PREDICTION OF PERSONAL HEALTH RISK FACTORS IN METABOLIC SYNDROME

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Abstract

In European health systems the metabolic syndrome has become of major concern in public health. The same tendency has been observed also in developing countries of South East Asia. The metabolic syndrome is an important health risk factor often related to Diabetes and cardiovascular disease. A successful approach to the prevention of the metabolic syndrome therefore contributes to the stabilization of the present and future health system of the European Union and specific parts of Asia decisively. Practical guidelines for the prevention of diabetes and metabolic syndrome are needed urgently. Laboratory diagnostics provide a practicable tool in the early diagnosis of the metabolic syndrome. In this article new laboratory markers such as **Adiponectin, Proinsulin and Asymmetric Dimethylarginine (ADMA)** are discussed as markers of metabolic risk.

Key words: metabolic syndrome – diabetes – Adiponectin, Proinsulin, Asymmetric Dimethylarginine (ADMA)

REVIEW

INTRODUCTION

The metabolic syndrome has become of major concern in public health worldwide and represents one of the top health problems in welfare coiuntries. The metabolic syndrome is a decisive health risk factor of Diabetes and cardiovascular disease. A major aspect of the metabolic syndrome is related to the insulin resistance regarded a precursor of Diabetes type II. In Germany already 6.3 Mio. People suffer from diabetes with a rising tendency. According to epidemiological data this number will double in the next 10 years. Today lifetime risk for newly born babies to acquire diabetes in future life already reaches already 35% in developed countries. This tendency means than every 3rd newly born baby will be a diabetes patient in future. In fact, the number of future diabetics (Type II) turning in to the full stage of diabetes in the next twenty years is estimated up to the amount of 40% of the total population. Under theses circumstances a considerable economical problem will mount up in so called developed countries, because a considerable part of the costs of the social health system will have to be spend on treatment of chronic disease (Miller 2007).With a change of dietarian habits there is a high risk that this tendency will spread to developing countries in the nearest future. Practical concepts of prevention are urgently at request. In this review innovative means of early diagnostics will be considered as an essential tool.

METABOLIC SYNDROME

The definition of the metabolic syndrome includes at least three of the following five criteria (Miller 2007):

- abdominal fat mass, determined by a hip extent more than 102 cm with men or more than 88 cm with women;
- triglycerides above 150 mg/dL;
- HDL cholesterol less than 40 mg/dL with men and/or <50 mg/dL with women;
- blood pressure of 135/85 mm Hg or more;
- blood sugar of more than 110 mg/dL (or presence of diabetes type 2).

The body fat distribution pattern seems to be of utmost importance in the evaluation of the cardiovascular risk factors. Especially abdominal fat produces hormone activity with impact on fat and carbohydrate metabolism (carbohydrate metabolism). Abdominal fat produces hormones such as Leptin and Adiponectin determining the energy metabolism and body fat consumption.

The measurement of the waist circumference is therefore regarded as a simple and fast way of obesity assessment (Miller 2007). In a long-term study over 6 years with 2924 men at the age of 60–79 years the risk doubled for a metabolic syndrome with increasing waist extent. The mortality rate increased with the weight in a study with 2739 women.

The metabolic syndrome affects approximately 24% of the adult population in industrialized countries (it. US); according to the Third National Health and Nutrition Examination Survey (NHANES III) criteria, about 47 million people have a metabolic syndrome, including 44% of those in the >/=50-year age group. Metabolic syndrome is present in 10% of women and 15% of men with normal glucose tolerance; 42% and 64% of those with impaired fasting glucose; and 78% and 84% of those with type 2 diabetes. Most patients (>80%) with type 2 diabetes have metabolic syndrome.

Metabolic syndrome (without type 2 diabetes) significantly increases the risk of coronary heart disease (CHD). Recent sub analyses of the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) showed that placebo controls with metabolic syndrome (but not type 2 diabetes) were at ~1.5 times higher risk of coronary events than those without metabolic syndrome. Risk increased strikingly when type 2 diabetes developed. Notably, the presence of metabolic syndrome increased the risk of major coronary events irrespective of 10-year absolute coronary risk above or below 20%, the ATP threshold for initiating treatment to reduce low-density lipoprotein cholesterol (LDL-C) to levels of 100 mg/dL or below (Prentice and Jebb 2001).

Increased blood fats result from a too high dietarian fat intake or on the basis of genetic defects in the fat processing. A drastic fat reduction can contribute to a risk reduction for Type-II-diabetes. It is important to note, that a change in life style can reverse the dangerous effects of the metabolic syndrome. The metabolic syndrome is dominated by the prevalence of hyperinsulinaemia. A constant high Insulin excretion by the pancreas will contribute to a decay of peripheral insulin receptor sensitivity which is regarded Insulin resistance (Lakka et al. 2002).
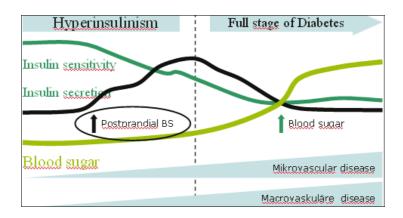

Fig. 1. Blood sugar in Hyperinsulinism and manifest Diabetes mellitus

Insulin sensitivity is reduced in the cause of hyperinsulinism parallel to an increase of insulin secretion prior to full stage of diabetes diagnosis. Blood sugar levels are not affected in the early stage of hyperinsulinism significantly. The early diagnosis of hyper-insulinism prevents from vascular consequences of carbohydrate metabolism.

- ***The metabolic syndrome is domi-nated by the prevalence of hyper-insulinaemia***
- ***Change in life style can reverse the dangerous effects of the metabolic syndrome.***

The pathophysiology of the metabolic syndrome is under the control of body weight and of blood glucose concentrations. Both depend on the exquisite coordination of the function of several organs and tissues, in particular the liver, muscle and fat. These organs and tissues have major roles in the use and storage of nutrients in the form of glycogen or triglycerides and in the release of glucose or free fatty acids into the blood, in periods of metabolic needs. These mechanisms are tightly regulated by hormonal and nervous signals, which are generated by specialized cells that detect variations in blood glucose or lipid concentrations. The hormones insulin and glucagon not only regulate glycaemia levels through their action on these organs and the sympathetic and parasympathetic branches of the autonomic nervous system, which are activated by glucose or lipid sensors, but also modulate pancreatic hormone secretion and liver, muscle and fat glucose and lipid metabolism. Other signalling mo-lecules, such as the adipocyte hormones Leptin and Adiponectin, have circulating plasma concentrations that reflect the level of fat stored in adipocytes. These signals are integrated at the level of the hypothalamus by the melanocortin pathway, which produces orexigenic and anorexigenic neuropeptides to control feeding behaviour, energy expenditure and glucose homeostasis. Work from several laboratories, has explored the physiological role of glucose as a signal that regulates these homeostatic processes and has tested the hypothesis that the mechanism of glucose sensing that controls insulin secretion by the pancreatic beta-cells is also used by other cell types (Kennedy et al. 2009).

Nutritional fat and other calories are stored in body fat by means of insulin. Insulin guarantees a constant blood sugar level even after eating or drinking and while fastening. A peripheral effect of insulin decay will evolve from fatty liver degeneration. Less receptor activity will be answered by an increase of central insulin production to the extent that deposits will also increase in the peripheral vessels leading to less flexibility. Usually it takes several decades for patients to develop diabetes mellitus type II after the first signs of metabolic syndrome have become visible. A metabolic syndrome entails an extended risk for inflammation or inflammatory deregulations (Thorens 2008).

- ***Early recognition of personal health risk factors is essential for the effective prevention of the metabolic syndrome. Diabetes mellitus is usually diagnosed 5–10 years too late.***
- ***Often serious consequences are already present. Four from 5 pa-tients with heart attacks suffer from diabetes mellitus (Deveci et al. 2009).***

Health risk assessment by means of reliable biomarkers of laboratory medicine

The biological assessment of the waist extent lacks scientific accuracy since no general agreement exists for the reference point of this measurement currently. Several recommendations differ regarding the set points. The International diabetes society regards a waist extent >94 cm with men and >80 cm with women as critical (Li et al. 2008).

It is important to remember that waist extent is only one factor related to risk for disease. For assessing someone's likelihood of developing overweight- or obesity-related diseases, it is recommended to look at further risk predictors such as the body mass index (BMI) (Gallagher 1996).

The correlation between the BMI number and body fatness is fairly strong; however the correlation varies by sex, race, and age.

It has to be taken in consideration that:
- At the same BMI, women tend to have more body fat than men.

- At the same BMI, older people, on average, tend to have more body fat than younger adults.
- Highly trained athletes may have a high BMI because of increased muscularity rather than increased body fatness.

Body Mass Index (BMI) is a number calculated from a person's weight and height. BMI is a reliable indicator of body fatness for people. BMI is therefore used as a screening tool to identify possible weight problems for adults. BMI does not measure body fat directly, but research has shown that BMI correlates to direct measures of body fat, such as underwater weighing and dual energy x-ray absorptiometry. BMI can be therefore considered an alternative for direct measures of body fat. Additionally, BMI is an inexpensive and easy-to-perform method of screening for weight categories that may lead to health problems (Garrow and Webster 1985, Mei et al. 2002).

Table 1. BMI calculation

Measurement units	Formula and calculation
Kilograms and meters (or centimeters)	Formula: weight (kg)/[height (m)]^2 With the metric system, the formula for BMI is weight in kilograms divided by height in meters squared. Since height is commonly measured in centimeters, divide height in centimeters by 100 to obtain height in meters. Example: Weight = 68 kg, Height = 165 cm (1.65 m) Calculation: $68 \div (1.65)^2 = 24.98$

Table 2. Interpretation of BMI

BMI	Weight status
Below 18.5	Underweight
18.5–24.9	Normal
25.0–29.9	Overweight
30.0 and above	Obese

In the medical laboratory the diagnosis of Diabetes mellitus is usually based by measuring blood sugar. "Hba1c" (a specific fraction of the hemoglobin which reacts to repeatedly increased blood sugar concentrations) is suitable only for the control of already known diabetes. The oral glucose tolerance test = OGTT is also accepted generally as an early indicator. Also increased HOMA-IR-Values >2 indicate an insulin resistance: This value is calculated from following equation:

Table 3. Meassuring HOMA-IR

HOMA-IR = sober insulin (pU/ml) × sober glucose (mg/dl)/405

The HOMA-Index represents a early biomarker of the metabolic syndrome. Measuring the HOMA Index requires complicated pre-analytical circumstances (40. EASD-Jahreskongress 2004).

Since HOMA- Index and OGTT are rather time consuming or require intense preanalytic caution new biomarkers of early onset diagnosis practical in use have been searched for lately. Such parameters have been established meanwhile for Metabolic Syndrome with reliable accuracy in the prediction of health risk derived from the metabolic syndrome. Such parameters in use

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are **Adiponectin, Intact Proinsulin and Asymmetric Dimethylarginine (ADMA)**.

Adiponectin

Adiponectin is a protein hormone that modulates a number of metabolic processes, including glucose regulation and fatty acid catabolism. Adiponectin is exclusively secreted from adipose tissue into the bloodstream and is very abundant in plasma relative to many hormones. Levels of the hormone are inversely correlated with body fat percentage in adults. The hormone plays a role in the suppression of the metabolic changes that may result in type 2 diabetes, obesity, atherosclerosis and non-alcoholic fatty liver disease. Supplementation of adiponectin was successful improving insulin control, blood glucose and triglyceride levels in mouse models. A striking similarity to TNF alpha was observed, despite unrelated protein sequences.

Adiponectin is secreted into the bloodsteam where it accounts for approximately 0.01% of all plasma protein at around 5–10 μg/mL. Plasma concentrations reveal a sexual dimorphism, with females having higher levels than males. Levels of adiponectin are reduced in diabetics compared to non-diabetics. Weight reduction significantly increases circulating levels (Díez and Iglesias 2003, Ukkola and Santaniemi 2003, Matsuzawa et al. 2004, Lara-Castro et al. 2007, Vasseur et al. 2007).

Intact proinsulin

Proinsulin is a precursor molecule for insulin and is synthesised by the pancreatic ß-cells. Under normal circumstances, virtually all proinsulin is cleaved at residues 32–33 and 65–66 to produce insulin during the formation of secretory granules. Some unmodified proinsulin is released into the circulation, though it is believed to have little or no biological activity. Increased concentrations of circulating proinsulin may occur in insulin-resistant syndromes such as non-insulin dependent (type II) diabetes and in patients with insulinoma. If the demand for insulin triggered by insulin resistance is arriving at a certain threshold, an insufficiency of the cleavage capacity of beta-cell carboxypeptidase H leads to an increased secretion of intact proinsulin in addition to the desired insulin molecule. Proinsulin, however, has been demonstrated to be an independent cardiovascular risk factor by stimulating plasminogen activator inhibitor-1 secretion and blocking fibrinolysis. A recently introduced intact proinsulin assay is able to distinguish between intact proinsulin and its specific and non-specific cleavage products. This assay allows for a pathophysiological staging of type 2 diabetes based on beta-cell secretion (Pfützner et al. 2004, Forst and Pfützner 2006, Pfützner et al. 2006).

Asymmetric dimethylarginine (ADMA)

Asymmetric dimethylarginine (ADMA) is a naturally occurring chemical found in blood plasma. It is a metabolic by-product of continual protein modification processes in the cytoplasm of all human cells. It is closely related to L-arginine, a conditionally-essential amino acid. ADMA interferes with L-arginine in the production of nitric oxide, a key chemical involved in normal endothelial function and, by extension, cardiovascular health. It is formed as a metabolic byproduct of continuous protein turnover in all cells of the body. ADMA plays a prominent role in the pathogenesis and in the progression of cardiovascular diseases – specifically atherosclerosis. The clinical role of ADMA as a marker of cardiovascular risk can be deduced from an increasing number of clinical studies that have demonstrated the presence of a statistically significant and independent relationship between ADMA and the incidence of major adverse cardiovascular events or death.

Asymmetric dimethylarginine is created in protein methylation, a common mechanism of post-translational protein modification. This reaction is catalyzed by an enzyme set called S-adenosylmethionine protein N-methyltransferases The methyl groups transferred to create ADMA are derived from the methyl group donor S-adenosylmethionine, an intermediate in the metabolism of homocysteine. After synthesis, ADMA migrates into the extracellular space and thence into blood plasma. The quantification of ADMA levels in serum or plasma therefore provides evidence beyond information gained by traditional risk markers, which help in a more profound risk analysis for the patient – and, therefore, a more specific therapeutic approach.

ADMA concentrations are elevated by native or oxidized LDL cholesterol. High endothelial LDL levels cause an increase of ADMA values, which in turn inhibit NO production which is needed to promote vasodilation. The elimination of ADMA occurs through urine excretion and metabolism by the enzyme dimethylarginine dimethylaminohydrolase (DDAH). The role of homocysteine as a risk factor for cardio-vascular disease is suggested to be mediated by homocysteine down-regulating production of DDAH in the body.

With the availability of the competitive ADMA®-ELISA a simple and rapid, yet spe-cific, sensitive, and fully validated method is now available for diagnostic assessment of ADMA concentration. With raised levels of ADMA seemingly to be associated with adverse human health consequences for cardiovascular disease, metabolic diseases and also a wide range of diseases of the elderly, the possible lowering of ADMA levels may have important therapeutic effects (Vallance et al. 1992, Böger et al. 1998, Kielstein et al. 1999, Zoccali et al. 2001, Stühlinger et al. 2002, Böger 2003, Lu et al. 2003, Nijveldt et al. 2003, Savvidou et al. 2003).
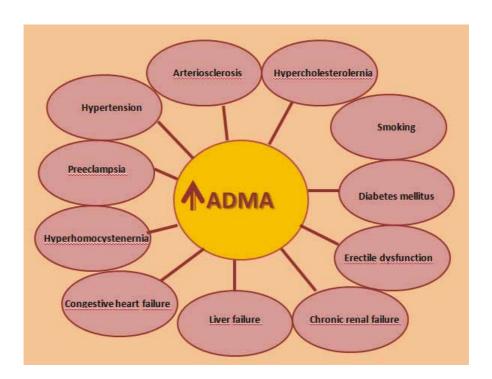

Fig. 2. Health risk factor Asymmetric Dimethylarginine (ADMA) in Metabolic Syndrome (attached separatly)

Order Id	20000002
Order date	05.02.2010
Print date	06.02.2010
Name	**Mustermann**
First name	**Peter**
Date of birth	**01.01.1960**

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Corpulence / obesity

Test	Result	Unit	Standard range	---	--	-		+	++	+++
Proinsulin intact	7,2	pmol/l	< 11							
Adiponectin	9,5	µg/ml								

Cardiovascular risk

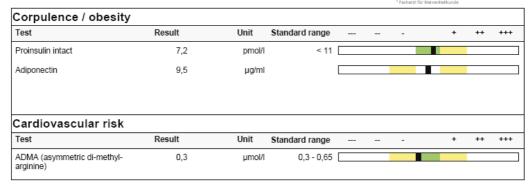| Test	Result	Unit	Standard range	---	--	-		+	++	+++
ADMA (asymmetric di-methyl-arginine)	0,3	µmol/l	0,3 - 0,65							

Fig. 3. Protocol of Proinsulin, Adiponectin and ADMA in Metabolic syndrome with normal values

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Corpulence / obesity

Test	Result	Unit	Standard range	---	--	-		+	++	+++
Proinsulin intact	12,7	pmol/l	< 11							
Adiponectin	14	µg/ml								

Cardiovascular risk

Test	Result	Unit	Standard range	---	--	-		+	++	+++
ADMA (asymmetric di-methyl-arginine)	1,6	µmol/l	0,3 - 0,65							

Fig. 4. Protocol of Proinsulin, Adiponectin and ADMA in Metabolic syndrome with critical values

Table 4. Overview of screening parameters in the metabolic syndrome

Biomarker	Medium	Methods	Standards	Remarks*
Adiponectin	Serum	Elisa	>5.6 µg/ml (m) >7.1 µg/ml (w)	Low levels of Adiponectin predict Diabetes risk already 2 years before manifestation.
Proinsulin	Serum chilled or frozen	Radio-immunoassay (RIA)	>11 pmol/l	Proinsulin should be rechecked after 3 month (diet and therapy). A successful intervention will be proved by a significant chance of Proinsulin secretion.
Asymmetric Dimethylarginine (ADMA)	EDTA-plasma and serum	Competitive Enzym immunoassay Samples are stable for one week at 2–8 °C.	0.45 ± 0,19 µmol/l	Strong haemolytic and lipaemic samples often show wrong concentrations.

* Kitts are available at: Immundiagnostik AG Stubenwald-Allee 8a D-64625 Bensheim Germany (www.immundiagnostik.com).

CONCLUSIONS

Prevention of the metabolic syndrome is based on the early diagnose of personal risk factors. Obese patients reveal a higher risk for metabolic syndrome, however the metabolic syndrome is characterised by further factors which may be expressed to a various extent.

The tendency to end in a metabolic syndrome can be easily diagnosed even years before the actual onset by crucial and sensitive laboratory diagnosis measurements such as **Adiponectin, Proinsulin and Asymmetric Dimethylarginine (ADMA)**. These parameters are very valuable for the early diagnosis of health risk factors. Convincing the patient to enter into a diet or into early treatment may reduce the incidence of the metabolic syndrome in future. Therefore, it should be in the concern of public health to screen the population at risk by these parameters.

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