GIMBE®
Gruppo Italiano per la Medicina Basata sulle Evidenze
Evidence-Based Medicine Italian Group

Workshop
Evidence-based Medicine
Le opportunità di un linguaggio comune 2ª ed.

Como, 21-22 maggio 2004

SNAMID
Sezione di Como

Workshop Clinici Interattivi (1)

Sindrome metabolica e rischio cardiovascolare
Perché la strada non passa sempre per il diabete?

Alessandro Di Pasquale

Discussant: Mario Parenti, Gianluca Perseghin

Scenario Clinico (1)

• La signora Francesca è un'insegnante di 44 anni, sposata con due figli, in buone condizioni generali.

• In sovrappeso dall'adolescenza, con pregressa diagnosi di sindrome dell'ovaio policistico, ha recentemente riscontrato una lieve iperglicemia a digiuno.

• 5 anni prima, nel corso dell'ultima gravidanza, riscontro di lieve diabete gestazionale (trattato con sola dieta).

Scenario Clinico (1)

Anamnesi familiare

• Madre obesa, ipertesa, dislipidemica (deceduta a 75 anni per ictus).
• Padre deceduto a 58 anni per infarto del miocardio.
• Familiarità per diabete tipo 2.

Scenario Clinico (1)

Anamnesi fisiologica

• Menarca a 11 anni, con cicli successivi molto irregolari.
• Prolungata assunzione di estroprogestinici, interrotta 3 anni fa. Attualmente in amenorrea.
• Attività fisica scarsa, alimentazione regolare, fuma 10-15 sigarette al dì e non beve alcolici.

Scenario Clinico (1)

Obiettivamente

• BMI 29.7. kg/m2, circonferenza vita 91 cm
• Irsutismo di grado lieve-moderato, lieve epatomegalia.
• PAO 135/88 mmHg.

Dati di laboratorio (1)

Profilo metabolico basale

• Glicemia	112 mg/dl
• Colesterolo totale	221 mg/dl
• HDL-colesterolo	42 mg/dl
• Trigliceridi	187 mg/dl
• LDL-colesterolo	141 mg/dl
• Insulinemia	22 mU/l

OGTT

• Glicemia 120 min	176 mg/dl

Indagini strumentali (1)

Ecografia addome e pelvi
• Fegato lievemente ingrandito, steatosico; ovaie di volume lievemente aumentato, con multipli piccoli follicoli alla periferia.

ECG
• Nella norma

Ecodoppler TSA
• Lievi ispessimenti intimali bilaterali

CLINICAL QUESTIONS

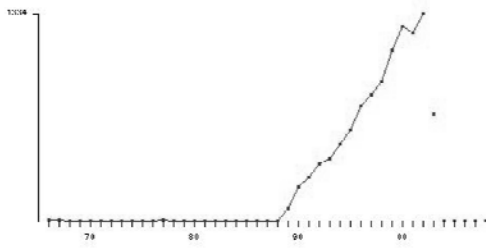
?

1. Sindrome Metabolica e rischio cardiovascolare.

A. Quale tra i seguenti, non rientra tra i criteri diagnostici della sindrome metabolica?

1. Circonferenza addominale
2. Trigliceridi
3. LDL
4. HDL
5. Pressione arteriosa
6. Glicemia a digiuno

MEDLINE
"Metabolic Syndrome X"[All] OR "Metabolic Syndrome"[ti]: 1210 articoli



Metabolic Syndrome

Two recent events have focused the attention of the medical community on the metabolic syndrome

1. The inclusion of the syndrome in the recently published ATP III guidelines
2. The creation of an ICD 9 diagnostic code (277.7) which makes reimbursement for treating the syndrome possible

Hill JO, et al. Arch Intern Med 2003

Alexander CM

The Coming of Age of the Metabolic Syndrome

Diabetes Care, November 1, 2003

MEDLINE

"Metabolic Syndrome X"[All] OR "Metabolic Syndrome"[ti]: **1210 articoli**

- 464 Review, Editoriali, Lettere
- 46 Clinical trial
- 24 Randomized controlled trials

Sindrome metabolica

- **1983**. The clustering of the atherosclerotic risk factors that identify the metabolic syndrome was first recognized.
- **1988**. **Reaven** introduced the term syndrome X, with insulin resistance (IR) as a common denominator.
- **1988-1998**. Other **synonyms**: multiple metabolic syndrome, IR syndrome, deadly quartet, DROP syndrome (Dyslipidemia, iR, Obesity,and high blood Pressure).

Scott CL. Am J Cardiol 2003

Sindrome metabolica

- **1998**. The **WHO** recommended a unifying definition and chose the term metabolic syndrome, because current data did not establish IR as the cause of all components of the syndrome.
- **2001.** The **ATP III** (NIH) define the metabolic syndrome as a new secondary target for cardiovascular risk reduction therapy beyond LDL cholesterol lowering
- **2003**. Position statement of **ACE/AACE** (a back step?)

Scott CL. Am J Cardiol 2003

American Heart Association
National Heart, Lung, and Blood Institute.

Definition of metabolic syndrome

Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition.

Circulation 2004;109:433-8.

Sindrome metabolica: quali criteri diagnostici?

- **1988**. WHO
- **2001**. ATP III
- **2003**. ACE/AACE

Sindrome metabolica: quali criteri diagnostici?

TABLE 1. ATP III Clinical Identification of the Metabolic Syndrome

Risk Factor	Defining Level
Abdominal obesity, given as waist circumference*|	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL‡

NHLBI/AHA, 2004

Sindrome metabolica: quali criteri diagnostici?

TABLE 2. WHO Clinical Criteria for Metabolic Syndrome*

Insulin resistance, identified by 1 of the following:

- Type 2 diabetes
- Impaired fasting glucose
- Impaired glucose tolerance
- or for those with normal fasting glucose levels (<110 mg/dl), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions

Plus any 2 of the following:

- Antihypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic)
- Plasma triglycerides ≥150 mg/dL (≥1.7 mmol/L)
- HDL cholesterol <35 mg/dL (<0.9 mmol/L) in men or <39 mg/dL (1.0 mmol/L) in women
- BMI >30 kg/m^2 and/or waist:hip ratio >0.9 in men, >0.85 in women
- Urinary albumin excretion rate ≥20 μg/min or albumin:creatinine ratio ≥30 mg/g

NHLBI/AHA, 2004

Sindrome metabolica: quali criteri diagnostici?

TABLE 3. AACE Clinical Criteria for Diagnosis of the Insulin Resistance Syndrome*

Risk Factor Components	Cutpoints for Abnormality
Overweight/obesity	BMI ≥25 kg/m^2
Elevated triglycerides	≥150 mg/dL (1.69 mmol/L)
Low HDL cholesterol	
Men	<40 mg/dL (1.04 mmol/L)
Women	<50 mg/dL (1.29 mmol/L)
Elevated blood pressure	≥130/85 mm Hg
2-Hour postglucose challenge	≥140 mg/dL
Fasting glucose	Between 110 and 126 mg/dL
Other risk factors	Family history of type 2 diabetes, hypertension, or CVD Polycystic ovary syndrome Sedentary lifestyle Advancing age Ethnic groups having high risk for type 2 diabetes or CVD

*Diagnosis depends on clinical judgment based on risk factors.

NHLBI/AHA, 2004

Sindrome metabolica: quali criteri diagnostici?

- **1988**. WHO
  - Requires: glucose tolerance testing, insulin concentration measurements, microalbuminuria testing.
- **2001**. NHBLI. ATP III
  - Easier to use in clinical practice
- **2003**. ACE/AACE.
  - Hybrid (WHO, ATP III)
  - No defined number of risk factor is specified
  - Diagnosis is left to clinical judgment

NHLBI/AHA, 2004

National Heart, Blood and Lung Institute

Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

JAMA 2001;285:2486-97

ATP III

1. **LDL cholesterol**: the primary target of therapy

2. Benefit beyond LDL lowering: the **metabolic syndrome** as a secondary target of therapy

NHBLI. ATP III. JAMA 2001

Metabolic Syndrome

- A constellation of lipid and non-lipid risk factors of metabolic origin, closely linked to a generalized metabolic disorder called insulin resistance
- The risk factors of the metabolic syndrome enhance risk for CHD at any given LDL cholesterol level.

NHBLI. ATP III. JAMA 2001

Sindrome Metabolica: criteri ATP III

Diagnosis is made when 3 or more of the risk are present

Risk Factor	Defining Level
• Abdominal obesity* (waist circumference)†	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
• Triglycerides	≥150 mg/dL
• High-density lipoprotein cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
• Blood pressure	≥130/≥85 mm Hg
• Fasting glucose	≥110 mg/dL

NHBLI. ATP III. JAMA 2001

Ford ES, Giles WH.

A comparison of the prevalence of the metabolic syndrome using two proposed definitions

Diabetes Care 2003;26:575-81

RESULTS

- Among 8608 participants aged >or=20 years, the age-adjusted prevalence was 23.9% using the ATP III definition and 25.1% using the WHO definition.
- Among all participants, 86.2% were classified as either having or not having the metabolic syndrome under both definitions.

CONCLUSIONS

- A universally accepted definition of the metabolic syndrome is needed.

Ford ES, et al. Diabetes Care 2003

TABLE 4. Impact on Prevalence of Metabolic Syndrome if Impaired Glucose Tolerance Plus 2 or More Risk Factors Is Added to the National Cholesterol Education Program Definition*

Demographic Characteristics	% Meeting Current National Cholesterol Education Program Definition	% Meeting Revised Definition
Overall	37.9	43.5
Race/ethnicity		
Non-Hispanic white	38.2	43.6
Non-Hispanic black	34.6	38.9
Mexican American	43.5	53.4
Other	35.9	43.1
Age group, y		
50–59	30.6	36.5
60–69	41.5	48.1
70–79	42.6	48.4
80+	43.3	43.3

*Data derived from NHANES III. Data analysis provided by Dr Steven Haffner.

NHLBI/AHA, 2004

Metabolic Syndrome

Risk Factor	Defining Level	**Sig.ra Letizia**
• Abdominal obesity* (waist circumference)†		
Men	>102 cm (>40 in)	
Women	>88 cm (>35 in)	**89 cm**
• Triglycerides	≥150 mg/dL	**187 mg/dL**
• High-density lipoprotein cholesterol		
Men	<40 mg/dL	
Women	<50 mg/dL	**42 mg/dL**
• Blood pressure	≥130/≥85 mm Hg	**135/88 mmHg**
• Fasting glucose	≥110 mg/dL	**112 mg/dL**

NHBLI. ATP III. JAMA 2001

Issue of Oral Glucose Tolerance Test

- Both WHO and AACE include IGT, detected by oral glucose tolerance test (OGTT) or 2-hour postglucose challenge,among the risk factors for metabolic syndrome.
- ATP III did not include it because of the added inconvenience and cost of OGTT in clinical practice.
- Its added value for CVD risk prediction appears small.
- Several conference participants suggested adding OGTT at the physician's discretion in nondiabetic patients with ATP III–defined metabolic syndrome or ≥ 2 metabolic risk factors

NHLBI/AHA, 2004

Diagnosi

Sindrome metabolica
(discreta insulinoresistenza, sovrappeso, IGT, lieve dislipidemia, valori pressori borderline), in paziente con sindrome dell'ovaio policistico

B. Utilizando i criteri ATP III, quale percentuale della popolazione generale, ritieni sia affetta da sindrome metabolica?

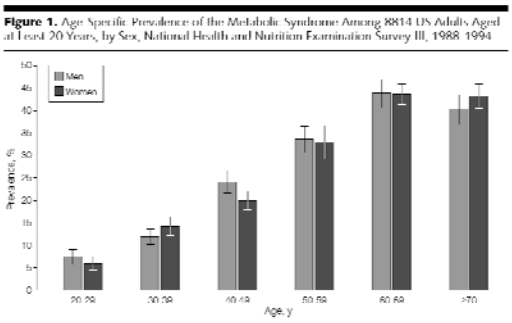
1. < 10%
2. 11-20%
3. 21-30%
4. > 30%

Ford ES, Giles WH, Dietz WH.

Prevalence of the metabolic syndrome among US Adults.
Findings from the third National Health and Nutrition Examination Survey

JAMA 2002;287:356-359

Age-adjusted prevalence of the MS= 23.7%



Ford ES, et al. JAMA 2002

C. Qual è il trattamento di prima scelta per la sig.ra Francesca?

1. Estroprogestinici
2. Metformina
3. Modificazioni dello stile di vita
4. Antiandrogeni

Sindrome metabolica: quali obiettivi terapeutici

1. **To reduce underlying causes (ie, obesity and physical inactivity)**
2. To treat associated risk factors (nonlipid and lipid)

NHBLI. ATP III. JAMA 2001

Sindrome metabolica: la riduzione del peso

- Weight reduction will enhance LDL lowering and reduce all of the risk factors of the metabolic syndrome.

Weight reduction is a first-line therapy

NHBLI. ATP III. JAMA 2001

Sindrome metabolica: attività fisica

Regular physical activity
- reduces VLDL levels
- raises HDL cholesterol
- in some persons, lowers LDL levels
- can lower blood pressure
- reduce insulin resistance
- improve cardiovascular function

Regular physical activity is a routine component in management of metabolic syndrome

NHBLI. ATP III. JAMA 2001

Regardless of diagnostic criteria used, there is full agreement that **therapeutic lifestyle change**, with emphasis on weight reduction, **constitutes first-line therapy for metabolic syndrome**.

AHA/NHBLI. Circulation 2004

Sindrome metabolica
Riduzione del peso e attività fisica

Dramatic evidence from recent prospective intervention studies showing that the combination of weight loss and increased physical activity can significantly decrease the development of type 2 diabetes in high-risk individuals.

- **Finnish Diabetes Prevention Study**. *May, 2001*
- **Diabetes Prevention Program Group**. *February, 2002*

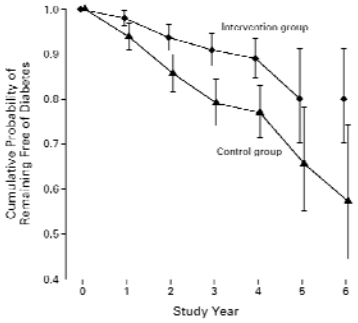
ACE-AACE, 2003

Tuomilehto J, Lindstrom J, Eriksson JG, et al.

Prevention of type 2 diabetes by changes in lifestyle among subjects with impaired glucose tolerance

N Engl J Med 2001;344:1343-1350.

The Finnish Diabetes Prevention Study



Tuomilehto J, et al
N Engl J Med 2001

The Finnish Diabetes Prevention Study

Lifestyle-intervention program vs control for the prevention of type 2 diabetes mellitus in patients with impaired glucose tolerance at a mean follow-up of 3.2 years

NNT 8 (5 to 15)

NNT= Numero necessario di pazienti da trattare per preventire un evento (diabete)

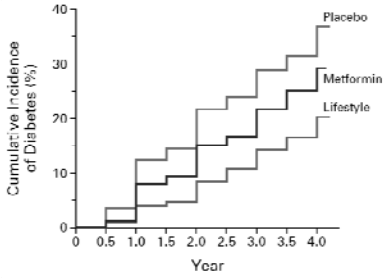
Tuomilehto J, et al. N Engl J Med 2001

Knowler WC, Barrett-Connor E, Fowler SE, et al.

Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin

N Engl J Med 2002;346:393-403.

The Diabetes Prevention Program Group



The study initially included a fourth intervention, troglitazone, which was discontinued because of the drug's potential liver toxicity.

Knowler WC, et al. N Engl J Med 2002

The Diabetes Prevention Program Group

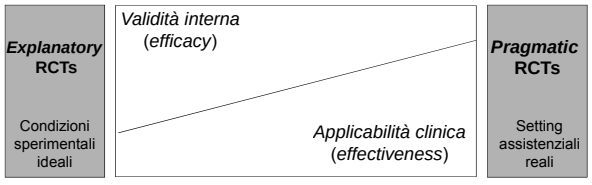
Intensive life-style intervention (ILI) or metformin plus standard lifestyle vs placebo plus standard lifestyle for prevention of type 2 diabetes at 3 years

NNT

- ILI vs placebo NNT 7 (6 to 10)
- Metformin vs placebo NNT 14 (9 to 34)

NNT= Numero necessario di pazienti da trattare per preventire un evento (diabete)

Knowler WC, et al. N Engl J Med 2002



Cartabellotta A. Occhio Clinico 2002

The Diabetes Prevention Program Group

• Modest weight loss (5%-7%) and modest increases in physical activity (~150 min/wk) can have substantial benefits in preventing diabetes.

Decisione clinica (1)

• La paziente viene istruita su come modificare il suo stile di vita:
  - Dieta bilanciata moderatamente ipocalorica
  - Programma di attività fisica moderata: 30 minuti al dì per 5 giorni alla settimana.
  - Abolizione del fumo.

• Controllo ambulatoriale dopo 4 settimane.

Scenario Clinico (2)

• La paziente si presenta regolarmente ai controlli, ma non smette di fumare.

• Dopo iniziale calo ponderale di 5.5 Kg in due mesi, con miglioramento di glicemia e trigliceridi, il peso riprende a salire lentamente, tornando al livello di partenza dopo 8 mesi.

• I ripetuti tentativi di ottenere una migliore compliance alle prescrizioni comportamentali danno risultati transitori.

• La signora Francesca rimane amenorroica.

Dati di laboratorio (2)

	Baseline	1 anno
BMI	29.7	**30.9**
Glicemia	112	**120**
HbA1c	-	**6.1**
Colesterolo tot.	221	**225**
Colesterolo HDL	42	**41**
Colesterolo LDL	141	**143**
Trigliceridi	187	**205**
Uricemia	6.0	**6.7**
PAO	135/88	**135/90**

CLINICAL QUESTIONS

?

1. Sindrome Metabolica e rischio cardiovascolare.

D. Quale trattamento farmacologico, in relazione alle prove di efficacia disponibili, ritenete più appropriato?

1. Nessuno*
2. Estroprogestinici
3. Metformina
4. Ipolipemizzanti

*mantenere solo le modificazioni dello stile di vita

Decisione clinica (2)

• Si prescrive metformina (500 mg alla sera, poi 500 mg x 2), ma il farmaco viene sospeso dopo 3 settimane per pirosi e disturbi dell'alvo.

• La paziente mantiene le prescrizioni comportamentali, ma il calo ponderale è ancora modesto e fugace.

• Il fumo viene sospeso, ma solo transitoriamente.

• Per l'amenorrea, dopo esame ginecologico, viene prescritta terapia ciclica con soli progestinici (nomegestrolo, 1cp 5mg per 10gg/mese), con ripresa delle mestruazioni.

• Dopo alcuni mesi, la paziente viene persa al follow-up.

The Diabetes Prevention Program Group

TABLE 3. ADVERSE EVENTS.

EVENT	PLACEBO	METFORMIN	LIFESTYLE
Gastrointestinal symptoms (no. of events/100 person yr)*	30.7	77.8†	12.9†
Musculoskeletal symptoms (no. of events/100 person yr)‡	21.1	20.0	24.1†
Hospitalization			
One or more admissions (% of participants)	16.1	15.9	15.6
Rate (no. of admissions/100 person-yr)	7.9	8.4	8.0
Median stay (days)	3	3	3
Deaths (no./100 person yr)	0.16	0.20	0.10

*Gastrointestinal symptoms included diarrhea, flatulence, nausea, and vomiting.

Knowler WC, et al. N Engl J Med 2002

CLINICAL QUESTIONS

?

1. Sindrome Metabolica e rischio cardiovascolare.

E. Ritenete che il rischio cardiovascolare della sig.ra Francesca avrebbe giustificato un trattamento farmacologico?

1. Anti-ipertensivi
2. Ipolipemizzanti
3. 1 + 2
4. Nessun trattamento*

*mantenere solo le modificazioni dello stile di vita

Sindrome metabolica: quali obiettivi terapeutici

1. To reduce underlying causes (ie, obesity and physical inactivity)
2. **To treat associated risk factors (non-lipid and lipid)**

NHBLI. ATP III. JAMA 2001

The ATP III does not specify whether subjects with the metabolic syndrome should receive more intense therapy for underlying conditions (ie, hypertension, lipid disorders)

Sindrome metabolica: quali obiettivi terapeutici

1. Behavioral
- Weight loss
- Increased physical activity

2. Pharmacological (treat underlying conditions)
- Lipid disorders
- Hypertension
- Diabetes

3. Treat insulin resistance in non-diabetic subjects

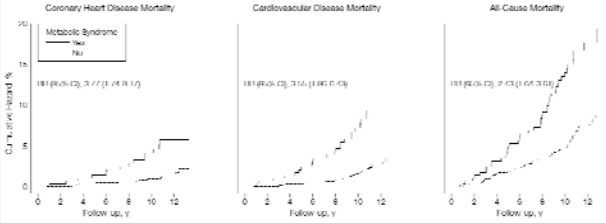
Haffner S, et al. Circulation 2003

Lakka HM, Laaksonen DE, Lakka TA, et al.

The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men

JAMA 2002;288:2709-16

Sindrome metabolica: il rischio cardiovascolare



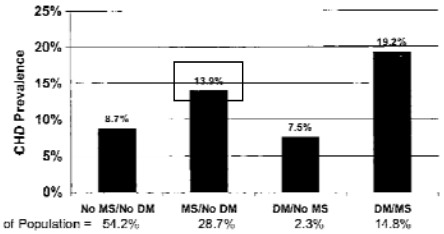
Cardiovascular disease and all-cause mortality are increased in men with the metabolic syndrome, even in the absence of baseline CVD and diabetes.

Lakka HM, et al. JAMA 2002

Alexander CM, Landsman PB, Teutsch SM, et al.

NCEP-defined metabolic syndrome, diabetes mellitus, and prevalence of coronary heart disease among NHANES III participants age 50 years and older

Diabetes 2003;52:1210-214



Age-adjusted prevalence of coronary heart disease in the US population >=50 years of age categorized by presence of metabolic syndrome (MS) and diabetes mellitus (DM). Combinations of metabolic syndrome and diabetes mellitus status are shown.[15]

Alexander CM, et al. Diabetes 2003

Sindrome metabolica: il rischio cardiovascolare

Although these results need to be replicated in other populations, particularly in prospective studies, suggest that **subjects with the NCEP-defined metabolic syndrome have an intermediate risk of CHD** and are not equivalent in risk to subjects with only CHD or type 2 diabetes.

Haffner S, et al. Circulation 2003

Schillaci G, Pirro M, Vaudo G, Gemelli F, Marchesi S, Porcellati C, Mannarino E.

Prognostic value of the metabolic syndrome in essential hypertension.

J Am Coll Cardiol 2004;43:1817-22.
May 19

METHODS

• We prospectively followed for up to 10.5 years (mean 4.1 years) a total of 1.742 hypertensive patients without cardiovascular disease (55% men; blood pressure [BP] 154/95 mm Hg; age 50 +/- 12 years).

RESULTS (1)

• During follow-up, 162 patients developed cardiovascular events (2.28 events/100 patient-years).
• Event rates in the groups with one to five characteristics of the MS were 1.54, 1.96, 2.97, 3.35, and 5.27 per 100 patient-years, respectively
• A total of 593 patients (34%) had the metabolic syndrome.

Schillaci G, et al. J Am Coll Cardiol 2004

RESULTS (2)

• Patients with the syndrome had an almost double cardiovascular event rate than those without.

• The syndrome was an independent predictor of both cardiac and cerebrovascular events (RR 1.48 and 2.11, respectively).

• The adverse prognostic value of the metabolic syndrome was attenuated among the 1,637 patients without diabetes (RR 1.43, 95% CI 1.02 to 2.08).

CONCLUSIONS

• In hypertensive subjects, the MS amplifies cardiovascular risk associated with high BP, independent of the effect of several traditional cardiovascular risk factors.

Schillaci G, et al. J Am Coll Cardiol 2004

Sindrome metabolica: quali obiettivi terapeutici

2. Pharmacological (treat underlying conditions)

- Lipid disorders
- Hypertension
- Diabetes

Should the treatment of these disorders be "more aggressive" because the subject has the metabolic syndrome?

Haffner S, et al. Circulation 2003

MINI-REVIEW: EXPERT OPINIONS

A Call for Aggressive Treatment

Our experts agree that early and aggressive therapy directed at dyslipidemia and insulin resistance, although at present unproven, is an attractive treatment strategy for the metabolic syndrome. In addition to behavioral intervention (weight loss, diet, and exercise), therapy with fibrates, metformin thiazolidinediones, and possibly dual peroxisome proliferator-activated receptor (α and γ) agents may be useful in addressing the central physiological disturbances. Treatment of clinical risk factors (dyslipidemia, hyperglycemia, and hypertension) should be even more intensive than called for by current guidelines based on the additive "global" risk posed for the syndrome itself. At present, no consensus optimal "targets" for LDL, blood pressure, etc, in the treatment of metabolic syndrome have been determined.

Kereiakes, DJ, et al. Circulation 2003

MINI-REVIEW: EXPERT OPINIONS

• We have little direct evidence on the treatment of non-diabetic subjects with the metabolic syndrome.

• No evidence-based guidelines address this issue at present

Haffner S, et al. Circulation 2003

LDL 143 mg/dL

Table 3. Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals*

- Cigarette smoking
- Hypertension (blood pressure ≥140/90 mm Hg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)†
- Family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years)
- Age (men ≥45 years; women ≥55 years)

NHBLI. ATP III. JAMA 2001

LDL 143 mg/dL

Table 5. LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories*

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)†
2+ Risk factors (10 year risk ≤20%)	<130	≥130	● 10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk factor‡	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

NHBLI. ATP III. JAMA 2001

LDL 143 mg/dL

TABLE 5. Clinical Approach to the Treatment of Dyslipidemia in the Metabolic Syndrome: Calculate Global Risk Even if Fewer Than 2 or More Major Risk Factors

Target therapy on the basis of global risk
If global risk is 15–20% and +metabolic syndrome, consider treating as if global risk is >20%*
If global risk is 5–10% and +metabolic syndrome, consider treating as if is high-risk primary prevention† ●

*CHD risk equivalent with LDL cholesterol goal <100 mg/dL.
†Global risk of 10–20% LDL cholesterol goal <130 mg/dL.

Haffner S, et al. Circulation 2003

Chobanian AV, Bakris GL, Black HR, et al.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure The JNC 7 report

JAMA 2003;289:2560-72

PAO 135/90 mmHg

Table 1. Classification and Management of Blood Pressure for Adults Aged 18 Years or Older

BP Classification	Systolic BP, mm Hg*		Diastolic BP, mm Hg*	Lifestyle Modification	Management* Initial Drug Therapy: Without Compelling Indication	Initial Drug Therapy: With Compelling Indications‡
Normal	<120	and	<80	Encourage		
Prehypertension	120-139	or	80-89	Yes	No antihypertensive drug indicated	Drug(s) for the compelling indications‡
Stage 1 hypertension	140-159	or	90-99	Yes	Thiazide-type diuretics for most; may consider ACE inhibitor, ARB, β-blocker, CCB, or combination	Drugs for the compelling indications. Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed.
Stage 2 hypertension	≥160	or	≥100	Yes	2 Drug combination for most (usually thiazide-type diuretic and ACE inhibitor or ARB or β-blocker or CCB)§	Drug(s) for the compelling indications. Other antihypertensive drugs (diuretics, ACE inhibitor, ARB, β-blocker, CCB) as needed.

JNC 7. JAMA, 2003

Sindrome metabolica: quali obiettivi terapeutici

3. Treat insulin resistance in nondiabetic subjects

Drug treatment to directly reduce insulin resistance is promising, but clinical trials to prove reduction of CVD are lacking.

NHLBI/AHA. Circulation 2004

Except for metformin, no clinical trial data support the use of drugs to improve insulin sensitivity in non-diabetic subjects, although this is an area of active interest

Haffner S, et al. Circulation 2003

There are no evidence-based guidelines to provide therapeutic targets for treatment of the central manifestations of the insulin resistance

ACE/AACE, 2003

Scenario Clinico (3)

- La paziente torna all'osservazione circa 8 anni dopo, all'età di 52 anni.
- Ha sospeso i progestinici dopo circa un anno di terapia e non ha più mestruato.
- A 47 anni comparsa di sintomi menopausali: il climaterio viene confermato dal ginecologo, che non prescrive terapia sostitutiva ormonale a causa dei problemi metabolici e del fumo.

Scenario Clinico (3)

- Negli ultimi tempi il peso è leggermente aumentato e i valori pressori risultano spesso elevati (fino a 160/100 mmHg).
- Recentemente, comparsa di malessere, astenia, dispnea da sforzo, cardiopalmo, occasionale senso di peso epigastrico, senza chiara relazione con i pasti e con l'attività fisica.
- Per l'incremento dei valori glicemici, ha iniziato terapia con glibenclamide 2.5 mg due volte al dì e dieta 1200 Cal. con limitato apporto di carboidrati.

Dati di laboratorio (3)

	Baseline	1 anno	9 anni
BMI	29.7	30.9	**33.6**
Glicemia	112	120	**243**
HbA1c	-	6.1	**8.9**
Colesterolo tot.	221	225	**251**
Colesterolo HDL	42	41	**38**
Colesterolo LDL	141	143	**148**
Trigliceridi	187	205	**284**
Uricemia	6.0	6.7	**7.0**
PAO	135/88	135/90	**140/100**

Indagini strumentali (3)

• ECG: Ritmo sinusale 84 bpm, alterazioni aspecifiche della ripolarizzazione.

• Holter-ECG: occasionali extrasistoli ventricolari monomorfe, breve episodio compatibile con ischemia (asintomatico).

• Eco-colordoppler TSA: placche hard bilaterali al bulbo estese al tratto iniziale delle carotidi interne, con stenosi non emodinamicamente significative (25% a dx, 30% a sin).

• EGDS negativa.

Indagini strumentali (3)

• Ecocardiogramma: discinesia ventricolare sin, con riduzione di grado moderato della frazione di eiezione.

• Coronarografia: stenosi coronariche multiple

Decisione clinica (4)

• La paziente è stata sottoposta a rivascolarizzazione coronarica ed ha iniziato trattamento con isosorbide mononitrato 50 mg/die, acido acetilsalicilico 100 mg/die, enalapril 10 mg/die, simvastatina 20 mg/die.

Esami di laboratorio (4)

	Baseline	1 anno	9 anni	Dopo 3 mesi
BMI	29.7	30.9	33.6	**30.5**
Glicemia	112	120	243	**167**
HbA1c	-	6.1	8.9	**7.1**
Colesterolo tot.	221	225	251	**190**
Colesterolo HDL	42	41	38	**45**
Colesterolo LDL	141	143	148	**110**
Trigliceridi	187	205	284	**176**
Uricemia	6.0	**6.7**	7.0	**7.4**
PAO	135/88	135/90	140/100	**120/75**