



# DIET AND DIETARY SUPPLEMENT IN PCOS

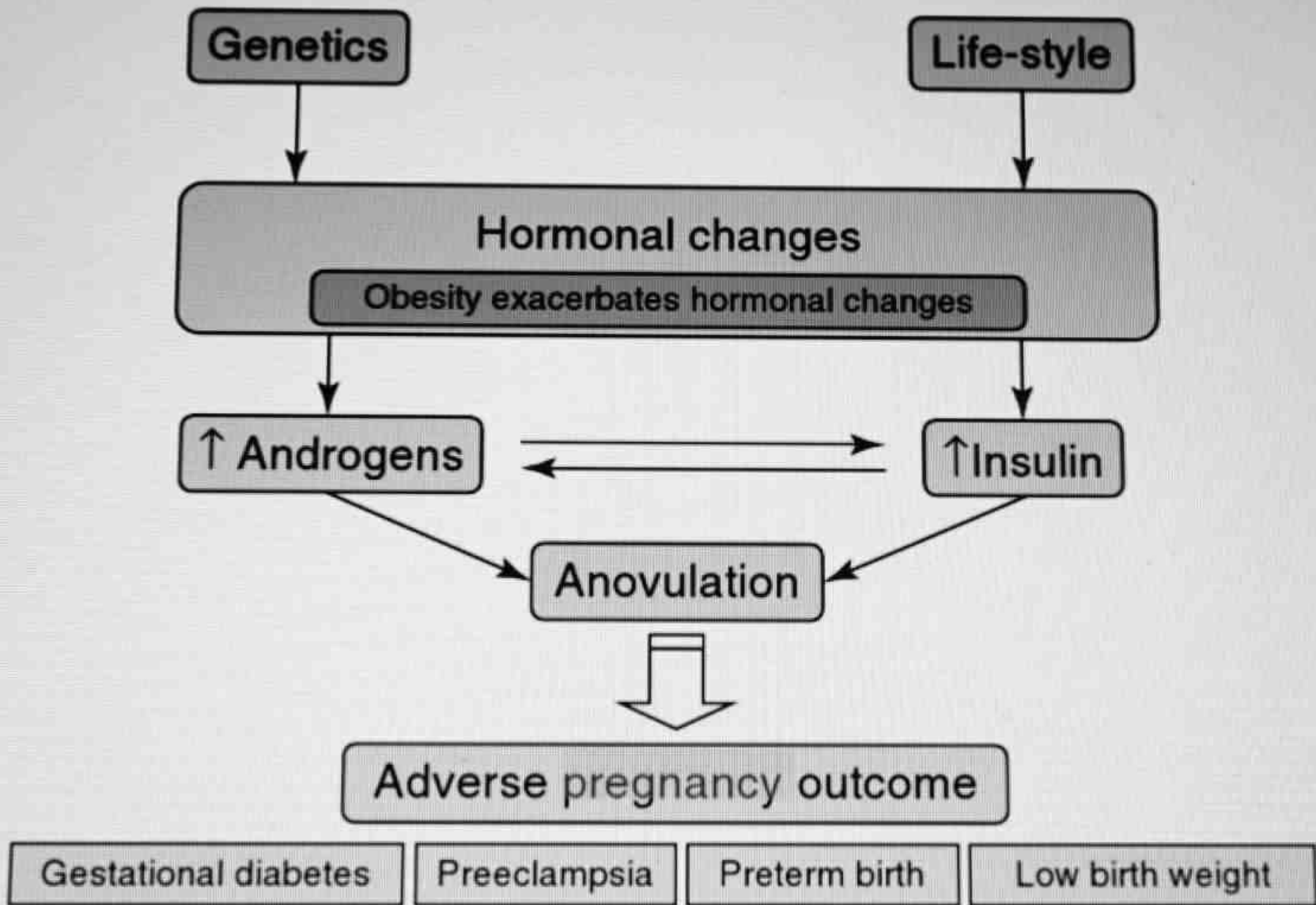
C. MANNA Biofertility Center - Rome

# POLYCYSTIC OVARY SYNDROME

- Endocrine-Metabolic disorder
- 6-8 % women in reproductive age (Azziz et al, 2009)
- 4 billions d. in US each year for health care (not obs)

2 out of 3 criteria in gynecologic setting:

- OVARIAN DISFUNCTION
- HYPERANDROGENISM
- POLYCYSTIC OVARIES BY ULTRASOUND



# PHYSIOPATHOLOGY OF PCOS

- PCOS possible origin: **epigenetic** phenomenon induced **by fetal androgen excess**
- **Chronic low- grade inflammation** with insuline resistance, visceral adiposity, hyperandrogenism
- **Metabolic Syndrome and Insuline Resistance** are chronic inflammatory conditions

Sears (Inflammation Research Foundation)

*The role of diet in inflammation and Metabolic Syndrome*  
*Springer, 2015*

# METABOLISM AND INFLAMMATION

- Inflammatory response starts with the most primitive immune system that we share with plants



This is why switch on-off agents are in diet

- Body inflammatory response needs a balance :  
PRO and ANTI-Inflammatory Diets and Nutrients

**Excess nutrient intake generates inflammation**

**Insulin** plays an important role in this imbalance

B. Sears (Inflammation Research Foundation)

*The role of diet in inflammation and Metabolic Syndrome*

*Springer, 2015*

# INFLAMMATION and METHABOLIC SYNDROME:DIET AGENTS

PROINFLAMMATORY	ANTI-INFLAMMATORY
Omega-6 fatty acids	Omega- 3 fatty acids
Saturated fatty acids	Polyfenols
Excess carbohydrates	
Excess nutrient intake	

B. Sears , 2105

# PCOS AND HEALTH RISKS

- METHABOLIC SYNDROME
- DIABETES
- HYPERTENSION
- CARDIOVASCULAR DISEASES
- UNBALANCED HYPERESTROGENISM AND ENDOMETRIAL HYPERPLASIA

# PREGNANCY AND PCOS

Androgen excess, Insuline resistance, Obesity, bad Diet

METABOLIC SYNDROME + PCOS = INFLAMMATION

**in pregnancy**



**increase chronic inflammatory status**



**abnormality in trophoblast and placental vascular tree**

*2012 Amsterdam ESHRE/ASRM Consensus Workshop Group*

*Duleba A and Dokras A 2012, Is PCOS an inflammatory process? Fertil Steril*



# PCOS AND REPRODUCTIVE PROBLEMS

*REDUCED OOCYTE QUALITY*

**MISCARRIAGE**

*INCREASED TWIN PREGNANCY*

*GESTATIONAL DIABETES*

*LARGE FOR GESTATIONAL AGE*

**PREGNANCY INDUCED HYPERTENSION**

**PREECLAMPSIA**

*CERVICAL INSUFFICIENCY*

*PRETERM BIRTH*

*2012 Amsterdam ESHRE/ASRM Consensus Workshop Group*

*Bjiercke, 2002 , Gynecol Obstet Invest 54:94-8*

*Boomsma, 2006 A meta-analysis of pregnancy outcome in women with PCO. Hum Reprod Update, 12:673-83*

# PCOS AND INFERTILITY THERAPIES

AVOID OHSS CANNOT BE THE ONLY AIM

- IMPLANTATION RATE SUCCESS MUST BE FOLLOWED BY TERM PREGNANCY  
( “*SET*” MAY BE NOT ENOUGH )



PERSONALIZATION OF THERAPY SHOULD INCLUDE  
**PRECONCEPTIONAL INTERVENTIONS**

# AGES and RAGEs : Inflammatory agents

**AGES** (Advanced Glycation End- products ) :

highly reactive molecules formed by non-enzymatic reactions of sugars with proteins, nucleic acids and lipids (O'Brien J, Morrissay P, 1989)

**RAGEs** :

cell receptors of AGEs

**Increase of AGEs and interaction of AGE-RAGE activate a pro-inflammatory and oxidative stress cascades (Unbarri et al., 2007).**

# AGEs and RAGEs

**AGEs increase in thermal modifications of food (cooked fast-food diet, Goldberg, 2004)**

**Body AGEs produced or absorbed with diet is exaggerated in women with PCOS (Garg,2015)**

**Increased RAGEs in PCOS ovarian tissue (Garg, 2015)**

RAGEs concentration in ovarian follicular fluid was positively correlated with embryo quality and In Vitro Fertilization (IVF) outcome (Bonetti et al,2013).

# EVIDENCES of AGEs on PCOS

Deepika G. and Zaher Merhi, *Nutrients* 2015, dec 7(12) 10129

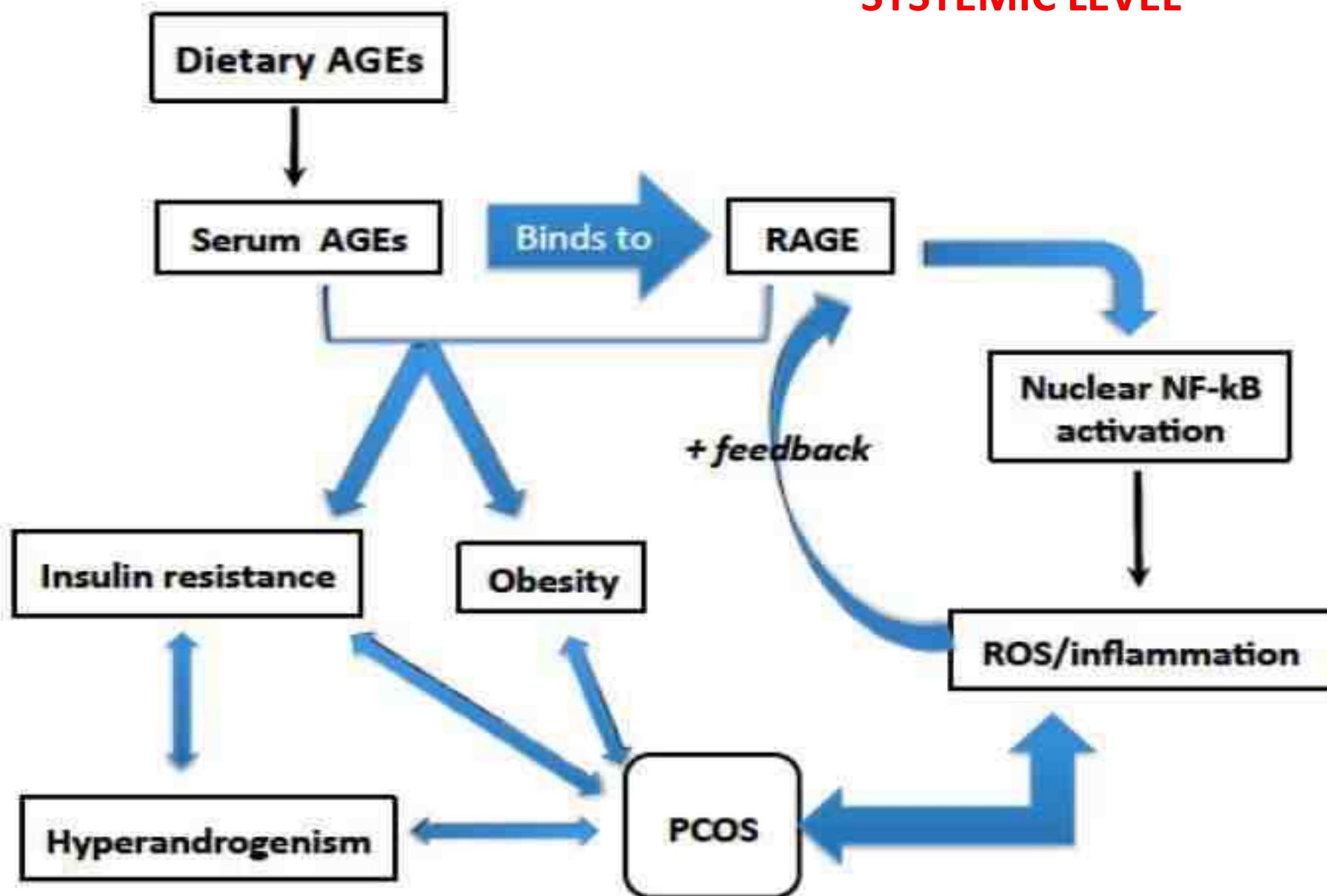
Nutrients

<i>et al.</i> , 2007 [20]	female rats	High-AGE vs. low-AGE diet
Gaens K.H. <i>et al.</i> , 2014 [21]	Obese RAGE- vs. RAGE + mice	Measured CML in plasma and adipose tissue
Diamanti-Kandarakis E. <i>et al.</i> , 2015 [22]	KGN: human granulosa cell line	Culture was done with HGA or insulin or both HGA + insulin
Diamanti-Kandarakis E. <i>et al.</i> , 2008 [23]	Young lean non-insulin resistant women with PCOS vs. healthy women and vs. women with isolated features of PCOS	Measurement of serum AGEs
Mark A.B. <i>et al.</i> , 2014 [24]	Overweight women	High-AGE vs. low-AGE diet
Tantalaki E. <i>et al.</i> , 2014 [12]	Women with PCOS	High-AGE vs. low-AGE diet
Diamanti-Kandarakis <i>et al.</i> , 2009 [25]	Women with or without PCOS	Measured serum AMH and AGEs
Diamanti-Kandarakis E. <i>et al.</i> , 2007 [10]	Women with or without PCOS	AGE and RAGE immunoreactivity
Diamanti-Kandarakis <i>et al.</i> , 2005 [26]	Women with or without PCOS	Measured serum AGE levels and RAGE expression in circulating monocytes
Gaens K.H. <i>et al.</i> , 2014 [21]	Human preadipocytes	Measured CML levels and RAGE expression




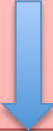
RAGE = receptors of advanced glycation end products; MG = methylglyoxal; AGE = Advanced Glycation End Products; ovary syndrome; HOMA = Homeostasis Model Assessment index; GLO-I = Glyoxalase 1; D-gal = D-galactose; AMH = ar



## SYSTEMIC LEVEL



# METHODS TO ATTENUATE AGE EFFECT

METHODS	EFFECT
Food at low temperature Short cooking Lemon Juice and Vinegar	 AGE intake
Vitamin D	 serum RAGE levels
Metformin	 serum AGEs in PCOS Women
Alpha Lipoic Acid(ALA)	 AGEs formation

Modified from Deepika G. and Zaher Merhi, Nutrients 2015, dec 7(12) 10129




DIET AND DIETARY ELEMENTS SEEM CRUCIAL IN  
PATHOGENESIS AND PCOS MAINTENANCE

WHAT TO DO?

HOW ?

# PCOS DIET: **MAIN PROBLEMS**

- Lack of robust large scale randomized trials
- Lack of consensus over optimal dietary guidelines
- Metabolic issues (  thermogenesis, Insuline resistance)
- Emotional distress

# PCOS DIET TYPES

- 1 Standard Low-Fat **Calorie-Deficient Diet (CDD)**:  
0,4-0,5 Kg / week and 8 Kg / 12 weeks loss
- 2 **Very Low-Calorie Diets (VLCDs)** (<800kcal/day) :  
1,5-2,5 Kg / week and 20 Kg / 12 weeks loss

*Atkinson et Al. JAMA 1993;270(8):967-974*

# Very Low-Calorie Diets (VLCDs)

modern commercial VLCDs diets maintains Lean Body Mass with :

- High levels of good-quality protein
- Inclusion of essential electrolytes (Na, K ,Bicarbonates,Chloride, Ca, Phosphate), fatty acids, minerals, vitamins
- Up to 3 months for obese who fail CDD

*National Institute for Health and Care Excellence. London: NICE,2014*

# PCOS and DIET IMPORTANCE

*“Women should be counseled about  
**weight loss***

*prior to attempting conception” 2015*

*1 Am. Association Clinical Endocrinologists*

*2 Am. College Endocrinology*

*3 Androgen Excess and PCOS Society Disease*

# *“How much weight should I loose ?”*

## 2%-5% WEIGHT LOSS MAY:

### 1 RESTORE OVULATION

Clark, 1998 Hum Repr 13(6),1502

Tolino,2005 Eur J Ob Gyn Rep Biol 119(1),87-9)

### 2 IMPROVE HORMONE PROFILE

Moran,2006 Am J Clin Nutr 84(1),77-87

### 3 IMPROVE INSULIN SENSITIVITY

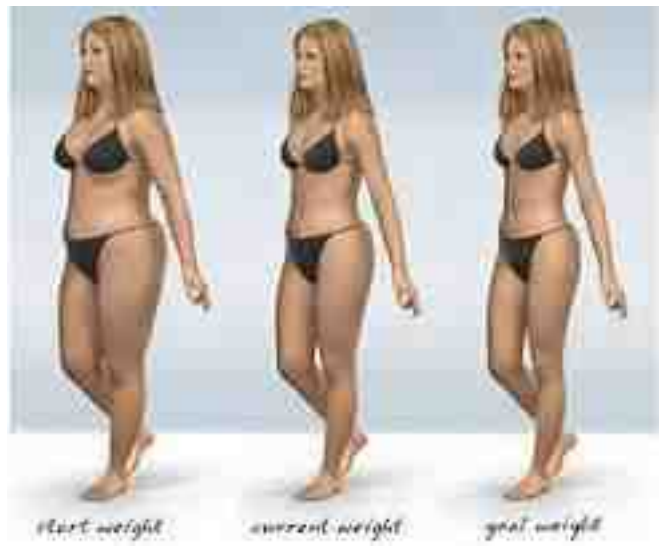
Holte,1995 J Clin End Met 80(9),2586



# HCG DIET

**LOSE 26 PDS  
IN 26 DAYS**  
LOSE POUNDS *and* INCHES

BEAUTY MARK  
(949) 600-7714





Lighter Life

Balanced Mind

Healthy Body



# DIET IN PCOS

## commercial diet plan advertisement

*“Why LighterLife works*

*We combine effective, nutritious plans to help you quickly reach the weight you want, with a ground breaking counselling techniques so you can change how you think about food”*

“our experts are drawn from both a medical and a psychological background”

# “LighterLife” DIET

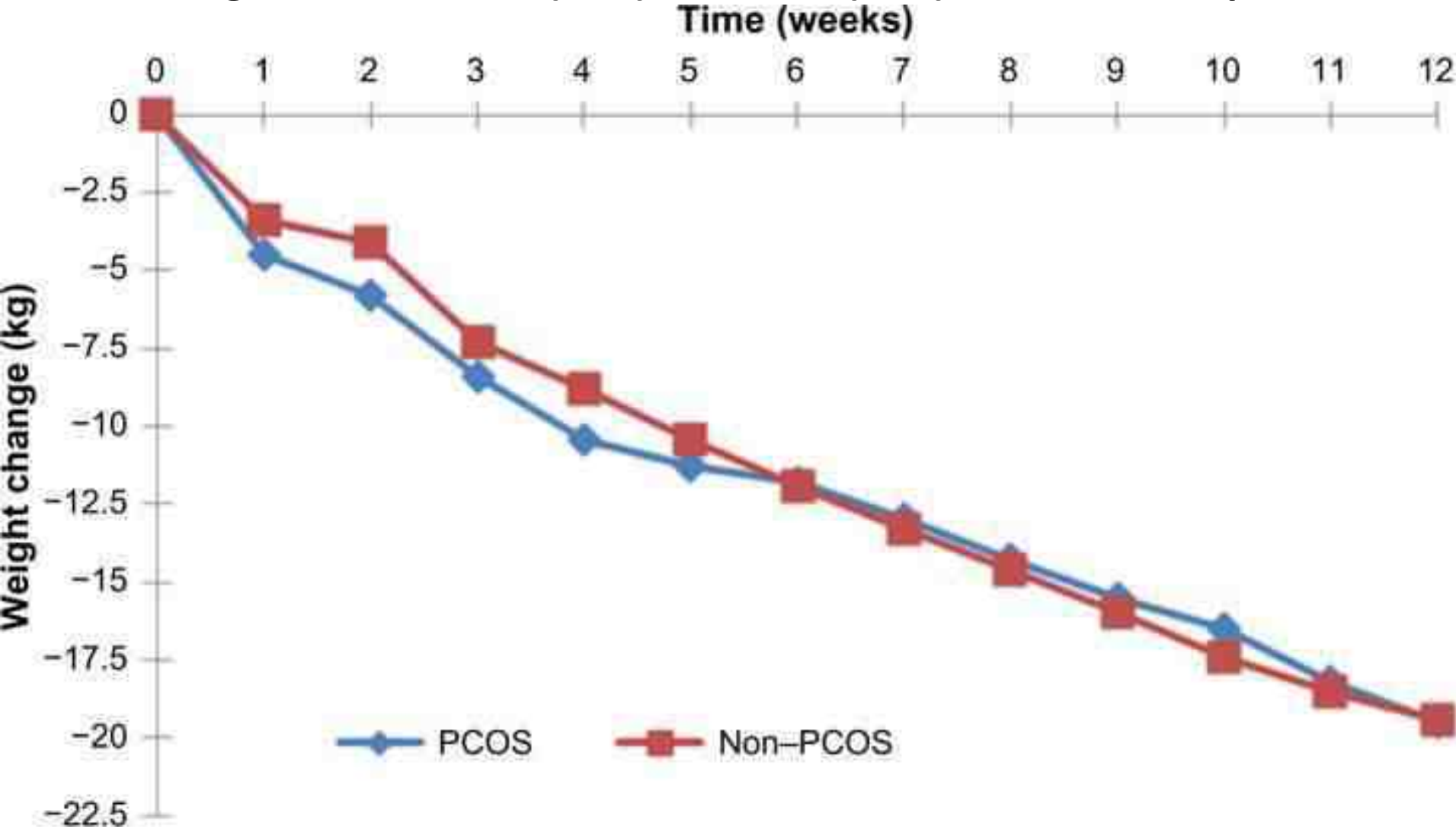
“Using recognised counselling techniques such as **Cognitive Behavioural Therapy and Transactional Analysis**, we help you to learn your own subconscious patterns of behaviour around food, so you will **become more self-aware** and better equipped **to make choices** that serve you far better”.

# “Lighter Life Total” commercial VLCD

Nikokavoura et Al., 2015 Diabetes Metab Syndr Obes. 2015; 8: 495–503.

- **Retrospective controlled trial**
- **12-week course** commercial VLCD + group-based behavior-change program
- **overweight-obese patients** : 508 non- PCOS vs 508 PCOS matched for age and BMI (137 vs 137 completers)
- **600 Kcal**(50 g prot., 50 g carb., 17 g fat)  
> recommended quantity of vitamins and minerals (vit A,C,D,E,K,B1,B6,B12,Ca,Fe,Folate,Mg,Z,Se,I,Fl)
- **Weekly cost 65 UK pounds** ( but less cost for food!)

# Week Weight loss in PCOS(137) and Non (137) 12 week completers



[Nikokavoura E., Diabetes Metab Syndr Obes. 2015; 8: 495–503.](#)

## Comparison of systolic and diastolic blood pressure between the PCOS and non-PCOS at baseline and 12 weeks

Parameter	PCOS (n=504)	Non-PCOS (n=507)	P
• Baseline systolic BP (mmHg)	127.4±12.5	127.0±14.0	0.598
• <b>Baseline diastolic BP (mmHg)</b>	<b>81.5±10.2</b>	<b>79.9±9.7</b>	<b>0.014**</b>
• Week 12 systolic BP (mmHg)	121.9±20.3	126.1±14.5	0.506
• Week 12 diastolic BP (mmHg)	80.8±16.1	79.4±9.9	0.206
• <b>Change in systolic BP (mmHg)</b>	<b>-5.5±6.1</b>	<b>-0.9±6.1</b>	<b>&lt;0.001***</b>
• Change in diastolic BP (mmHg)	-0.4±5.1	-0.6±4.4	0.517

[Nikokavoura E., Diabetes Metab Syndr Obes. 2015; 8: 495–503.](#)

# TYPES OF DIET THERAPY IN PCOS

## CHANGE IN FOOD PREPARATION



diet AGEs

\* brief heating time, lemon and vinegar

*Deepika, 2015*

## SUGGESTED DIET THERAPY

\* Hypocaloric diet

*127 studies, review, Rondanelli, 2014*



Sugar and Refined carbohydrate

Small and frequent meals (high caloric breakfast)



Fish intake( 4 times week)

\* Carbohydrates replacement with protein *Sorensen, 2012*

( high protein/carbohydrate “ad libitum” diet)

# DIET SUPPLEMENT TO ATTENUATE AGEs EFFECT

Deepika G., 2015

CHANGE IN FOOD PREPARATION  
(brief heating time, lemon and vinegar)  diet AGEs

VITAMIN D Supplement

 sRAGE

ALFA LIPOIC ACID (ALA)



AGEs formation

Vit B6



AGEs formation

# ZINC supplement

- Randomized, double blind, placebo controlled trial  
52 PCOS women (Foroozanfard E., 2015)

220 mg Zinc Sulfate per day for 8 weeks

METABOLIC IMPROVEMENT

(  Insulin sensitivity,  VLDL Chol,  TG )




# OMEGA-3 fatty acid

- Randomized, double blind, placebo controlled trial  
64 obese PCOS women (Mohammadi E., 2012)

180 mg eicosanpentanoic +

120 mg docosahexanoic acid per day for 8 weeks

METABOLIC IMPROVEMENT

( Glucose, Insulin , HOMA-IR, VLDL Chol, TG )

# SELENIUM supplement



- Randomized, double blind, placebo controlled trial  
70 PCOS women (Jamilian M., 2015)

200 mcg Selenium per day for 8 weeks



METABOLIC IMPROVEMENT (  Insulin sensitivity,  
 Insulin resistance, VLDL Chol, )

# VITAMIN D supplement

- Randomized, double blind, placebo controlled trial  
35 PCOS obese adolescents ( Belenchia A., 2013)
- 4000 IU Vitamin D per day for 12 weeks

•  Insuline resistance HOMA-IR,  Insuline

# FOLATE supplement

- Randomized, double blind, placebo controlled trial  
81 PCOS obese women ( Asemi Z., 2014)
- 5 mg Folate per day for 8 weeks
-  Insuline resistance,  LDL Chol

# N-Acetyl-cysteine (NAC) supplement

- Prospective controlled trial 31 PCOS obese women ( Fulghesu., 2002)

- 1,8 g NAC per day for 5-6 weeks

-  Insuline resistance,  Testosteron

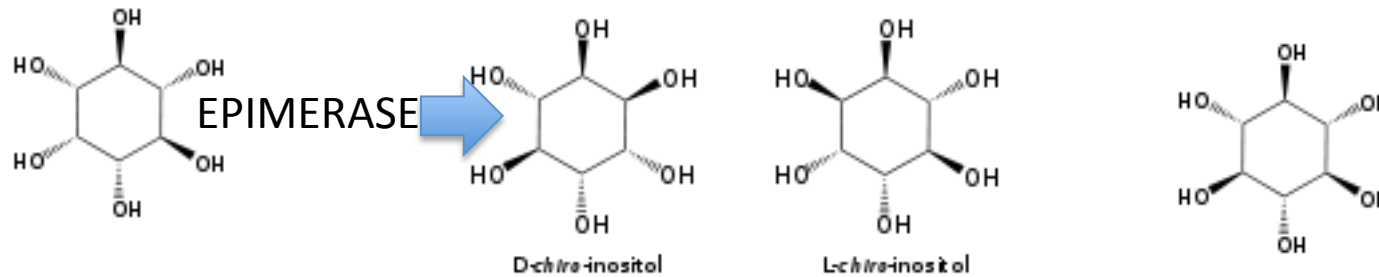
# Alpha lipoic acid+ DCI supplement

- Prospective, controlled trial (Cianci A., 2015)  
  
46 PCOS women (26 treated ,20 not treated)  
1000mg DCI+ 600mg ALA per day for 6 months

Metabolic and Clinical improvement :  
BMI, Menstrual cycles, Insulin resistance

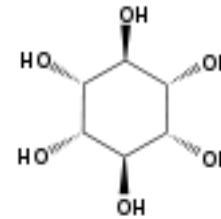
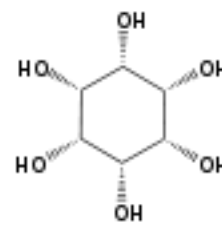
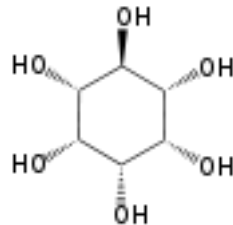
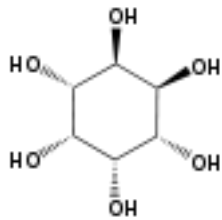
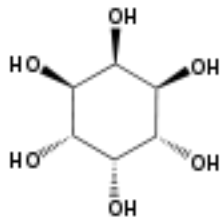
# INOSITOL AND ITS 9 STEREOISOMERS ( Complex B VITAMIN)

$C_6H_{12}O_6$  or  $(-CHOH)_6$ , a six-fold alcohol (polyol) of cyclohexane secondary messengers in eukaryotic cells



Myo-Inositol  
MYO







D-Chiro-inositol  
DCI



**DCI** : incorporated in cell membrane phospholipid (DCI-IPG)  
**cellular transducer of Insulin signal** (Larner J., 1994)

Metformin  Insulin action by DCI-IPG release (Baillargeon J., 2004)

# CLINICAL TRIALS OF INOSITOL EFFECTS ON PCOS

AUTHOR	TRIAL	DRUG	Dose Duration	BMI	Insulin resistance Hormones	OTHER
La Marca 2014	Cohort Retr. Study 47 pts	DCI	1000- 1500 mg/day 10 Months	NO CHANG ES	HOMA I AMH 	51% regular cycles
Laganà 2014	Cohort Pros Study 48 pts <b>BMI &lt; 25</b>	DCI + Folic acid	1000 mg /day <b>6 Months</b>		HOMA Ind Androgens LH/FSH 	<b><u>62% regular Cycles</u></b> Less Irsut.
Genazzani 2014	Prospective 22 Obese pt BMI>26	DCI	500 mg/day 3 Months		Gluc/Ins Insulin Androgens LH/FSH 	Better when diabetic relatives
Genazzani 2012	Prospective 42 Obese pt BMI>26	<b>MYO</b>	2000 mg 2 Months		Gluc/Ins Insulin Androgens LH/FSH 	



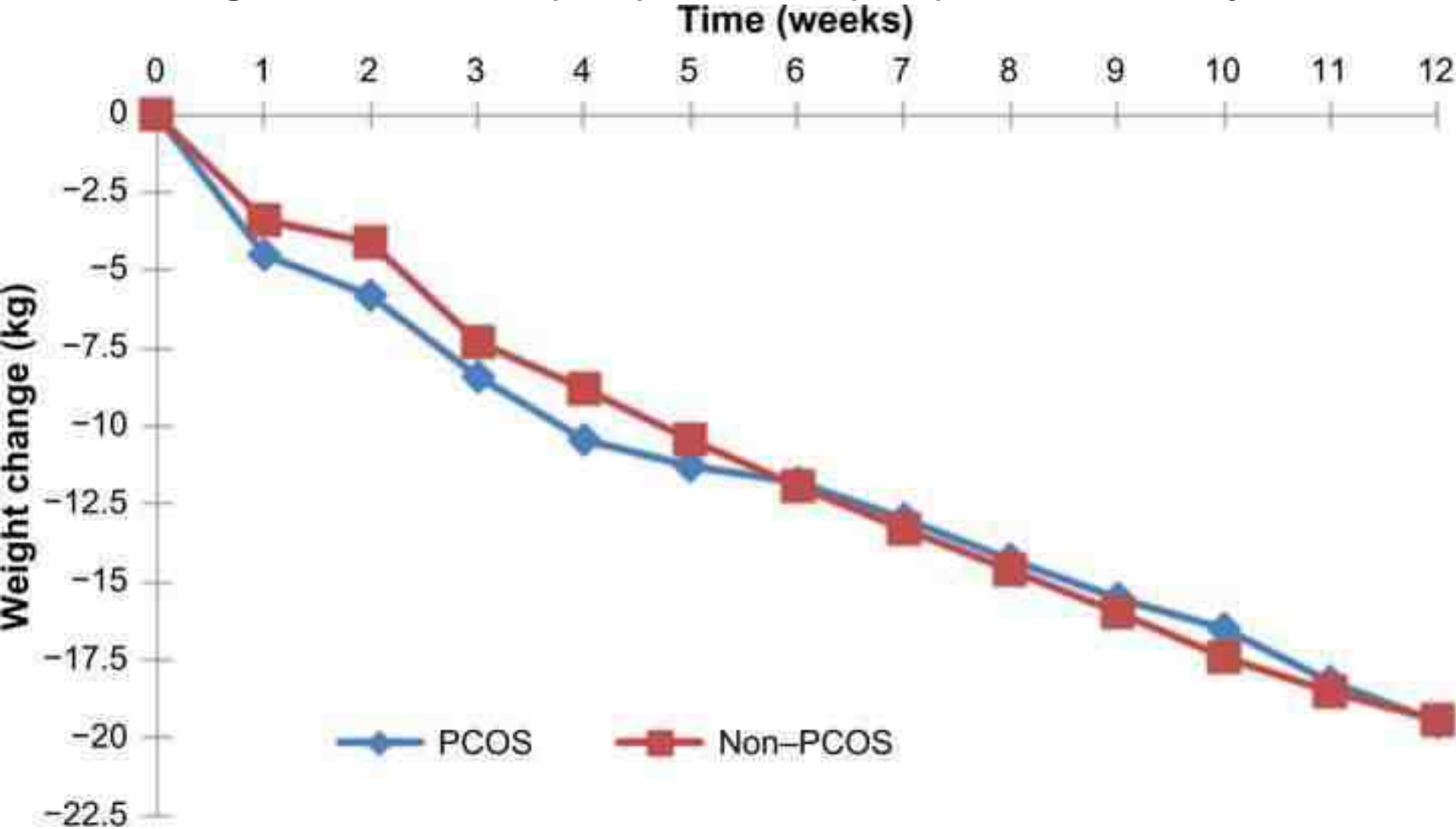
# COMMERCIAL PRODUCTS CONTAINING INOSITOL

DENOMINATION	INOSITOL	DOSE	OTHER SUPPLEMENT
<i>CHIROFERT</i>	DCI	500 mg X 2	Folate 400 mcg Alfa lipoic 600 mg Nac 600 mg Mn 4 mg
<i>KIROGEN</i>	MYO DCI	2000 mg 400 mg	Folate 400 mcg Mn 10 mg
<i>NOSIFOL-D</i>	MYO DCI	2000 mg 50 mg	Folate 400 mcg Zn 7,5 mg Vitamin D 5 mcg Vit B6 1 mg
<i>INOFOLIC PLUS</i>	MYO	2000 mg	Folate 200 mcg Melatonin 1,5 mg

# CONCLUSIONS

- QUANTITATIVE (**low calories**) and QUALITATIVE (**Low AGEs**) DIET IN PCOS IS THE GOLD STANDARD
- DIET MAY BE MORE EFFECTIVE IN SPECIAL SETTING (**group therapy**)
- DIETARY SUPPLEMENTS are USEFULL  
(**INOSITOL, Vit D, ALA, NAC, OMEGA-3 FA, Vit B6, Zinc**)
- INOSITOL IMPROVES PCOS METABOLISM (Insulin 2° messenger ) AND IS NOT HARMFULL (increasing clinical trials)
- **DIET AND SUPPLEMENTS MAY BE USED TOGETHER!**
- NEEDED MORE Contr. Random. Prosp. Trials

# Week Weight loss in PCOS(137) and Non (137) 12 week completers



[Nikokavoura E., Diabetes Metab Syndr Obes. 2015; 8: 495–503.](#)