



## Review Article

## Metabolic syndrome and obesity in peritoneal dialysis



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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.

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## 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 hyperglycemia 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- $\alpha$ , 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 multi-center 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	TG $\geq$ 1.7 or HDL-cholesterol < 0.9 (M), < 1.0 (F)	TG > 2.0 or HDL-cholesterol < 1.0	TG $\geq$ 1.7	TG $\geq$ 1.7	TG > 1.7
HDL chol			HDL-cholesterol < 1.0 (M), < 1.3 (F)	HDL-cholesterol < 1.0 (M), < 1.3 (F)	HDL-cholesterol < 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 $\geq$ 6.1	FBS $\geq$ 6.1	FBS > 5.6, or DM, or IGT
Hypertension	> 140/90	FBS $\geq$ 6.1 $\geq$ 140/90 or on medication	$\geq$ 135/85 or on medication	$\geq$ 135/85	$\geq$ 135/85 or on medication
Others	Microalbuminuria > 20 $\mu$ g/min				

All biochemistry units are in mmol/L unless specified, BMI unit is in kg/m<sup>2</sup>.

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.

difference between those with and without MS, disregarding which definition was used. In a smaller study from Taiwan on 139 nondiabetic PD patients, MS, as defined according to NCEP-ATPIII, was found to be only associated with inflammatory markers but not patient survival [19]. However, although also from Taiwan and using the same NCEP-ATPIII definition, Liao et al [17] found that incident nondiabetic PD patients ( $n = 280$ ) with MS had poorer patient survival compared to those without MS for both total and cardiovascular event-free patient survival. Similarly, higher patient mortality was found in the nondiabetic Indian PD patients with MS compared to those without ( $n = 163$ ) [18]. Sample size variation may be an explanation for the different conclusions. A large-scale study is needed to address this issue.

### *Impact of obesity on patient survival*

The most popular parameter to represent obesity is BMI for its simplicity and general correlation with fat mass. However, the amount of fat tissue for the same BMI varies between ethnicity; thus, the WHO has different criteria of BMI to reflect obesity for the Caucasians and Asians [20]. In patients on hemodialysis (HD), it is well recognized that the reverse epidemiology phenomenon exists with protective effect on mortality with high BMI [21]. However, this is controversial in PD patients. There have been reports on reduced, similar, and increased mortality risk with obesity. It is plausible that ethnicity may have interfered the effect of obesity on mortality. For example, there was difference in effect in the Caucasians and aboriginals according to the Australia New Zealand Dialysis and Transplant Registry [22]. The recent reports from several Asian countries added into this controversy. Zhou et al [23] found an increased mortality risk in PD patients in China with BMI over 25 kg/m<sup>2</sup>. In Hong Kong, we have analyzed the relationship between BMI and mortality among incident PD patients in Hong Kong, excluding those with Kt/V failed to be adjusted to above 1.7/wk, and found that the increased risk with obesity mainly existed in diabetic patients and patients with pre-existing cardiovascular diseases [24]. The increased risk was minimal among nondiabetic patients. Kim et al [25] from Korea and Prasad et al [26] from India found similar risk of mortality between their obese and normal BMI patients. The reasons for the different observations still need to be identified, but it may be related to the duration of study (longest in our study in Hong Kong), prevalence of diabetes mellitus and cardiovascular disease, and the level of solute clearance indices achieved. When using BMI to reflect obesity, we have to bear in mind that it also reflects the hydration status and it cannot differentiate the body weight from muscle mass or fatty tissue. Using creatinine excretion as a reflection of muscle mass, Ramkumar et al [27] found that the amount of creatinine excretion was predictive of survival rather than the BMI, suggesting that muscle mass is protective against mortality in PD patients. BMI also does not differentiate central obesity from generalized obesity. Future studies should also focus on the effect of central obesity on patient survival.

### *Weight changes after PD and its impact on survival*

Increasing weight and obesity is commonly found in patients started on PD. In a large-scale cohort from Brazil, 60% of PD patients were noted to have increase in body weight more

than 3% in the first year and 20% had gained more than 7% of weight [28]. However, patients who gained weight did not have an increased risk of mortality compared to those with stable weight. In contrast, those who lost weight more than 3% had increased mortality risk. In a small-scale study using the computed tomography scan to assess the amount of fat gained over the first year of PD, Choi et al [29] found that there was substantial increase in both subcutaneous and visceral fat in the first 6 months, but there was no further increase in the next 6 months, suggesting that fat tissue gain mainly occurs in the initial phase of PD. In our own series, 58% of patients gained more than 5% body weight in the first year, and this occurred more in patients with low and normal BMI. There was no increased mortality risk observed in this group of patients. Instead, a slightly reduced mortality risk, though statistically insignificant, was observed in the overweight and obese patients who had weight loss over 5% in the first year (unpublished data) suggesting that weight reduction in the overweight PD patients may be beneficial to their survival. It is highly plausible that the effect of weight gain or loss differs among patients with different baseline BMI. This needs further investigation. When addressing the issue of weight gain or reduction, we also need to ask whether this is a healthy gain or loss.

Is it true that weight gain is more common in PD than in HD patients? There was a report comparing the weight gain among propensity score-matched PD and HD patient cohort. In contrast to the common impression, it is found that PD patients actually had less weight gain compared to HD patients [30]. Pellicano et al [31] did a small-scale comparative study investigating the body composition change between different dialysis modalities. They found that both PD and HD patients gained weight similarly, but PD patients tend to gain more visceral fat. It is desirable to have a prospective study on the patterns of weight changes among different dialysis modalities and their impact on patient survival, respectively. If we believe that gaining visceral fat is proinflammatory, we should develop measures to prevent the increase in visceral fat.

### *New-onset hyperglycemia*

Szeto et al [32] looked at nondiabetic patients started on continuous ambulatory peritoneal dialysis (CAPD), and fasting blood sugar was taken 4 weeks after CAPD commenced. He found that 23.4% of patients had increased fasting blood sugar including 4.4% with fasting blood sugar over 200 mg/dL (11.1 mmol/L). Age and comorbidity but not obesity and glucose load were associated with new-onset hyperglycemia. Compared to patients with fasting blood sugar below 100 mg/dL, those above 100 mg/dL had poorer survival after 12 months. However, these patients had 1.5% dextrose dialysate overnight dwell. In our own experience, fasting blood sugar often returns to normal if they had empty peritoneal cavity overnight. In addition, owing to its association with older age and comorbidity, the association with poorer survival had to be interpreted with care. Liao et al [17] reported that only 5% of patients developed *de novo* diabetes after a mean follow-up of 49 months.

Is glucose load from PD predisposed patients to new-onset hyperglycemia? Szeto et al [32] did not find the association. Woodward et al [33] analyzed the new-onset diabetes mellitus before and after renal transplantation in PD and HD patients; they found that in 2 years before transplantation, 12.7% of HD

patients developed new-onset diabetes, whereas it was only 10.7% in PD patients. Similarly, more HD patients developed new-onset diabetes than PD patients after transplantation. In a prospective randomized control trial on using low glucose load biocompatible dialysate (the Hong Kong PEN study—one to two bags of 1.5% Physioneal, one bag of Extraneal and one bag of Nutrineal vs. conventional Dianeal, peritoneal dialysate fluid products from Baxter Healthcare) versus conventional Dianeal, there was no difference in fasting blood sugar, TG, low-density lipoprotein, and HDL cholesterol after 1 year [34]. Thus, there was no strong evidence that glucose load or PD *per se* increased risk of new-onset diabetes or hyperglycemia in PD patients. A recent publication on insulin resistance in nondiabetic PD patients showed that it was related to obesity rather than glucose load or peritoneal transport [35].

### Prevention of MS in PD patients

Liao et al [17] reported that the proportion of patients with MS had increased from 41% to 65% over a mean follow-up of 49 months. Although the significance of MS on survival is still controversial, prevention of MS development should be our target until proven otherwise. There was no randomized control trial on the efficacy of different means to prevent MS in PD patients. We should minimize the glucose load as much as possible as this carries the potential advantage of gaining less visceral fat and less dyslipidemia, although its effect on reducing new-onset diabetes still waits to be proved. Exercise and diet control is another area that should be explored. We had shown that fasting blood sugar can be reduced after a 3-month exercise program for PD patients compared to non-randomized controls, with a marginal increase of HDL cholesterol [36]. Pennell et al [37] developed a weight management program involving dietary and exercise advice and monitoring, using which body weight could be reduced significantly in 16% of obese patients. Research into this area is needed.

### Conclusion

Both preexisting and new-onset MS and its components are very common among end-stage renal failure patients on PD. Although the significance of it is still controversial, given the current understanding of its pathophysiology, we should prevent the development of MS in our PD patients. This may involve minimization of glucose load, dietary modification, and exercise.

### Conflicts of interest

All authors have no conflicts of interest to declare.

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