The metabolic syndrome in older persons: a loosely defined constellation of symptoms or a distinct entity?

The concept of the metabolic syndrome originated with the Dutch physician, Nicolas Tulp, in the 17th century when he defined the hypetriglyceridaemia syndrome. It was more fully defined in the next century by Giovanni Baptiste Morgagni who wrote about central obesity, hypertension, hyperuricaemia, atheroma and sleep apnoea as a cluster of conditions commonly found together.

The addition of abnormal glucose metabolism to the syndrome occurred in the 1920s. In 1977, Haller coined the term ‘metabolic syndrome’. Towards the end of the 20th century, it was suggested that insulin resistance and compensatory hyperinsulinaemia were central to the pathogenesis of the syndrome. Young and middle-aged persons with the metabolic syndrome have a marked increased risk for developing atherosclerotic heart disease and diabetes mellitus [1].

Several definitions of the metabolic syndrome have been proposed (Appendix 1, available at Age and Ageing online) including those of the World Health Organisation, National Cholesterol Education Programme and the International Diabetes Federation [2–4]. The latter developed criteria which they hoped would satisfy both research and clinical needs and allow better comparisons between different study populations.

In the United States, the metabolic syndrome is present in >5% of individuals between 20 and 30 years, in >20% between 40 and 50 years and in >40% in persons >60 years of age [5]. It is more common in men than women. The recognition of the central role of visceral (intra-abdominal) obesity has become more recognised in the last decade leading to the proposal that it would be better termed the visceral fat syndrome [6]. Mesenteric and omental adipose tissues have an increased level of lipolysis, inflammatory cytokine secretion and reduced levels of adiponectin, an insulin-sensitising hormone. Free fatty acids released from visceral adipose tissue pass directly into the portal circulation enhancing lipid synthesis and gluconeogenesis as well as producing insulin resistance in the liver (Figure 1).

Family studies suggest that the heritability of the metabolic syndrome is between 10 and 24% [7]. However, in most cases, individual components have higher heritability than does the syndrome [8]. Genes that have so far been determined to be associated with obesity, e.g. melanocortin-4 receptor (MC4R) and fat mass and obesity-associated (FTO) genes, are not necessarily associated with visceral obesity. While these genes are associated with the development of diabetes mellitus, MC4R is associated with low blood pressure [9].

The metabolic syndrome is driven to a high degree by environmental factors, i.e. poor physical activity and excess caloric intake (especially sucrose). Stress and other factors that increase catecholamines, e.g. sleep apnoea, lead to increased lipolysis, especially from visceral fat depots and as such may initiate the pathophysiological processes associated with metabolic syndrome. Increased caloric intake drives the increase in uric acid which plays a role in the pathogenesis of hypertension [10]. The lack of physical activity results in increased adiposity, decreased lipoprotein lipase, hypertriglyceridaemia, low- and high-density lipoprotein and hyperglycaemia. In addition, the lack of exercise leads to poorer cardiac function, increased blood pressure and decreased oxygen uptake into tissues.

Ageing factors predisposing to the metabolic syndrome

Besides the increase in adiposity and visceral obesity that occurs with ageing, there are two other factors associated with ageing that predispose to increasing elements of the metabolic syndrome. These two factors are hypovitaminosis D and, in males, hypogonadism. Both 25(OH) vitamin D levels and, in males, testosterone decrease with ageing [11]. Low testosterone is associated with an increased waist to hip ratio. Testosterone replacement in older males decreases fat mass [12]. Androgen deprivation therapy is associated with diabetes mellitus. There is also some evidence that low testosterone is associated with insulin resistance [13]. However, testosterone replacement tends to decrease HDL cholesterol and may increase blood pressure slightly.

Low 25(OH) vitamin D levels are extremely common in older persons [14]. Low 25(OH) vitamin D levels are associated with the metabolic syndrome and adverse cardiovascular outcomes [15]. Vitamin D deficiency leads to an increased parathyroid hormone level (secondary hyperparathyroidism) that leads to insulin resistance, increased systemic inflammation and activation of the renin–angiotensin–aldosterone system. Activation of the rennin–angiotensin system leads to hypertension and myocardial fibrosis. The BB form of
Figure 1. Pathophysiology of the metabolic syndrome. This schema places the development of visceral obesity at the centre of the development of the syndrome.

The metabolic syndrome and the older person

In younger persons, there is controversy over whether the presence of metabolic syndrome is more predictive of future cardiovascular disease than are its individual components. This controversy is even more pertinent in an older population where many of the components of the metabolic syndrome occur even more commonly in the population. In the Italian Longitudinal Study on Aging, non-diabetic males with metabolic syndrome had a 12% greater risk of death from cardiovascular disease over a 4-year follow-up [19]. However, metabolic syndrome failed to predict cardiovascular mortality in females. In a Japanese study, age was a better determinant of a carotid artery intima thickness than was the
metabolic syndrome [20]. Originally, in the Cardiovascular Health Study, it was reported that the metabolic syndrome was associated with the development of cardiovascular disease over an 11-year period. However, in a follow-up analysis, both hypertension and elevated fasting glucose alone were better predictors of total and cardiovascular mortality than was the metabolic syndrome [21]. Sattar et al. [22] investigated the relationship of metabolic syndrome with diabetes and cardiovascular disease in two large elderly cohorts (PROSPER and the British Regional Heart Study). While the metabolic syndrome was associated with diabetes mellitus, it was not associated with cardiovascular disease in either study. In the Finnish study with a 14-year follow-up of persons aged 65–74 years, the metabolic syndrome was not a better predictor of cardiovascular disease, stroke nor peripheral vascular disease but not better than its component parts, especially diabetes mellitus [23]. Metabolic syndrome was not associated with gait speed impairment, but abdominal obesity was associated with it in women [24]. Metabolic syndrome was associated with progressive disability but to less an extent than is seen in persons with diabetes mellitus [25].

In the Health, Aging and Body Composition study of 70–79 years olds, abnormalities within the metabolic syndrome cluster such as hyperglycaemia and abdominal obesity predicted mobility limitation independent of diabetes or cardiovascular disease.

These findings are despite the fact that the metabolic syndrome in persons in the seventh decade of life was associated with higher levels of C-reactive protein, interleukin-6 and tumour necrosis factor-alpha and plasminogen activator inhibitor-I and lower levels of adiponectin. Surprisingly, the metabolic syndrome is relatively rare in nursing home residents (24%) and is associated with a pro-inflammatory state and maintenance of body fat [26].

Cognitive dysfunction is associated with both the metabolic syndrome and central obesity in older persons. This could be due to the fact that high triglycerides have been demonstrated to impair cognition [27]. Physical activity partly attenuates this association, which is in concert with the emerging literature that physical activity is an excellent therapy to improve cognition [28]. At present, there are few studies examining the relationship of the metabolic syndrome with the emerging concept of an objective frailty syndrome [29], although in the Cardiovascular Health Study, Fried and colleagues studied individuals aged 69–74 years over at least 9 years and concluded that both insulin resistance and inflammation, two factors implicated in the metabolic syndrome, are involved in incident frailty.

Conclusions

The metabolic syndrome is a seductive concept. It has become, moreover, an extremely popular one in modern medicine. While there is a reasonable amount of evidence to support its existence in young persons, it is a less distinct entity in older persons.

Nevertheless, the metabolic syndrome in older persons is strongly associated with a number of negative modifiable lifestyle factors, including being overweight, physical inactivity, a high carbohydrate diet and cigarette smoking. In addition, the metabolic syndrome is associated with depressive and anxiety symptoms and an increased psychosocial risk [8]. For these reasons, it would appear prudent to counsel older persons with the metabolic syndrome to alter their lifestyle. The exception may be to suggest dieting in view of the poor outcomes associated with weight loss even in persons with diabetes mellitus [30]. In addition, measurement of 25(OH) vitamin D and replacement of vitamin D when levels are <30 ng/dl would seem to be reasonable advice.

Finally as a large number of older persons with diabetes mellitus fail to be diagnosed, it is reasonable to screen persons with a large waist circumference for diabetes mellitus.

Supplementary data

Supplementary data are available at Age and Ageing online.

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References

Clostridium difficile-associated diarrhoea (CDAD): new and contentious issues

The last decade has seen the prevention of healthcare-associated infections (HAIs) become a public and NHS priority [1, 2]. The resultant local and national targets have started to reap some benefits, with a fall in the rate of methicillin-resistant Staphylococcus aureus (MRSA) bacteraemia [3] and a decline in the rate of Clostridium difficile-associated diarrhoea (CDAD) [4]. Despite this, CDAD remains one of the most frequent nosocomial infections (annual incidence >50,000 cases in 2007) [4].

PCR ribotype 027 (also known as BI/NAP1), a previously uncommon strain, has been associated with recent outbreaks in North America [5], Europe and the UK [6]. Ribotype 027 has emerged as the dominant strain in England representing 41% of isolates (up to 60% in certain regions) [7]. Strains of this ribotype are believed to be linked to increased disease severity often manifested with leucocytosis, raised creatinine, hypoalbuminaemia, toxic megacolon, need for colectomy, shock, death and higher rates of relapse. However, this is not always the case. A recent study comparing matched cases of CDAD caused by 027 versus non-027 strains showed that severity as defined by shock, paralytic ileus, pseudomembranous colitis or toxic megacolon was not linked to ribotype 027 and can occur with any strain [8]. Enhanced molecular fingerprinting, which enables strain subtyping to a greater extent than ribotyping, may provide further clues about the epidemiology and possible association of ‘hypervirulent’ strains with disease severity.

Community-acquired CDAD is emerging as a previously unrecognised entity. A recent case-control study demonstrated that community-acquired CDAD may be...