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Diet, exercise, long chain polyunsaturated omega-3 fatty acids and the metabolic syndrome

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Summary
Up to now after many definition what is called metabolic syndrome includes this kind of dismetabolism: abnormal body fat distribution atherogenic dyslipidemia (including elevated trygliceride and small LDL particles) dysglycemia, insuline resistant, vascular dysregulation (beyond elevated blood pressure) prothrombotic state and hormonal factors which still are under study. Metabolic syndrome is not a disease per se, but is an "ensemble" of risk factors for cardiovascular disease and diabetes. In the present paper data will be presented on: a) a tentative to unify the diagnostic criteria after a deep loup in MS; b) effective interventions to reduce the incidence of MS; c) a comparison with the practical advices for life style intervention with the guide line prescribed by Enerzone; d) the rational for use at least twice a week of fatty fish from deep and cold water and the supplementation with LC PUFA Omega-3 fatty acids; e) the suggestion to study the relationship of simple and complex measures of the components of the MS to clinical events.

Riassunto
A tutt'oggi, dopo molte definizioni la situazione indicata con il termine di Sindrome metabolica comprende i seguenti dismetabolismi: distribuzione anormale del grasso corporeo, dislipidemia aterogenetica (comprendente un elevato aumento dei trigliceridi e la presenza di particelle LDL piccole), disglicemia, resistenza insulinica, disfunzioni vascolari (oltre a una pressione elevata), stato protrombotico e fattori ormonali non ancora ben definiti. La Sindrome metabolica non è una malattia per sé ma un "ensemble" di fattori di rischio per la malattia cardiovascolare e per il diabete. Nel presente lavoro verranno presentati dati riguardanti: a) un tentativo di unificare i criteri diagnostici dopo un escursus esauriente sulla MS; b) interventi effettivi per ridurre l'incidenza della MS; c) un confronto fra i suggerimenti pratici per modificare lo stile di vita con le linee guida previste dalla Enerzona; d) il razionale per l'uso, almeno due volte alla settimana, di pesci grassi provenienti da acque profonde e fredde e per la supplementazione con acidi grassi LC PUFA Omega-3; e) le ipotesi e i suggerimenti per studiare le relazioni fra i risultati, dai più semplici a quelli più complessi, dei fattori che sono compresi nella Sindrome metabolica, e gli eventi clinici ad essa correlati

Introduction

The constellation of dyslipidemia (hypertriglyceridemia and low levels of high-density lipoprotein- cholesterol), elevated blood pressure, impaired glucose tolerance, and central obesity is identified as metabolic syndrome. Soon metabolic syndrome will overtake cigarette smoking as the number one risk factor for heart disease among the U.S. population. Effective interventions include diet, exercise, and judicious use of pharmacologic agents to address specific risk factors. Weight loss significantly improves all aspects of the metabolic syndrome. Increasing physical activity and decreasing caloric intake by reducing portion sizes will improve metabolic syndrome abnormalities, even in the absence of weight loss. Specific dietary changes that are appropriate for addressing different aspects of the syndrome include reducing saturated fat intake to lower insulin resistance, reducing sodium intake to lower blood pressure, and reducing high-glycemic-index carbohydrate intake to lower triglyceride levels. A diet that includes more fruits, vegetables, whole grains, monounsaturated fats, fat fishes (and/or long chain polyunsaturated omega-3 fatty acids, LCPUFA omega-3) and low-fat dairy products will benefit most patients with metabolic syndrome.
In summary the major characteristics of metabolic syndrome include insulin resistance, abdominal obesity, elevated blood pressure, and lipid abnormalities.

A brief story to define the metabolic syndrome

The metabolic syndrome concept progressively emerged from the works of pioneer physicians who established in 1974 a correlation between body fat distribution and the risk of diabetes. The concept of a constellation of abnormalities (including impaired fasting glucose, dyslipidemia, state of insulin resistance), was developed during the next decades. Epidemiological studies showed also an association with overweight or obesity. Because such abnormalities are associated with a high risk of cardiovascular events several groups developed their own set of criteria to identify affected patients

Three sets of clinical criteria were raised initially to identify people with metabolic syndrome

A) 1998 Word Health Organization (WHO)
Insulin resistance (identified by the clamp technique, or defined as the presence of impaired fasting glucose or type 2 diabetes)
+
any two of the following:
Blood pressure >140/90 mm Hg
Plasma triglycerides >1.7 mmol/l
HDL-cholesterol <0.9 mmol/l (men) or < 1 mmol/l (women)
Body mass index >30 Kg/m^2 or waist/hip ratio >0.9 (men) or 0.85 (women)
Urinary albumin >20 mg/min or albumin/creatine >30 mg/g

B) 1999 European Group for the study of Insulin Resistance (EGIR)
Hyperinsulinemia (>95th percentile)
+
any two of the following:
Waist circumference >94 cm (men) or 80 cm (women)
Plasma triglycerides >2.0 mmol/l or HDL-cholesterol <1 mmol/l
Blood pressure >140/90 mm Hg
Fasting glucose >6.1 mmol/l

C) 2001 National Cholesterol Education Program-Adult Treatment Panel III (NCEP)
Any three of five:
Abdominal obesity (waist circumference >102 cm (men) or 88 cm (women)
Plasma triglycerides >150 mg/dl
HDL-cholesterol <40 mg/dl (men) or < 50 mg/dl (women)
Blood pressure >130/80 mm Hg
Blood glucose >100 mg/dl

In conclusion therefore MS is a group of risk factors linked primarily to overweight and obesity that increase the chance to have hearth disease and other health problems such as diabetes and stroke. The term

"metabolic" refers to the biochemical processes involved in normal functioning of the body.

The insulin resistance was definied in 2002 by the Association of Clinical Endocrinologists (AACE) by the following parameters

2002 American Association of Clinical Endocrinologists (AACE)
Diagnosis depends on clinical judgment:

- Impaired fasting glucose (100-126 mg/dl) or 2-h post oral glucose (>140 mg/dl).
- Blood pressure >130/85 mm Hg.
- Abdominal obesity (waist circumference >102 cm (men) or 88 cm (women).
- HDL-cholesterol < 40 mg/dl (men) or < 50 mg/dl (women).
- Body mass index > 25 Kg/m^2.
- Other risk factors: family history of type 2 diabetes, hypertension or cardiovascular disease; PCOS, aging, physical inactivity, ethnic susceptibility to type 2 diabetes or cardiovascular disease.

Associated pathologies

Metabolic syndrome is associated with a proinflammatory/prothrombotic state that may include elevated levels of C-reactive protein, endothelial dysfunction, hyperfibrinogenemia, increased platelet aggregation, increased levels of plasminogen activator inhibitor 1. In this view studies on metabolic parameters such as the ratio arachidonic/ eicosapentaenoic acids and the homocisteine level (related to the –SH group and folate metabolism) deserve a future interesting opportunity. This hypothesis is further supported by the data reported in the following paragraph.

The IDF consensus worlwide definition of the MS

Platinum Standard definition – additional metabolic criteria for research

The IDF consensus group has highlighted a number of other parameters that appear to be related to the metabolic syndrome (Table 2) which

Table 1. A comparison of diagnostic criteria for metabolic syndrome according to who and the ATP III

Component	*WHO diagnostic criteria (insulin resistance* plus two of the following)*	*ATP III diagnostic criteria (three of the following)*
Abdominal/central obesity	Waist to hip ratio: >0.90 (men), 0.85 (women), or BMI >30 Kg per m^2	Waist circumference: >102 cm (40 in) in men, >88 cm (35 in) in women
Hypertriglyceridemia	≥150 mg per dl (≥1.7 mmol per L)	≥150 mg per dl
Low HDL cholesterol	<35 mg per dl (<0.9 mmol per L) for men, <39 mg per dl (<1.0 mmol per L) for women	<40 mg per dl (<1.036 mmol per L) for men, <50 mg per dl (<1.295 mmol per L) for women
High blood pressure	≥140/90 mm Hg	≥130/85 mm Hg
High fasting glucose	Impaired glucose tolerance, impaired fasting glucose, insulin resistance, or diabetes	>110 mg per dl (≥6.1 mm per L)§
Microalbuminuria	Urinary albumin to creatinine ratio: 30 mg per g, or albumin excretion rate: 20 mcg per minute	

WHO = World Health Organization; ATP = Adult Treatment Panel; BMI = body mass index; HDL = high-density lipoprotein.
*Insulin resistance is identified by type 2 diabetes mellitus or impaired fasting glucose
§ The American Diabetes Association recently has suggested lowering this threshold to 100

should be included in research studies to help determine the predictive power of these extra criteria for CVD and or diabetes. The use of these additional factors in research will also allow to ascertain if further modification of the definition is necessary and the validation of the new clinical definition in different ethnic groups.

A deep loup in MS

The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) (1) (Tab. 1, 2) identified the metabolic syndrome as a multiplex risk factor for cardiovascular disease (CVD). The National Heart, Lung and Blood Institute in collaboration with the American Hearth Association convened a conference to examine scientific issues related to definition of the metabolic syndrome: (1) major clinical outcomes, (2) metabolic components, (3) pathogenesis, (4) clinical criteria for diagnosis, (5) risk for clinical outcomes and (6) therapeutic interventions.

Components of Metabolic Syndrome

As previously indicated ATP III identified 6 components of the metabolic syndrome that relate to CVD:

- Abdominal obesity.
- Atherogenic dyslipidemia.
- Raised blood pressure.
- Insulin resistance + glucose intolerance.
- Prothrombotic state.

These components of the metabolic syndrome constitute a particular combination of what ATP III terms underlying, major, and emerging risk factors. According to the ATP III underlying risk factors for CVD are obesity (especially abdominal obesity), physical inactivity, and atherogenic diet; the major risk factors are cigarette smoking, hypertension, elevated LDL cholesterol, low HDL cholesterol, fa-

Table 2. Additional metabolic criteria for research

Abnormal body fat distribution	General body fat distribution Central fat distribution (CT/MRI) Adipose tissue biomarkers: leptin, adiponectin Liver fat content (MRS)
Atherogenic dyslipidemia (beyond elevated trygliceride and low HDL)	ApoB (or non-HDL-c) Small LDL particles
Dysglycemia	OGTT
Insulin resistance (other than elevated fasting glucose)	Fasting insulin/proinsulin levels HOMA-IR Insulin resistance by Bergman Minimal Model Elevated free fatty acids (fasting and during OGTT) M value from clamp
Vascular dysregulation (beyond elevated blood pressure)	Measurement of endothelial dysfunction Microalbuminuria
Proinflammatory state	Elevated high sensitivity C-reactive protein (SAA) Elevated inflammatory cytokines (eg TNF-alpha, IL-6) Decrease in adiponectin plasma levels
Prothrombotic state	Fibrinolytic factors (PAI-1) Clotting factors (fibrinogen)
Hormonal factors	Pituitary-adrenal axis

mily history of premature coronary hearth disease (CHD), and aging; and the emerging risk factors include elevated triglycerides, small LDL particles, insulin resistance, glucose intolerance, proinflammatory state and prothrombotic state.

Insulin resistance

Many investigators place a greater priority on insulin resistance than on obesity in pathogenesis of Metabolic Syndrome (2, 3). They argue that insulin resistance, or hyperinsulinemia, directly causes other metabolic risk factors. Identifying a unique role for insulin resistance is complicated by the fact that it is linked to obesity. Insulin resistance generally rises with increasing body fat content , yet a broad range of insulin sensitivities exists at any given level of body fat (4). Most people with categorical obesity (BMI > 30 Kg/m^2) have postprandial hyperinsulinemia and relatively low insulin sensitivity (5), but variation in insulin sensitivities exists even within the obese population (4). Overweight persons (BMI 25 to 29.9 Kg/m^2) likewise exhibit a spectrum of insulin sensitivities, suggesting an inherited component to insulin resistance. In some populations (e.g. South Asians), insulin resistance occurs commonly even with BMI <25 Kg/m^2 and apparently contributes to a high prevalence of type 2 diabetes and premature CVD. South Asians and others who manifest insulin resistance with only mild-to-moderate overweight can be said to have primary insulin resistance. Even with primary insulin resistance, however, weight gain seems to enhance insulin resistance and metabolic syndrome. Thus, dissociation of obesity and primary insulin resistance in patients with metabolic syndrome is difficult.
Insulin resistance per se does play a significant role in causation of metabolic syndrome. When insulin-resistant muscle is already overloaded with lipid from high plasma NEFA levels, some excess NEFA presumably is diverted to the liver, promoting fatty liver and atherogenic dyslipidemia. Hyperinsulinemia may enhance output of very low-density lipoprotein triglycerides, raising triglycerides. Insulin resistance in muscle predisposes to glucose intolerance, which can be worsened by increased hepatic gluconeogenesis in insulin-resistant liver. Finally insulin resistance may raise blood pressure by a variety of mechanisms.

Independent factors that mediate specific components of the metabolic syndrome

Beyond obesity and insulin resistance, each risk factor of the metabolic syndrome is subject to its own regulation through both genetic and acquired factors. This leads to variability in expression of risk factors. Lipoprotein metabolism, for instance, is greatly modulated by genetic condition; hence, expression of dyslipidemias in response to obesity and/or insulin resistance varies considerably. The same holds for blood pressure regulation. Moreover, glucose levels depend on insulin-secretory capacity as well as insulin sensitivity. This variation in distal regulation cannot be ignored as an important factor in causation of metabolic syndrome.

Other contributing factors

Advancing age probably affects all levels of pathogenic mechanism, which likely explains why prevalence of the metabolic syndrome rises with advancing age (6). Recently, a proinflammatory state has been implicated directly in causation of insulin resistance, as well as atherogenesis. These last two situations are in favour to modify the ratio between pro- and anti-inflammatory leukotriens and the increase of proinflammatory cytochines with the use of LCPUFA-omega 3 supplement. Finally, several endocrine factors have been linked to abnormalities in body-fat distribution and hence indirectly to metabolic syndrome. Thus pathogenesis of the metabolic syndrome is complex and ripe with opportunities for further research.

Table 3. A comparison of diagnostic criteria for metabolic syndrome according to who and the ATP III

Abnormality	*Diet and physical activity interventions*	*Practical advice*
Abdominal obesity	Reduce weight	Reduce portion size to lower calorie intake
	Increase physical activity	30 minutes of moderate-intensity exercise daily
Hypertriglyceridemia	Reduce weight	Reduce portion size to lower calorie intake
	Increase physical activity	30 minutes of moderate-intensity exercise daily
	Increase intake of low-glycemic-index foods	Replace refined carbohydrates (white bread, potatoes, pasta) with legumes, whole grains, and monounsaturated fats (nuts, avocado, extra vergin olive oil)
	Reduce total carbohydrate intake	Replace soda and juices with water and diet beverages
	Increase omega-3 fatty acids	Eat fatty fish from deep and cold water at least twice per week
	Limit alcohol consumption	Limit alcohol to no more than 6/7 g/die
Low HDL cholesterol level	Reduce weight	Reduce portion size to lower calorie intake
	Increase physical activity	30 minutes of moderate-intensity exercise daily
	Increase consumption of monounsaturated fats	Eat fatty fish from deep and cold water, nuts and avocados. Use extra vergin olive oil in salade dressing and for cooking
	Stop smoking	Join a smoking cessation program
High blood pressure	Reduce weight	Reduce portion size to lower calorie intake
	Increase physical activity	30 minutes of moderate-intensity exercise daily
	Reduce saturated fat intake	Choose low-fat dairy products and reduce consumption of red meat, butter, and full-fat dairy products
	Reduce sodium intake	Reduce sodium intake to no more than 2.4 g per day or 6 g per day of salt by using more herbs in cooking; read labels for sodium content; skip the salt shaker
	Increase consumption of fruits and vegetables	Consume more than five servings of fruits and vegetables every day
	Increase low-fat dairy products	Consume three servings of low-fat dairy products daily
	Limit alcohol consumption	Limit alcohol to no more than 6/7 g/die
High fasting glucose level	Reduce weight	Reduce portion size to lower calorie intake
	Increase physical activity	30 minutes of moderate-intensity exercise daily
	Reduce total carbohydrate intake; replace carbohydrates with monounsaturated fat	Replace refined grains with whole grains (oatmeal, brown rice, corn, and whole wheat) and monounsaturated fats (nuts, avocado, extra vergin olive oil)
	Increase dietary fiber (more than 30 g per day)	Add legumes and fruit for soluble fiber

Table 4. Adherence of enerzone prescriptions to the guideline for ms and references for the results obtained applying

Abnormality	*Interventions*	*Practical advice*	*Adherence*	*References*
Abdominal obesity	Reduce weight	Reduce portion size to lower calorie intake	Yes	
	Increase physical activity	Moderate exercise daily	Yes	
Hypertriglyceridemia	Reduce weight	Reduce portion size to lower calorie intake	Yes	*G.Fontani, et al. Eu. J. of Clin. Invest. (2005), 35, 499-507*
	Increase physical activity	30 min moderate exercise daily	Yes	
	Increase intake of LGI foods	Replace refined carbohydrates with legumes, whole grain and MUFA	Yes	
	Increase omega-3 fatty acids	Eat fatty fish from deep and cold water at least twice per week	Yes	
Low HDL cholesterol level	Reduce weight	Reduce portion size	Yes	*Spaggiari et al. Leadership Medica, (2006), n.2*
	Increase physical activity	30 min moderate exercise daily		
	Increase consumption of MUFA	Eat fatty fish from deep and cold water, use extra vergin olive oil	Yes	
High blood pressure	Reduce weight	Reduce portion size	Yes	
	Increase physical activity	30 min moderate exercise daily	Yes	
	Reduce saturated fat intake	Choose low-fat dairy products and reduce consumption of red meat, butter, and full-fat dairy products	Yes	
	Reduce sodium intake	Reduce sodium intake to no more than 2.4 g per day or 6 g per day of salt by using	Yes	

(Continued on next page)

		more herbs in cooking; read labels for sodium content; skip the salt shaker	
	Increase consumption of fruits and vegetables	Consume more than five servings of fruits and vegetables every day	Yes
	Increase low-fat dairy products	Consume three servings of low-fat dairy products daily	Yes
	Limit alcohol consumption	Limit alcohol to no more than 6/7 g/die	Yes
High fasting glucose level	Reduce weight	Reduce portion size to lower calorie intake	Yes
	Increase physical activity	30 minutes of moderate-intensity exercise daily	Yes
	Reduce total carbohydrate intake; replace carbohydrates with monounsaturated fat	Replace refined grains with whole grains and monounsaturated fats (nuts, avocado, extra vergin olive oil)	Yes
	Increase dietary fiber (more than 30 g per day)	Add legumes and fruit for soluble fiber.	Yes

Raccomandations in pills

No single diet is currently recommended for patients with metabolic syndrome; therefore, it may be best for physicians to focus on each patient's specific metabolic alterations when offering dietary advice (7) (Table 3). Sustained dietary changes may require referral to a registered dietitian to help implement suggestions and ensure adequate micronutrient intake (e.g. calcium, iron, folate) while reducing calories. There is debate about what proportions of macronutrients (i.e., protein, fat, and carbohydrates) will produce the best outcome (low-fat, low-carbohydrate, or Mediterranean diets). If a patient is consuming fewer calories than he or she is expending, the macronutrient composition of the diet is probably of secondary importance, because weight loss improves metabolic syndrome.

The primary goals of dietary management for persons with metabolic syndrome are to reduce the risk of cardiovascular disease and diabetes mellitus.

The long-term effects of low-carbohydrate diets have not been studied adequately in patients with metabolic syndrome, although short-term effects show benfit

Conclusions and perspectives

Metabolic symptoms are a cluster of conditions that occur together, increasing the risk for hearth disease, stroke and diabetes. Even if metabolic syndrome was recognized more than 30 years age, research into the complex underlying processes linking this group of conditions is still ongoing. As the name suggests metabolic syndrome is tied to the body's metabolism, possibly to a condition known as insulin resistance. Not all the experts agree on this definition or whether metabolic syndrome exists as a distinct medical condition; doctors have talked about

this constellation of risk factors for many years and many of them are still in favour to indicate metabolic syndrome as syndrome X. It is hoped that a consensus on a new definition (e.g. the one proposed by IDF), which emphasize the importance of central obesity, will be adopted worldwide and prove convenient and useful in clinical practice and epidemiological studies. This should encourage the clinical diagnosis and the identification of patients at considerably increased risk of developing CVD and/or type 2 diabetes. An unified definition will be enable easier comparison of data from different studies and the ongoing refinement of the definition as more information becomes available. The following areas of further research deserves to be explored.

- the aetiology of the metabolic syndrome;
- the best and most predictive definition of the metabolic syndrome and its components;
- how blood pressure is related to the other components of the syndrome;
- the relationship between the different constellations of factors to CVD outcomes;
- the relationship of simple and complex measures of the components of the metabolic syndrome to clinical events;
- the true impact of effective treatment of all components of the syndrome on CVD risk.

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