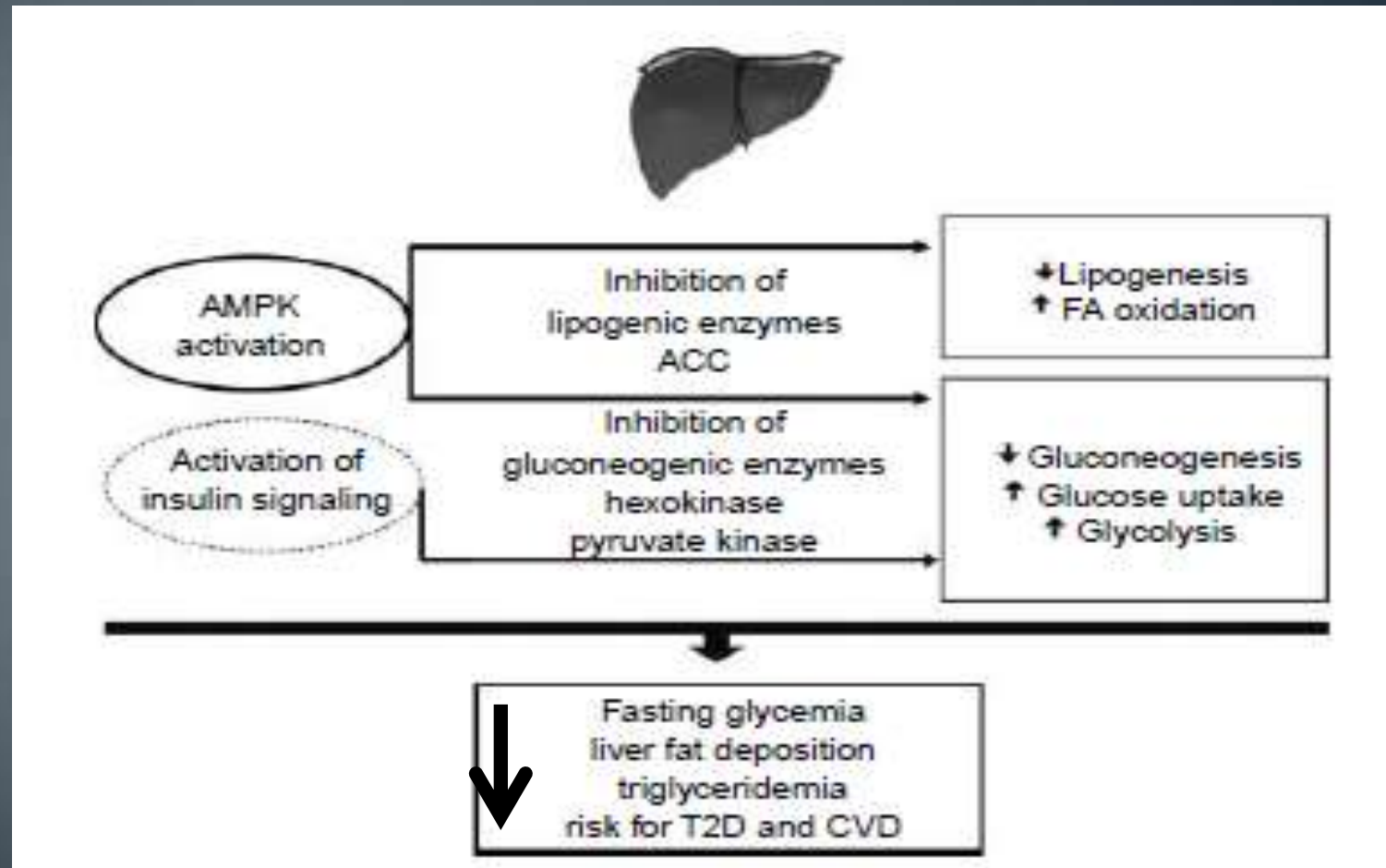
METFORMIN: CONTROLUL PROLIFERARII CELULARE SI CRESTERII TUMORALE



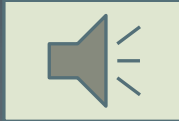
METFORMIN



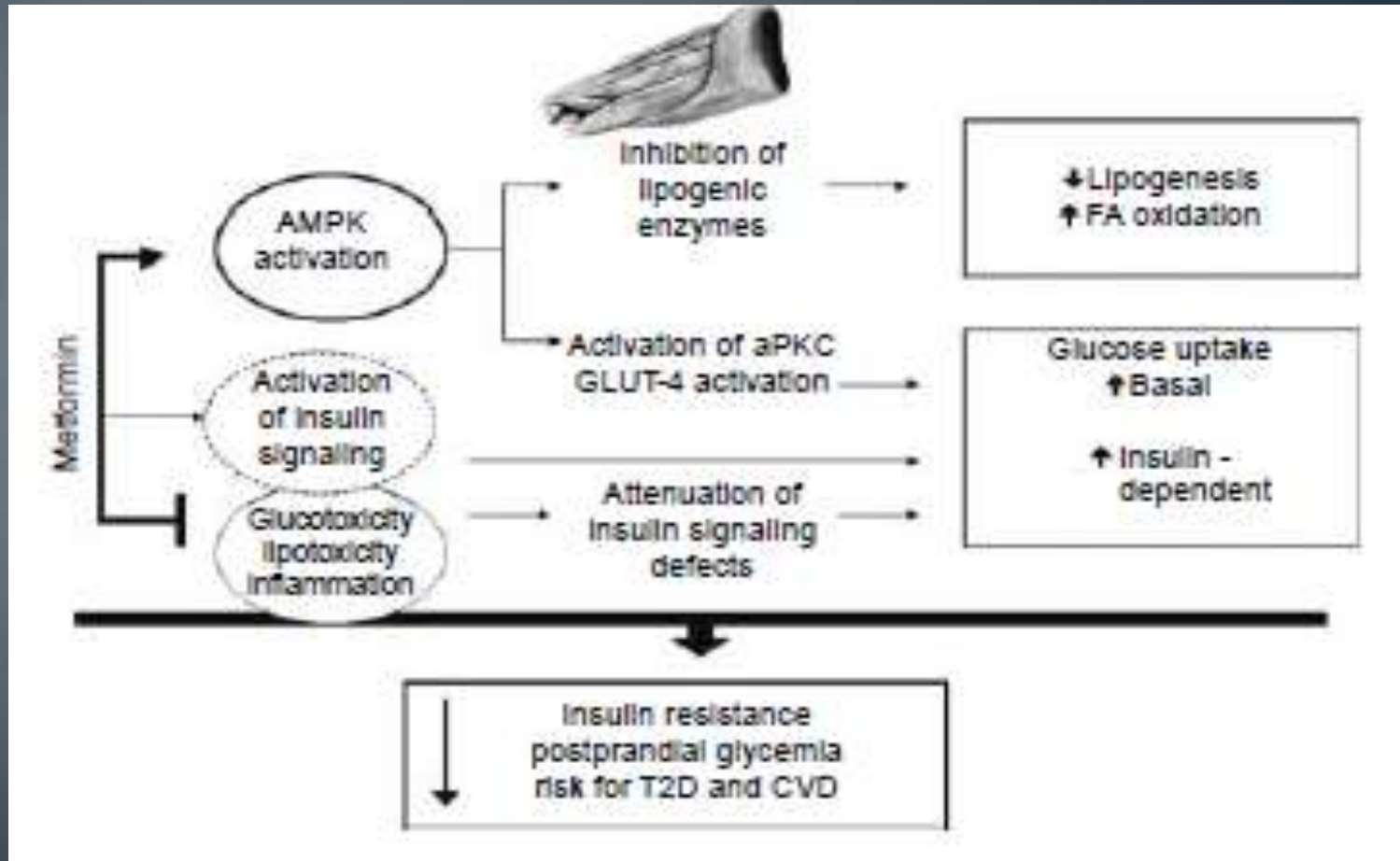
FICAT



METFORMIN



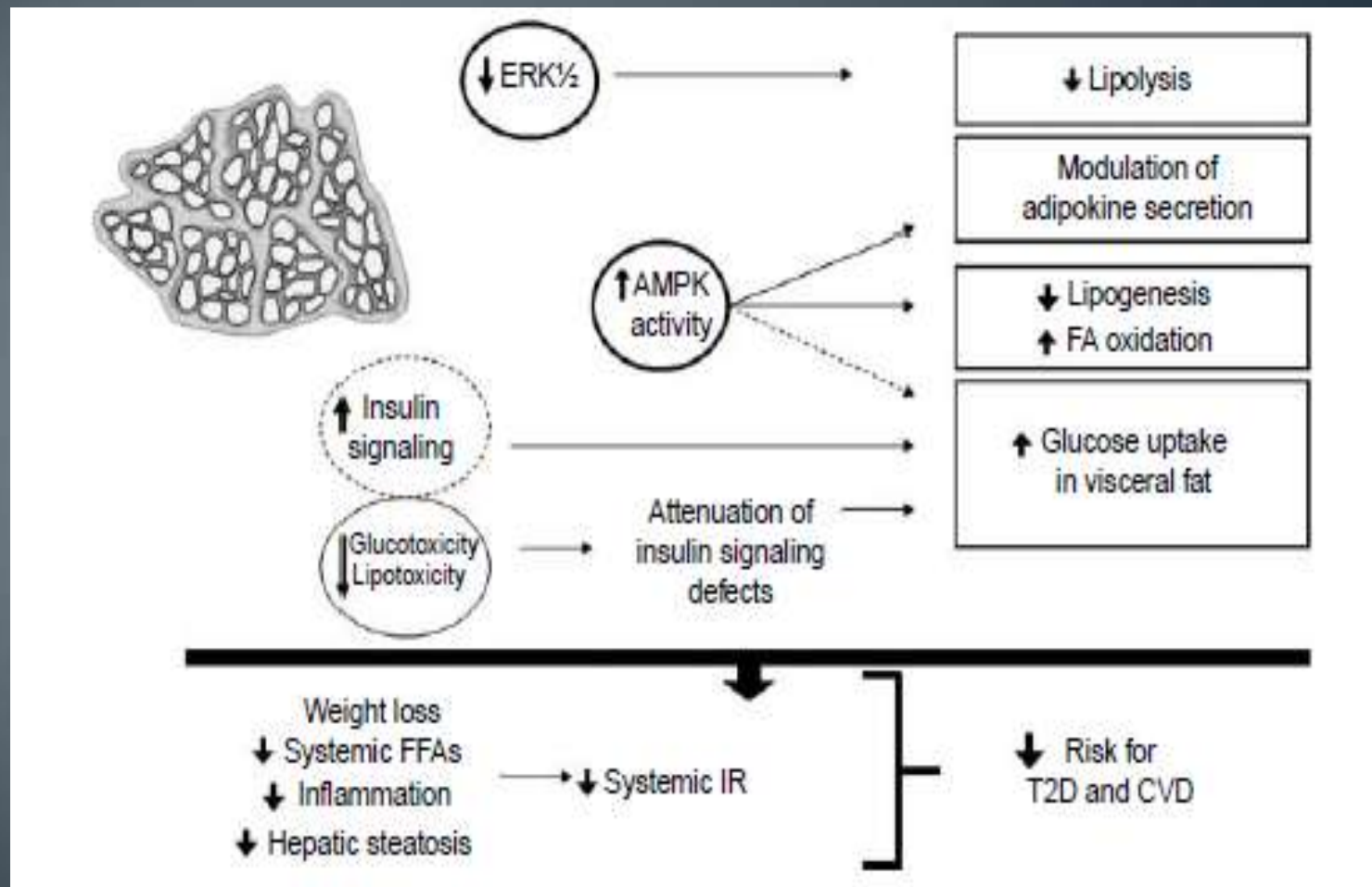
MUSCHI SCHELETIC



METFORMIN



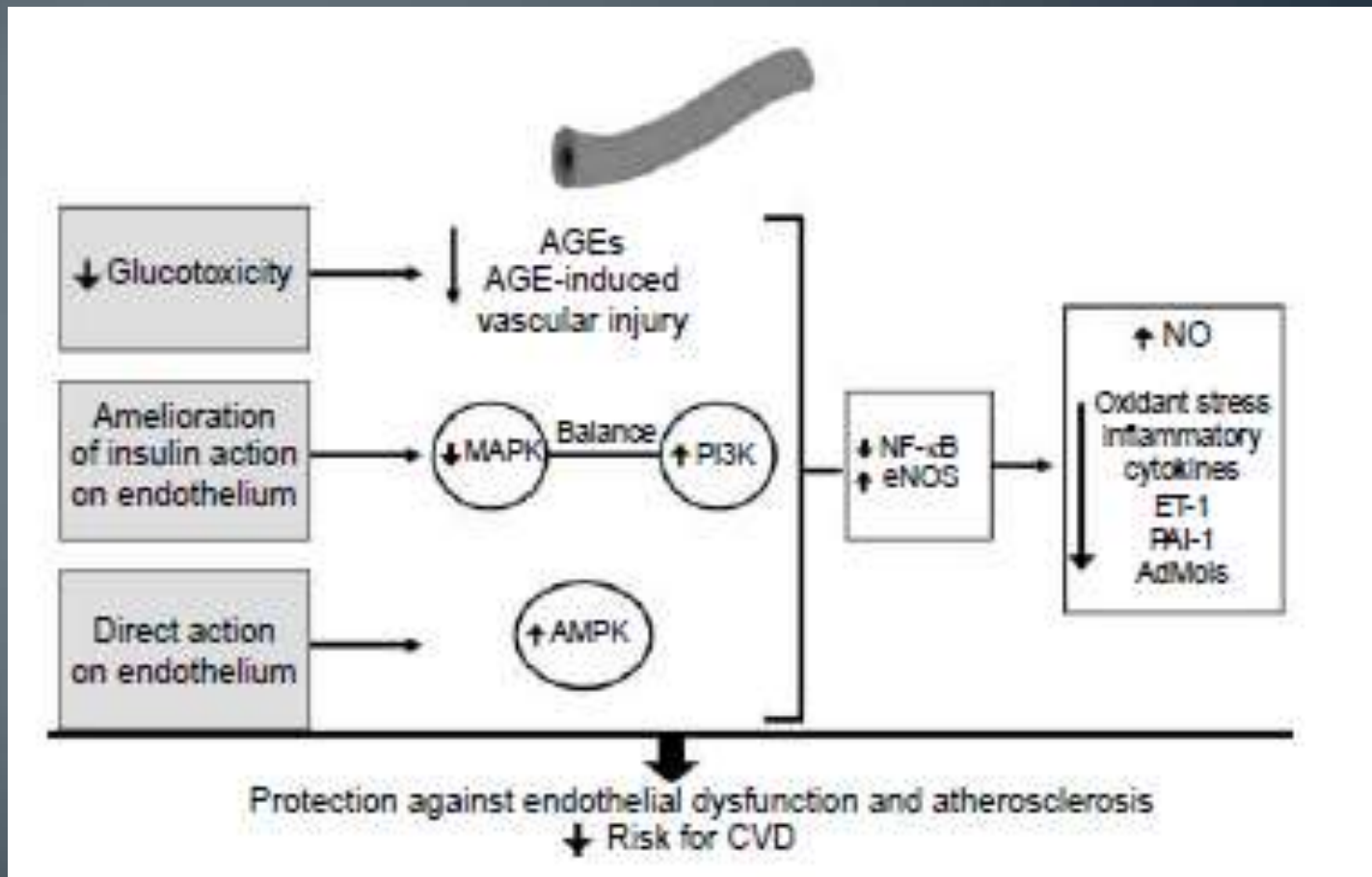
TESUT ADIPOS



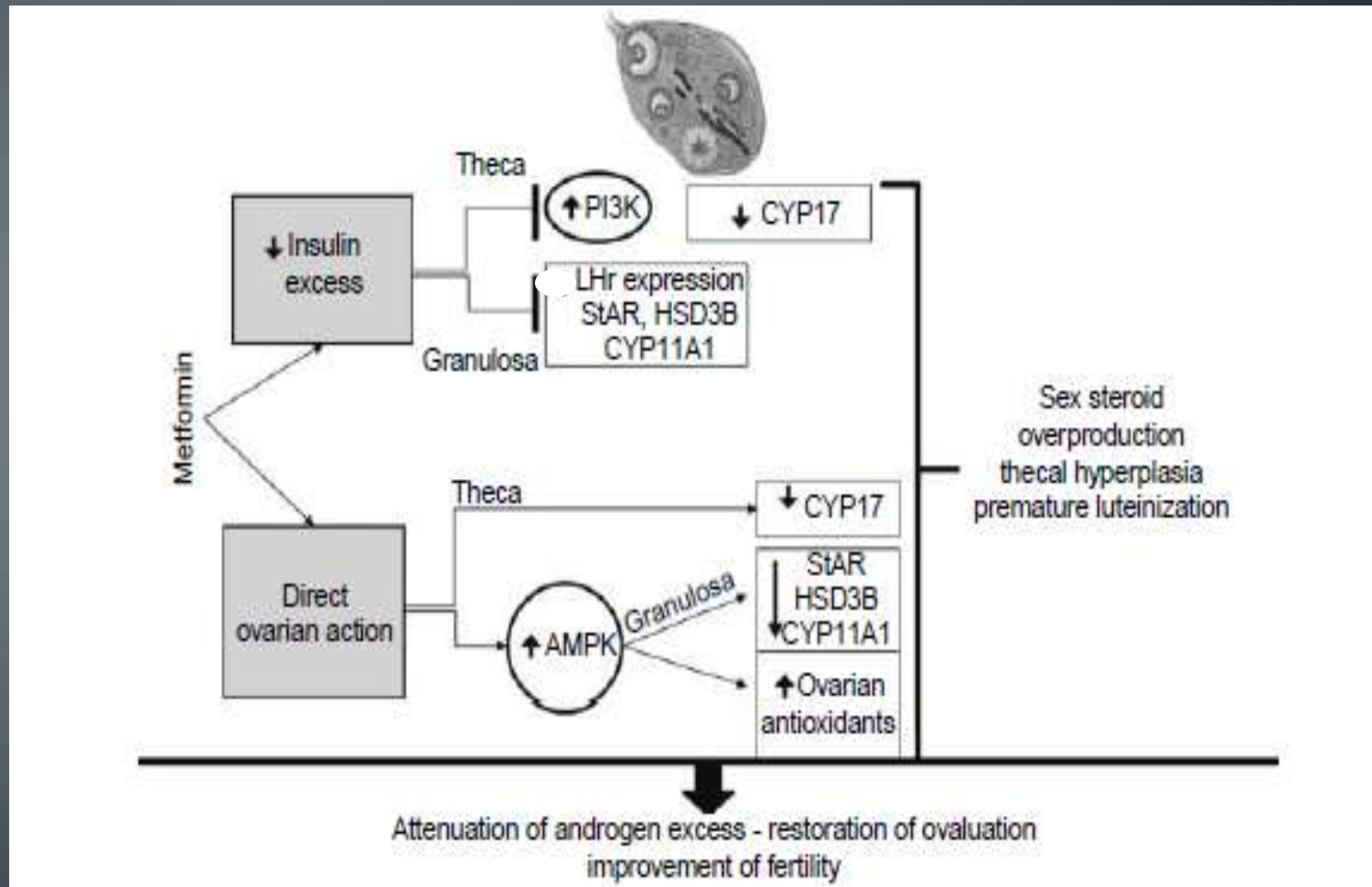
METFORMIN



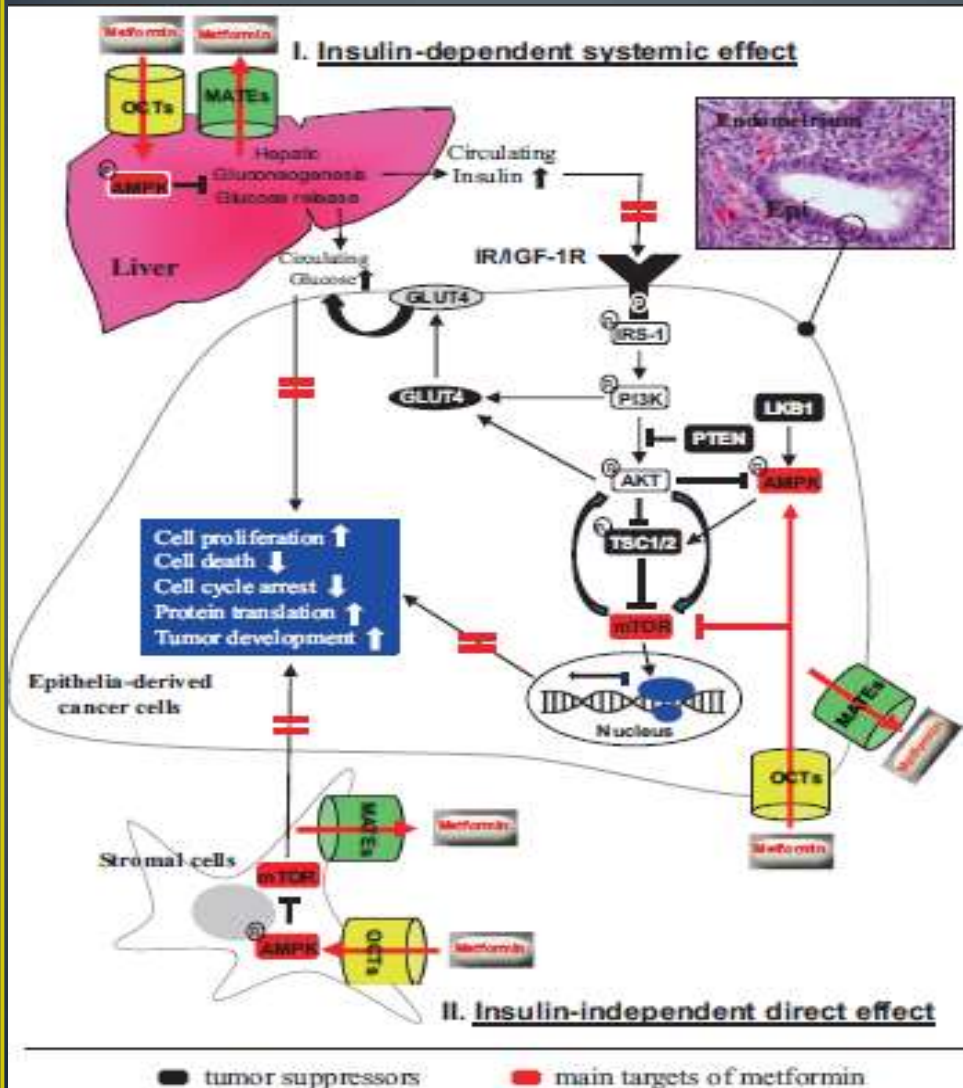
ENDOTELIU



METFORMIN OVAR



METFORMIN: EFECT PE ENDOMETRU



- Nu exista studii clinice care sa dovedeasca efectul M in cancerul de endometru dar, M in combinatie cu inhibitori de mTOR are efect in cancerul de endometru metastatic sau recurent.

Shao R et al., 2014

INDICATIILE METFORMINULUI IN PCOS

- Pacientele care doresc sa slabeasca, ca adjuvant la efortul fizic si dieta
- La pacientele cu DZ tip 2 sau toleranta scazuta la glucoza
- La pacientele cu multiple avorturi spontane (utilizare inainte si in timpul sarcinii).
- La pacientele care doresc o sarcina (rezistente la CC) ca adjuvant la terapia cu clomifen citrat sau inainte sau in timpul FIV.

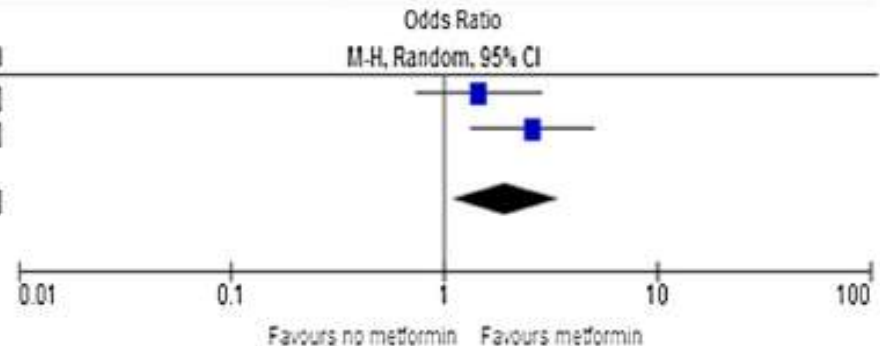
Valsamakis G et al., 2013

METFORMIN SI GONADOTROFINE

A) Outcome: Live-birth rate

Study or Subgroup	Metformin		Not metfor		Weight	Risk Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI
Palomba 2005	17	85	12	87	49.7%	1.45 [0.74, 2.85]
Begum 2013	24	213	12	276	50.3%	2.59 [1.33, 5.06]
Total (95% CI)		298		363	100.0%	1.94 [1.10, 3.44]
Total events	41		24			

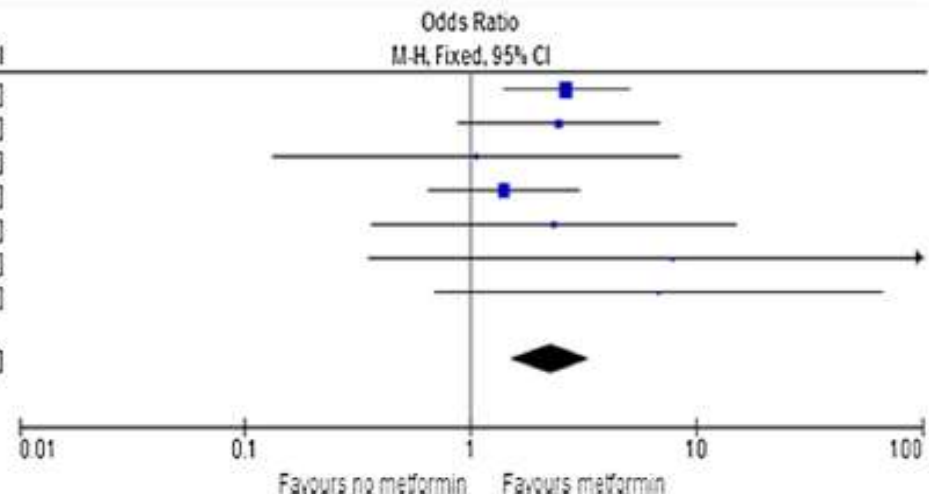
Heterogeneity: $\tau^2 = 0.05$; $\text{Chi}^2 = 1.44$, $\text{df} = 1$ ($P = 0.23$); $I^2 = 30\%$
 Test for overall effect: $Z = 2.28$ ($P = 0.02$)



B) Outcome: Pregnancy rate

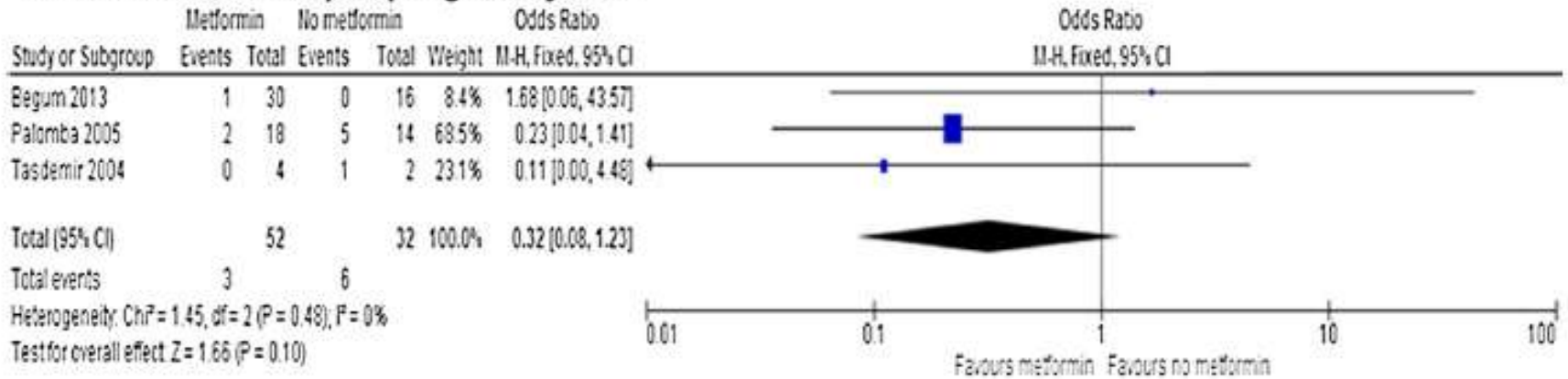
Study or Subgroup	Metformin		No metformin		Weight	Odds Ratio
	Events	Total	Events	Total		M-H, Fixed, 95% CI
Begum 2013	30	213	16	276	37.3%	2.66 [1.41, 5.03]
Cheng 2010	13	79	6	81	15.4%	2.46 [0.89, 6.84]
De Leo 1999	2	18	2	19	5.4%	1.06 [0.13, 8.47]
Palomba 2005	18	85	14	87	33.9%	1.40 [0.65, 3.04]
Tasdemir 2004	4	16	2	16	4.7%	2.33 [0.36, 15.05]
van Santbrink 2005	Favours no metformin		Favours metformin			35, 174.42]
Yarali 2002	0	16	1			3.69, 66.90]
Total (95% CI)		438		504	100.0%	2.25 [1.50, 3.38]
Total events	75		41			

Heterogeneity: $\text{Chi}^2 = 3.77$, $\text{df} = 6$ ($P = 0.71$); $I^2 = 0\%$
 Test for overall effect: $Z = 3.93$ ($P < 0.0001$)

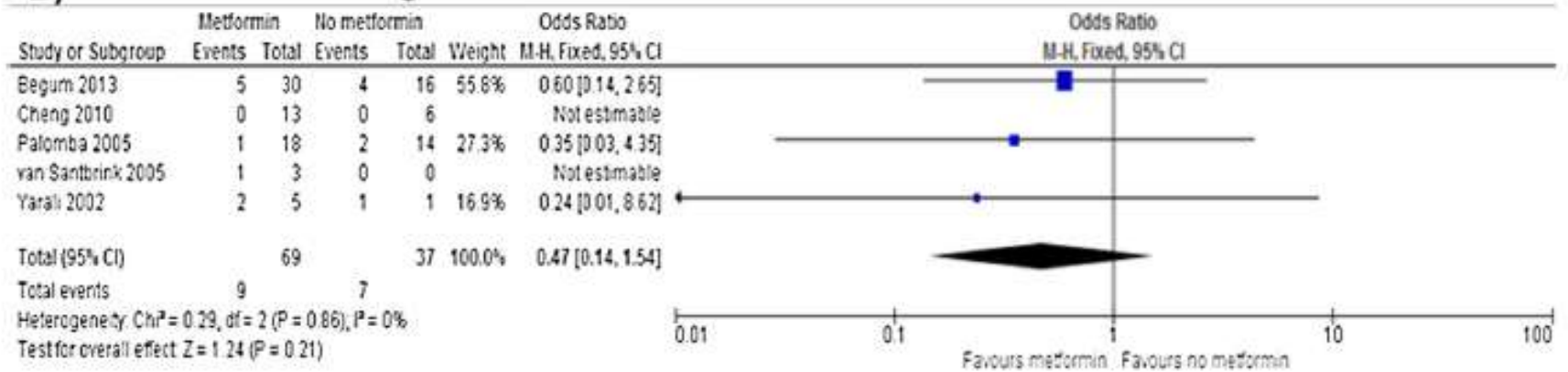


METFORMIN SI GONADOTROFINE

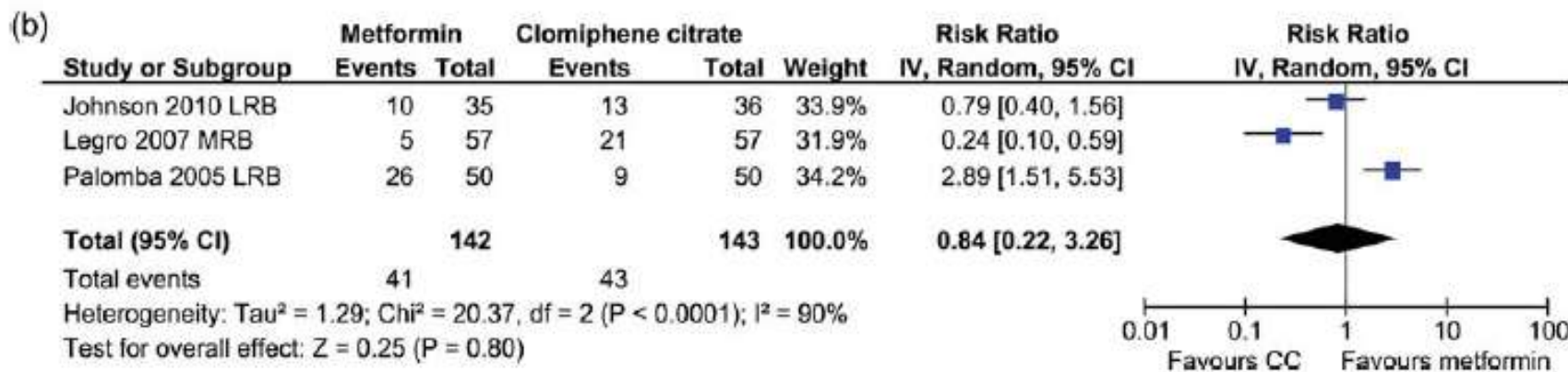
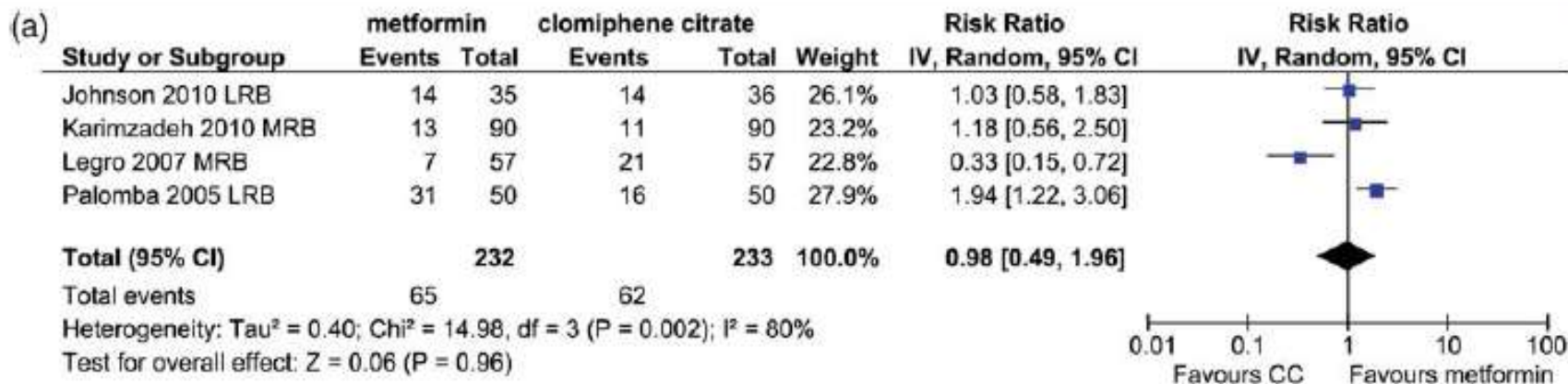
A) Outcome: Multiple pregnancy rate



B) Outcome: Miscarriage rate

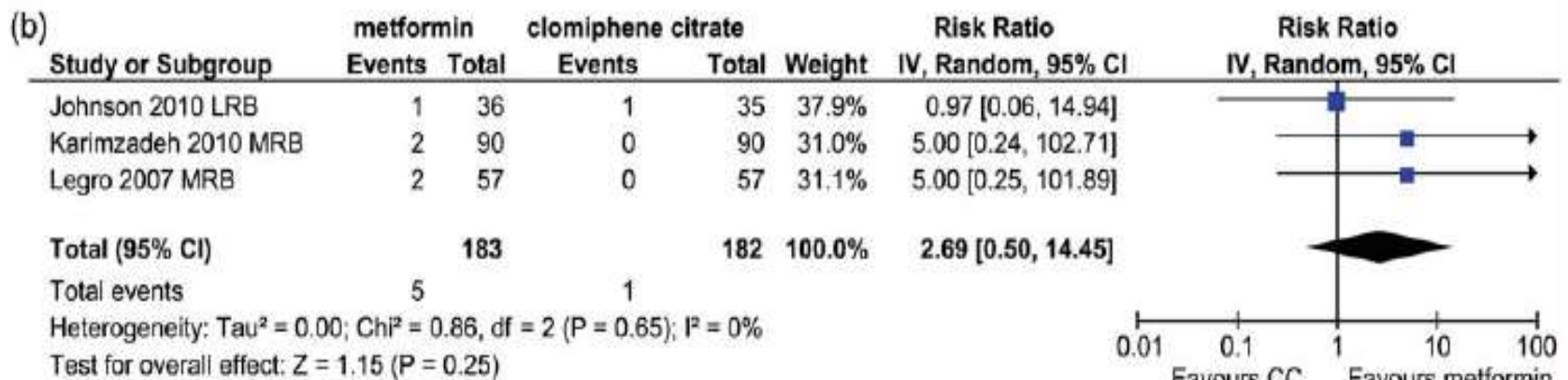
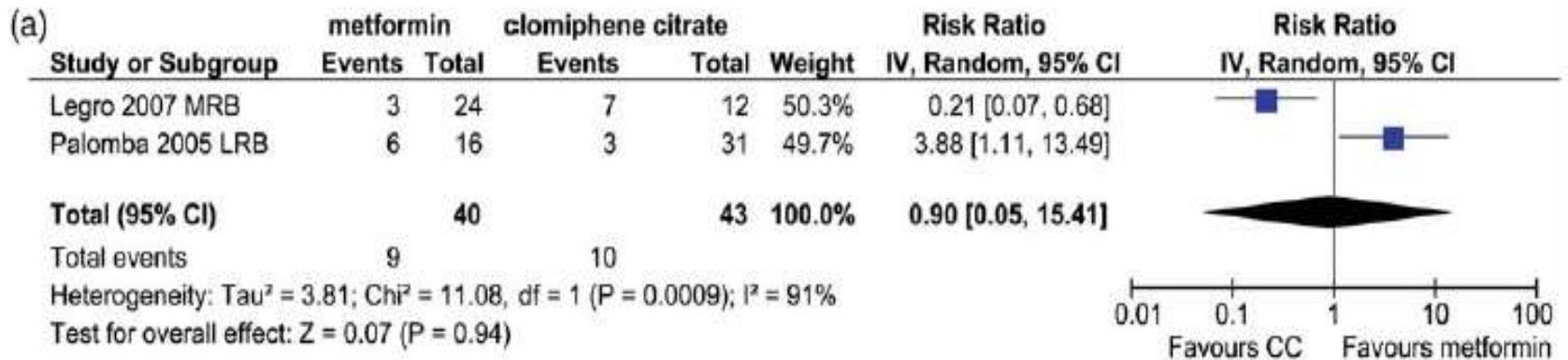


METFORMIN vs CC ca tratament al infertilitatii la pacientele cu PCOS non-obeze



- a) Sarcini/pacienta
- b) Nasteri feti vii/pacienta

METFORMIN vs CC ca tratament al infertilitatii la pacientele cu PCOS non-obeze



- a) Avorturi/pacienta
- b) Sarcini multiple/pacienta

ANOVULATIE INFERTILITATE

Study (Ref.)	Study population-PCOS definition	Primary outcome measures
Reproductive features		
Meta-analysis (74) 13 RCTs	543 PCOS (NIH)	Metf versus plac Metf+CC versus CC mono <u>↑ Ovulation rate</u> Metf+CC versus CC <u>↑ Pregnancy rate</u>
Meta-analysis (75) 12 RCTs, 2 cohorts, 16 uncontrolled descriptive studies	PCOS	Metf versus plac Metf+CC versus CC mono <u>↑ Ovulation rate</u> Metf+CC versus CC mono <u>↑ Pregnancy rate</u>
Meta-analysis (84) 27 RCTs	PCOS (Rotterdam)	Metf versus CC and Metf+CC versus CC ↔ Live birth rate in therapy-naive Metf+CC versus CC <u>↑ Live birth rate in CC resistant</u>
RCT double-blind (79)	100 PCOS (NIH)	Metf+plac versus CC+plac: ↔ ovulation rate <u>↑ Pregnancy rate</u> <u>↓ Abortion rate</u>
RCT (82)	626 PCOS (NIH)	Trend ↑ for live birth rate CC+plac and CC+metf versus metf+plac <u>↑ Live birth rate</u>
RCT double-blind (83)	225 PCOS (NIH)	Metf+CC versus CC+plac <u>↑ Pregnancy rate</u> in older and visc obese

ANOVULATIE INFERTILITATE

- Monoterapie: amelioreaza rata ovulatiei fara a ameliora rata sarcinilor.
- Terapia combinata (M+CC) nu imbunatateste rata fertilitatii (sarcini duse la termen).
- La femeile rezistente la CC, tratamentul combinat (M+CC) este superior in termeni de nasteri de feti vii.
- In timpul FIV co-administrarea de M reduce riscul de hiperstimulare ovariana.

SARCINA

TEORIE

- Insulino-rezistenta
- PAI-1
- Tromboza
- Insuficienta placentara
- Glycodelin
- Implantare embrion

PRACTICA

- Trece bariera feto-placentara
- In vivo (model animal) creste rata de implantare embrion.
- ! Sarcini complicate cu perfuzie placentara deficitara M poate interfera cu mecanismele adaptative.
- Datele referitoare la siguranta si eficacitate nu sunt confirmate de studii randomizate.

METABOLISM GLUCIDIC

- Efect protector impotriva DZ tip2 prin scaderea glicemiei si ameliorarea sensibilitatii la insulina.
- Prezervarea rezervei de celule β pancreatice.
- Rata de conversie anuala din toleranta normala in intoleranta la glucoza scade de la 16-19% la cele netratate la 1,4% la cele tratate.
- Nu exista studii randomizate, dublu-orb, placebo-controlate privind efectul M la paciente cu PCOS.

METFORMIN SI PIOGLITAZONA

In summary, although metformin is preferred for the treatment of PCOS, it seems that pioglitazone is better at improving the insulin effectiveness in obese and lean PCOS women at the cost, however, of increased body weight. On the other hand, the addition of pioglitazone in metformin-resistant treated PCOS women significantly ameliorates metabolic and hormonal defects. Based on these findings, combined metformin/pioglitazone treatment could have a role in the management of PCOS women, especially in those with more severe phenotypes. A low-dose and short-term treatment course (e.g. 6 months) with pioglitazone might be better in view of weight gain and the recent suggestions by CHMP. It should be

GREUTATE CORPORALA SI DISTRIBUTIA TESUTULUI ADIPOS

Metabolic features ± menstrual frequency		
RCT double-blind (34)	56 PCOS (NIH)	Metf versus plac in obese ↓ BMI, SBP, FG, HOMA, Testo ↑ HDL
RCT double-blind (35)	40 PCOS (NIH)	Metf versus plac ↔ Fat distribution
RCT (137)	76 PCOS (Rotterdam)	Metf + diet versus plac + diet ↑ Menstrual frequency ↓ Glucose-stimulated insulin levels
RCT double-blind (139)	143 PCOS (Rotterdam)	Metf + diet versus plac + diet ↔ BMI, menstrual frequency, QUICKI ↓ WC, FAI

- Scaderea adipozitatii viscerale in combinatie cu modificarile stilului de viata
- Scaderea adipozitatii de tip central la doze > 2500mg/zi

MANIFESTARI CARDIOVASCULARE

- Scaderea TA sistolice
- Scaderea LDL-colesterol
- Cresterea HDL-colesterol
- Reducerea markerilor inflamatiei
- Reducerea ET-1 puternic vasoconstrictor
- Reducerea AGEs (mediatori oxidativi ai disfunctiei epiteliale).

FACTORI PREDICTIVI AI EFICACITATII

- BMI bazal
- Virsta inaintata si perioada indelungata de infertilitate
- Gradul de insulinorezistenta & BMI
- Gradul de hiperandrogenism
- Genotipul ? (polimorfism STK11 sau LKB1).

EFECTE ADVERSE

Efecte secundare

- Diaree (10-50%)
- Dureri abdominale
- Flatulenta
- Meteorism
- Dispepsie
- Anorexie
- Gust metalic
- Malabsorbție vit. B12 (10-30%)
- Acidoza lactică

Contraindicații

- Insuficiență renală
- Insuficiență hepatică
- Insuficiență cardiacă congestivă severă
- Alcoolism

MASURI DE PRECAUTIE

- 500 mg/zi la masa principala
- Crestrea dozei cu 500mg/saptamina
- Maximum 2500-2550 mg/zi divizat in 3 doze
- Renuntare la tratament in caz de diaree prelungita
- Masurarea nivelului plasmatic de vit. B12
- Monitorizarea semnelor si simptomelor de anemie megaloblastica

CONCLUZII

- Metformin: tratament de prima intentie al oligomenoreei la pacientele obeze/supraponderale cu PCOS.
- Metformin: tratamentul infertilitatii la pacientele cu PCOS rezistente la CC si care doresc sa evite sarcinile multiple.
- Metformin posibil potential de reducere a riscului de diabet gestational.
- Metformin posibil efect benefic asupra endometrului.
- Metforminul nu trebuie considerat ca tratament al obezitatii asociate PCOS.
- Metformin amelioreaza markerii BCV in PCOS.

BIBLIOGRAFIE

1. Diamanti-Kandarakis E et al. Metformin : an old medication of new fashion: evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome. *European Journal of Endocrinology* (2010) 162, 193-212.
2. Misso ML et al. metformin versus clomiphene citrate for infertility in non-obese women with polycystic ovary syndrome: a systematic review and meta-analysis. *Human Reproduction Update* (2013) 19, 2-11.
3. Pappa T, Alevizaki M. Metformin and Thyroid: an update. *European Thyroid Journal* (2013) 2, 22-28.
4. Palomba S et al. Metformin and gonadotrophins for ovulation induction in patients with polycystic ovary syndrome: a systematic review with meta-analysis of randomized controlled trials. *Biology and Endocrinology* (2014) 12, 1-15.
5. Palomba et al. Evidence-based and potential benefits of Metformin in the polycystic ovary syndrome: a comprehensive review. *Endocrine Reviews* (2009) 30, 1-50.
6. Shao R et al. Direct effects of Metformin in the endometrium: a hypothetical mechanism for the treatment of women with PCOS and endometrial carcinoma. *Journal of Experimental & clinical Cancer Research* (2014) 33-41.
7. Valsamakis G et al. Metabolic and other effects of pioglitazone as an add-on therapy to metformin in the treatment of polycystic ovary syndrome (PCOS). *Hormones* (2013) 12, 363-378.
8. Viollet B et al. Cellular and molecular mechanisms of metformin: an overview. *Clinical Science* (2012) 122, 253-270.