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Review article

Macrovascular complications of metabolic syndrome: an early intervention is imperative

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Abstract

The metabolic syndrome is a widespread clinical condition and an important cluster of atherothrombotic disease risk factors. The inclusion of this syndrome in the recently published Adult Treatment Panel III (ATP III) guidelines focused the attention of the physicians on this entity. Abdominal obesity, PPAR modulation, insulin resistance (with or without glucose intolerance), atherogenic dyslipidemia, elevated blood pressure, prothrombotic and proinflammatory states are the principal factors of this multifaceted syndrome. There are two major pathways of metabolic syndrome progress: (1) With preserved pancreatic beta cells function and insulin hypersecretion, which can recompense for insulin resistance. This pathway leads mostly to the macrovascular complications of metabolic syndrome. (2) With substantial injure of pancreatic beta cells leading to gradually reduced insulin secretion and to hyperglycemia (e.g. overt type 2 diabetes). This pathway leads to both microvascular and macrovascular complications. Because macrovascular complications of insulin resistance state precede the onset of hyperglycemia, early intervention in patients with metabolic syndrome is particularly important.

Since central obesity (accompanied by insulin resistance even in the absence of hyperglycemia) is the key factor leading to development of metabolic syndrome and its future macrovascular complications, we assume that next logical step is the recognition of central obesity itself as a major risk factor for cardiovascular diseases.

Keywords: Metabolic syndrome; Diabetes mellitus; Peroxisome proliferator-activated receptors (PPAR); Obesity; Insulin resistance

1. Introduction

The metabolic syndrome is a widespread clinical condition and an important cluster of atherothrombotic disease risk factors. The inclusion of this syndrome in the recently published Adult Treatment Panel III (ATP III) guidelines and the creation of an *International Classification of Diseases*, *Ninth Revision* diagnostic code, 277.7 have focused the attention of the physicians on this condition [1–5].

Factors characteristic of the metabolic syndrome, also known as dysmetabolic syndrome X, are abdominal obesity, atherogenic dyslipidemia (elevated triglyceride [TG] levels, small low-density lipoprotein [LDL] particles, low high-density lipoprotein cholesterol [HDL-C] levels), elevated blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states [6–10].

2. Type 2 diabetes mellitus in obese patients as a subtype of metabolic syndrome

Type 2 diabetes mellitus and obesity, major health problems worldwide, are considered to be closely related [11–16]. In the majority of cases type 2 diabetes is now widely considered to be one component within the metabolic syndrome. The factor that dominates in obesity is the permanent elevation of plasma free fatty acid (FFA) and the predominant utilization of lipids by muscles inducing a diminution of glucose uptake and insulin resistance. An insulin-resistant state—as the key phase of metabolic syndrome—constitutes the major risk factor for the development of diabetes mellitus. Hyperinsulinemia appears to be a

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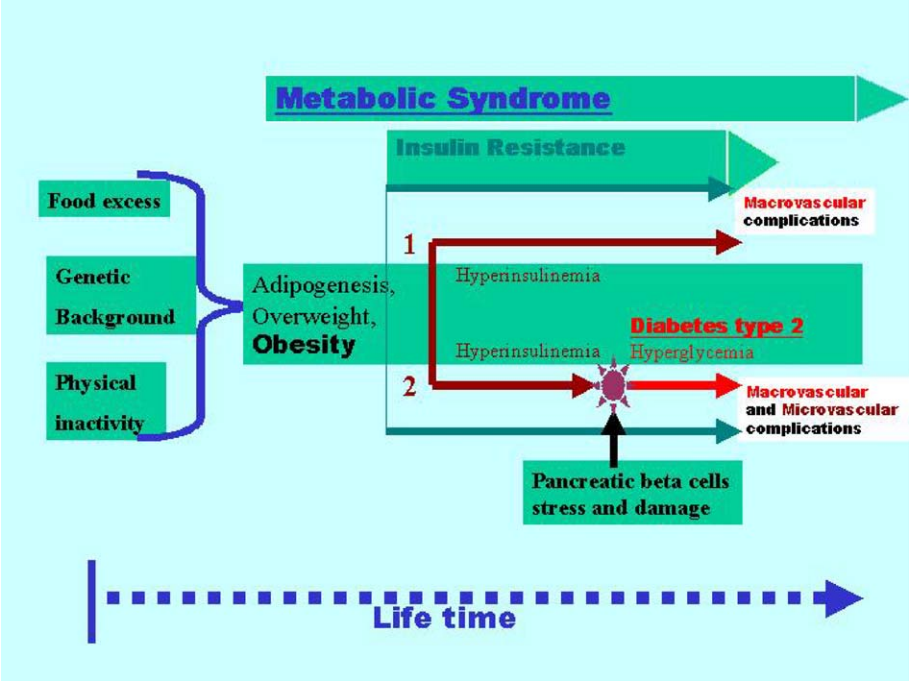

Fig. 1. The relationship between metabolic syndrome, insulin resistance, hyperinsulinemia and hyperglycemia (overt type 2 diabetes). An insulin-resistant state is the key phase of metabolic syndrome initiation. Afterwards, there are two major pathways of metabolic syndrome progress: (1) with preserved pancreatic beta cells function and insulin hypersecretion, which can recompense for insulin resistance. This pathway leads mostly to the macrovascular complications of metabolic syndrome; (2) with substantial injure of pancreatic beta cells leading to gradually reduced insulin secretion and to hyperglycemia (e.g. overt type 2 diabetes). This pathway leads to both microvascular and macrovascular complications. Time-related scheme.

compensatory mechanism that responds to increased levels of circulating glucose. People who develop type 2 diabetes usually pass through the phases of excessive adipogenesis (obesity), nuclear peroxisome proliferator-activated receptors (PPAR) modulation, insulin resistance, hyperinsulinemia, pancreatic beta cells stress and damage leading to progressive decrease of insulin secretion, impaired glucose postprandial and fasting levels [17–21]. Fasting glucose is presumed to remain normal as long as insulin hypersecretion can compensate for insulin resistance. The fall in insulin secretion leading to hyperglycemia occurs as a late phenomenon and, in fact, separates the patients with metabolic syndrome from those with or without overt diabetes (Fig. 1).

3. Diagnostic criteria and evaluation for the metabolic syndrome

Table 1 shows the current diagnostic criteria for the metabolic syndrome. The common underlying element of these adverse risk factors for progression of atherosclerosis is insulin resistance [1,2].

Metabolic syndrome is a term used to define a patient who presents with three or more of the five risk factors: (1) Abdominal obesity and waist circumference for men greater than 102 cm or 40 in., and for women greater than 88 cm or 35 in. (2) Elevated TGs, defined as equal to or greater than 150 mg/dl. (3) Low HDL-C. Overall for the Adult Treatment Program (ATP)-III guidelines, low HDL-C is defined as under 40 mg/dl; previously it was under 35 mg/dl (for the purposes of the metabolic syndrome, there are different values for men and women: less than 40 mg/dl for men and less than 50 mg/dl for women). (4) Elevated blood pressure, defined according to lower values than those usually used to define hypertension: systolic over 130 mmHg or diastolic over 85 mmHg. (5) Fasting glucose equal to or greater than 110 mg/dl [1,2].

Aggressive screening for the metabolic syndrome may require changes in the way that patients are evaluated in the routine clinical practice now. Currently, most physicians already obtain measurements for four of the diagnostic criteria for the metabolic syndrome—blood pressure, glucose, HDL-C, and TG levels—but do not routinely assess waist circumference [4]. Patients with central obesity are

Table 1
Diagnostic criteria for the metabolic syndrome (three of the five criteria are sufficient for the diagnosis) [1,2]

Abdominal obesity (waist circumference>102 cm [40 in.] in men, >88 cm [35 in.] in women)
Hypertriglyceridemia ($\geq$ 150 mg/dl)
Low HDL-C ($<$40 mg/dl in men, $<$50 mg/dl in women)
High blood pressure ($\geq$ 130/85 mmHg)
High fasting glucose (IGT [blood sugar $\geq$ 110 mg/dl and $<$126 mg/dl] without diabetes)

more likely to develop the metabolic syndrome than individuals with the same amount of body fat stored more peripherally. Waist circumference is a good predictor of central obesity and is why a high waist circumference is the only weight-related variable included in the ATP III definition of the metabolic syndrome. However, the prevalence of the metabolic syndrome shows clear association with BMI as well. Although BMI is not one of the diagnostic criteria for the metabolic syndrome, a BMI greater than 27 strongly increases the likelihood that this syndrome will be present [3–5]. Evaluation of BMI in routine clinical setting is simpler than waist circumference. Therefore, for the purpose of more aggressive screening for metabolic syndrome, a BMI greater than 27 probably should be included in the diagnostic criteria of this condition as an alternative measurement. In our opinion, the next step in evaluation of high risk patients for the metabolic syndrome should include routine measurement of fasting insulin level with simple calculation of the homeostatic index of insulin resistance (HOMA IR) [22,23].

The 2001 ATP III guidelines have called specific attention to the importance of targeting the cardiovascular risk factors of the metabolic syndrome as a method of risk reduction therapy [1]. Since central obesity (accompanied by insulin resistance even in absence of hyperglycemia) is the principal factor leading to development of this syndrome and its future macrovascular complications, we assume that next logical step is the recognition of central obesity itself as a major risk factor for cardiovascular diseases.

4. Peroxisome proliferator-activated receptors (PPARs)

Acquired causes of the metabolic syndrome include overweight, physical inactivity, and high carbohydrate diet in some individuals in which the carbohydrate intake makes up more than 60% of the total caloric intake. Moreover, there are genetic causes, which have not been clearly defined. However, our understanding of the metabolic syndrome has been improved with the discovery of nuclear PPARs [17,18,24–26]. PPARs are ligand-activated transcription factors belonging to the nuclear receptor superfamily, which also includes the steroid and thyroid hormone receptors. As transcription factors, PPARs regulate the expression of numerous genes and affect glycemic control, lipid metabolism, vascular tone and inflammation.

The so-called orphan receptors (identified before their natural ligand) include PPAR and retinoid X receptors (RXR). There are currently three known subtypes of PPAR: alpha, delta and gamma (g_1 and g_2).

Activated PPAR-alpha stimulates the expression of genes involved in fatty acid and lipoprotein metabolism. PPAR-alpha activators, such as the normolipidemic fibric acids, decrease TG concentrations by increasing the expression of lipoprotein lipase and decreasing apo C-III concentration. Furthermore, they increase HDL-C by increasing the expression of apo A-I and apo A-II. PPAR-alpha activation by fibric acids improves insulin sensibility and decreases thrombosis and vascular inflammation. PPAR-alpha ligands also mediate potentially protective changes in the expression of several proteins not involved in lipid metabolism but implicated in the pathogenesis of heart disease. Clinical studies with bezafibrate and gemfibrozil support the hypothesis that these drugs may have a significant protective effect against cardiovascular disease [27,28].

Activation of the isoform PPAR-gamma improves insulin sensitivity, decreases inflammation, plasma levels of FFAs and blood pressure. These lead to inhibition of atherogenesis, improvement of endothelial function and reduction of cardiovascular events. The thiazolidinedione group of insulin-sensitizing drugs is PPAR-gamma ligands, and these have beneficial effects on serum lipids in diabetic patients and have also been shown to inhibit the progression of atherosclerosis in animal models [29–31]. However, their efficacy in the prevention of cardiovascular-associated mortality has yet to be determined.

Recent studies have found that PPAR-delta is also a regulator of serum lipids. However, there are currently no drugs in clinical uses that selectively activate this receptor.

The modulation of the expression of genes by either PPAR-alpha or -gamma activators, correlates with the rela-

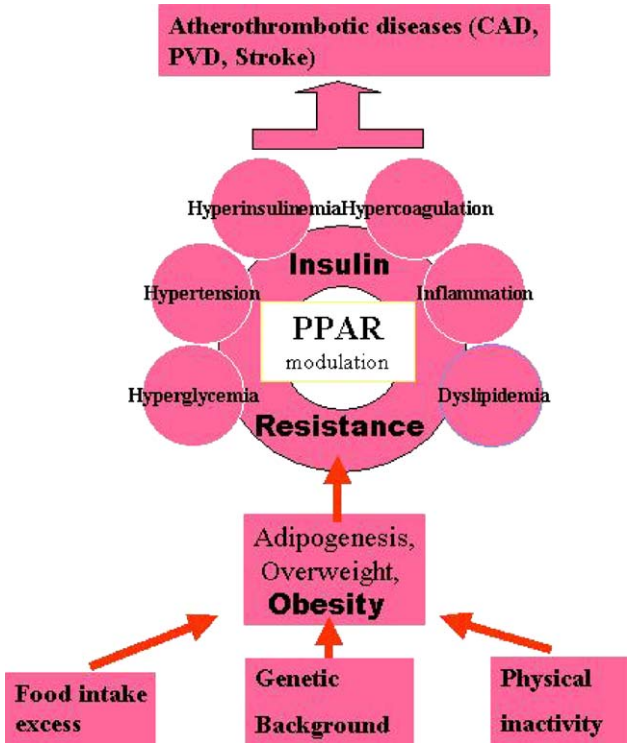

Fig. 2. The cluster of atherothrombotic disease risk factors, showing the complex interrelationship between hereditary and environmental factors in the pathogenesis of metabolic syndrome and atherothrombotic events. The central role of an insulin-resistant state following adipogenesis and nuclear PPARs deactivation is emphasized. CAD, coronary artery disease; PVD, peripheral vascular disease.

tively tissue-specific distribution of the respective PPARs: PPAR-gamma is expressed predominantly in adipose tissues, whereas PPAR-alpha in the liver.

PPAR-gamma was shown to have a key role in adipogenesis and proposed to be a master controller of the "thrifty gene response" leading to efficient energy storage.

More recently PPAR-gamma emerged from a role limited to metabolism (diabetes and obesity) to a power player in general transcriptional control of numerous cellular processes, with implications in cell cycle control, carcinogenesis, inflammation, atherosclerosis and immunomodulation. Based on these new concepts, we propose a new scheme of a cluster of metabolic syndrome, cardiovascular risk factors and diseases, which all are developed and linked through PPARs (Fig. 2).

5. Management of metabolic syndrome: PPAR-related approach

Because of its critical and central role in the development of metabolic syndrome, type 2 diabetes and many cardiovascular disorders, we believe that targeted treatment of PPAR (both alpha and gamma) will be a critical component of metabolic syndrome care in shortcoming future. Currently, PPAR-related treatment could be based on intensive lifestyle interventions, fibrates and thiazolidinedione group of insulin-sensitizing drugs. Treating metabolic syndrome can prevent or ameliorate cardiovascular disease and type 2 diabetes [32–37]. It is obvious that the cornerstones of treatment for the metabolic syndrome are dietary modification, weight reduction and increased physical activity. Evidence is increasing that in some populations, type 2 diabetes shares common causal factors with coronary artery disease (CAD) [38–42]. Patients with CAD and impaired functional capacity usually diminished their exercise activity with more positive energy balance. An inverse relationship between physical activity level and the risk of subsequent type 2 diabetes has been described [43–46]. Therefore, the thesis that patients with impaired functional capacity are prone to develop new diabetes seems to be based on a reliable theoretic background and has been stressed in previous reports [47–50]. The Diabetes Prevention Program (DPP) results have shown that individualized, systematic and intensive lifestyle interventions (including dietary changes, increased physical activity and weight loss) are the most effective means of prevention of type 2 diabetes in general high risk populations (unfortunately they are not easily applied in general practice) [32]. In addition, pharmacological interventions by some medications which influence primary glucose metabolism (metformin and acarbose) or induce weight loss (orlistat, combined with dietary intervention) can also effectively delay progression to type 2 diabetes [32–36], but the magnitude of the benefit seems to be somewhat less (58% for DPP lifestyle changes vs. 31% for metformin and 25% for acarbose).

6. Cigarette smoking cessation

Cigarette smoking is an additional important modifiable risk factor that could be targeted for prevention of diabetes. Number of previous epidemiologic studies found smoking to be positively associated with risk for type 2 diabetes [51–54]. These data strongly support an overwhelming importance of smoking cessation in framework of secondary prevention policy in patients with CAD and decreased functional capacity.

On the other hand, the relationship between smoking and type 2 diabetes may be much more complex. Smoking cessation commonly results in weight gain, which increases the risk for diabetes [55]. In accordance with previous studies [56], the relative risk for diabetes associated with cigarette smoking was stronger in leaner than in obese patients. Furthermore, in recent experimental study [57], long-term oral nicotine administration reduced insulin resistance in obese diabetic rats and contributed to lowering blood glucose levels. These results emphasized the crucial component in smoking cessation management: we need not only promote smoking termination but also concomitantly help patients avoid weight gain.

7. Cardiovascular risk factors: rationale for early pharmacological intervention

For the time being, the goals and methods of treating hypertension, inflammation, hypercoagulopathy and dyslipidemia are the same for people with metabolic syndrome and for the general population [32–37]. However, the relative clinical benefit achieved by these risk factors' management may be even greater in prediabetic or early diabetic phase of metabolic syndrome than in more advanced form [58] because adverse sequelae are easier to prevent than to reverse. Early intervention in patients with metabolic syndrome is particularly important, because macrovascular complications precede the onset of hyperglycemia, e.g. actually begin during the prediabetic phase. Moreover, the favorable macrovascular effect of tight blood sugar control by currently widely used sulfonylurea drugs (in contrast to metformin alone in obese patients) has not been proved [59,60].

All these emphasize the concept that hypertension, hypercoagulopathy and dyslipidemia in patients with metabolic syndrome should be recognized and treated very early and more aggressively than in the general population and similar to patients with overt diabetes.

8. Conclusion

The metabolic syndrome is a very widespread clinical condition. Obesity, PPAR modulation and insulin resistance are the principal factors of this multifaceted syndrome. The

decrease in insulin production leading to hyperglycemia divides patients with metabolic syndrome from those with or without overt diabetes. Because macrovascular complications of insulin resistance state precede the onset of hyperglycemia, early and more aggressive intervention in patients with metabolic syndrome is particularly important.

Since central obesity (accompanied by insulin resistance even in the absence of hyperglycemia) is the key factor leading to development of this syndrome and its future macrovascular complications, we assume that next logical step is the recognition of central obesity itself as a major risk factor for cardiovascular diseases.

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