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Review Article

Metabolic syndrome and obesity in peritoneal dialysis

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Abstract

Metabolic syndrome (MS) refers to clustering of features related to increased risk of cardiovascular disease, which include obesity or central obesity, dyslipidemia, diabetes mellitus or insulin resistance, together with hypertension. The prevalence of MS in end-stage renal failure patients on peritoneal dialysis is quite common, ranging from 40% to 60%, depending on the population studied and the definition used. However, there are controversies about the clinical outcome of patients with MS, particularly in the area of obesity. Whether peritoneal dialysis predisposes patients to MS is another unsolved issue. Despite these controversies, preventing patients from developing MS is important, at least from a theoretical point of view.

The concept of metabolic syndrome

The concept of metabolic syndrome (MS) arose as early as in 1950s when the association of upper body obesity with cardiovascular disease and diabetes mellitus was observed [1]. In 1988, Reaven [2] used the term “syndrome X” to describe the clustering association between insulin resistance, hyperglycemia, hypertension, low high-density lipoprotein (HDL) cholesterol, and raised very low-density lipoprotein triglycerides (TGs), but obesity was not included as part of this syndrome. The association of obesity and features of syndrome X caught much attention thereafter and was loosely described as MS. The World Health Organization (WHO) first attempted to define MS in 1998 [3]. It included diabetes mellitus, fasting hyperglycemia, impaired glucose tolerance, or insulin resistance as one of the mandatory criteria, together with 2 or more of the following 4 criteria: obesity or increased waist-to-hip ratio (WHR), dyslipidemia (raised TGs or reduced HDL cholesterol), hypertension, and microalbuminuria. In 1999, the European Group for the Study of Insulin Resistance defined MS in a slightly different way. It also used insulin resistance or fasting hyperinsulinemia as a mandatory criterion. Fasting hyperglycemia was regarded as an optional criterion [4]. Similar to the WHO definition, apart from the mandatory criterion, the European Group for the Study of Insulin Resistance also required 2 or more of 4 optional criteria, including fasting hyperglycemia, central obesity (defined by WHR), dyslipidemia (raised TGs or reduced HDL cholesterol), and hypertension. However, the definition of the different criteria slightly varies. In 2001, National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATPIII) of the United States defined MS in a different way [5]. There was no mandatory criterion. It requires 3 or more of 5 optional criteria, namely central obesity, hypertriglyceridemia, reduced HDL cholesterol, high blood pressure, and fasting hyperglycemia. It separated hyperglyceridemia and reduced HDL cholesterol into 2 different criteria and did not need the definition based on insulin resistance. In 2004, the International Diabetes Federation stressed the importance of central obesity by putting raised WHR as a mandatory criterion, together with any 2 of the other 4 optional criteria including hypertriglyceridemia, reduced HDL cholesterol, high blood pressure, and fasting hyperglycemia, impaired glucose tolerance, or insulin resistance [6]. Because of some obvious limitation in using waist circumference to reflect central obesity in peritoneal dialysis (PD) patients, Li et al [7] suggested to modify

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the definition of the central obesity of NCEP-ATPIII for PD patients by replacing central obesity according to body mass index (BMI) for Caucasians and Asians. The details of different definitions are summarized in Table 1.

Pathophysiology of MS

Despite the variation in the fine details of the definitions, the MS basically clusters around central obesity. Central obesity is reflective of increased visceral fat, which is expected to have a higher rate of flux of adipose tissue–derived free fatty acid into the liver through the splanchnic circulation leading to increased very low-density lipoprotein production, hypertriglyceridemia, increased glucose release from the liver into systemic circulation and subsequent hyperinsulinemia, and insulin resistance [8]. In addition, visceral fat has been documented to have higher capacity to release proinflammatory cytokines such as tumor necrosis factor-α, interleukin-6, and C-reactive protein. A higher level of these cytokines is identified in MS [9] and in PD patients with obesity [10] and increased visceral fat [11]. Visceral fat, instead of subcutaneous fat, and waist circumference have also been demonstrated to be associated with atherosclerosis and cardiovascular disease in PD patients [12–14].

Prevalence of MS in PD patients

In the last few decades, obesity and diabetes mellitus have become an epidemic in many countries. It is expected that the incidence of MS is on the rise too. In general, the prevalence ranges from 20% to 40%, and a higher prevalence was found in more affluent countries and in the older population [8].

As expected, the prevalence of MS in PD patients also varies between countries and according to different definitions used. Szeto et al [15] compared the prevalence of MS in a single center in Hong Kong with 329 prevalent patients, including 31% of diabetics, and noted that the prevalence rates ranged from 53% to 66%, with higher prevalence according to the modified NCEP-ATPIII and then followed by the NCEP-ATPIII. Dong et al [16] found that the prevalence of MS in China from a multicenter study involving 4 different regions of China including 40% of diabetics was 55.4% according to NCEP-ATPIII. If diabetics are excluded, it is expected that the prevalence should be lower. In Taiwan, Liao et al [17] found that the prevalence was 52.9% among all PD patients, and it was 39.4% when diabetics were excluded. However, Prasad et al [18] reported 51.3% among nondiabetic PD patients. Therefore, there is substantial variation between countries and ethnicity, but the overall impression is that the prevalence is substantially higher than that in the general population even when diabetics are excluded.

Controversies about MS in PD patients

Clinical outcome of PD patients with MS

There is little argument against the detrimental effect of diabetes on patient survival among PD patients, yet it was arguable whether MS or its individual elements such as obesity, new-onset hyperglycemia, or dyslipidemia have effect on patient survival in PD patients. This is largely affected by the well-known reverse epidemiology in many different risk factors observed in dialysis patients.

There were both reports on the presence and absence of negative impact of MS on patient survival. Szeto et al [15] found that, among the 4 different definitions, only MS according to WHO carried an increased risk of mortality. But among the nondiabetics (n = 196), there was no significant

Table 1. Summary of different definitions of metabolic syndrome

Organization	WHO	EGIR	NCEP-ATPIII	Modified NCEP-ATPIII	IDF
Reference	[3]	[4]	[5]	[7]	[6]
Year	1998	1999	2001	2008	2005
Criteria required	1 mandatory + 2 others or more	1 mandatory + 2 others or more	Any 3 or more	Any 3 or more	1 mandatory + 2 others
Obesity	BMI > 30 or W/H ratio > 0.9 (M), > 0.85 (F)	Central obesity: waist circumference > 94 cm (M), > 80 cm (F)	Central obesity: waist circumference > 102 cm (M), > 88 cm (F)	BMI > 30 for Caucasians or > 25 for Asians	Waist circumference (ethnic specific) (mandatory)
TG HDL chol	TG ≥ 1.7 or HDL-chol < 0.9 (M), < 1.0 (F)	TG > 2.0 or HDL-chol < 1.0	TG ≥ 1.7 HDL-chol < 1.0 (M), < 1.3 (F)	TG ≥ 1.7 HDL-chol < 1.0 (M), < 1.3 (F)	TG > 1.7 HDL-chol < 1.03 (M), < 1.29 (F), or on treatment
Insulin resistance or hyperglycemia	DM, impaired fasting glucose, IGT, insulin resistance (mandatory)	Insulin resistance, fasting hyperinsulinemia (> 75 percentile of non-DM) (mandatory) FBS ≥ 6.1	FBS ≥ 6.1	FBS ≥ 6.1	FBS > 5.6, or DM, or IGT
Hypertension	> 140/90	≥ 140/90 or on medication	≥ 135/85 or on medication	≥ 135/85	≥ 135/85 or on medication
Others	Microalbuminuria > 20 μg/min				

All biochemistry units are in mmol/L unless specified, BMI unit is in kg/m^2.
Unit conversion: TG 1 mmol/L = 88.5 mg/dL, HDL chol 1 mmol/L = 38.6 mg/dL.
BMI, body mass index; DM, diabetes mellitus; EGIR, European Group for the Study of Insulin Resistance; FBS, fasting blood sugar; HDL chol, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; IGT, impaired glucose tolerance; NCEP-ATPIII, National Cholesterol Education Program's Adult Treatment Panel III; TG, triglyceride; WHO, World Health Organization; W/H ratio, waist-to-hip ratio.