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Review paper

Do we need to diagnose normal weight metabolic obesity?

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Abstract

Obesity is most commonly diagnosed based on the body mass index (BMI). However, it is known that some subjects with normal BMI have increased metabolic and cardiovascular risk associated with excessive visceral fat deposit. These subjects are defined as metabolic obese normal weight or metabolically unhealthy normal weight.

Metabolic obese normal weight is particularly frequent among young people, and low physical activity level is indicated as its primary cause. Metabolic obese normal weight is very rarely recognised in clinical practice.

The aim of this manuscript is a discussion of this phenotype of obesity and its diagnostic criteria.

Key words: metabolic obesity, diagnostic criteria, clinical implications.

Obesity is most commonly diagnosed based on the body mass index (BMI). However, it is known that some subjects with normal BMI have increased metabolic and cardiovascular risk associated with excessive visceral fat deposit. These subjects are defined as metabolic obese normal weight (MONW) or metabolically unhealthy normal weight (MUHNW).

Metabolic obese normal weight is particularly frequent among young people, and low physical activity level is indicated as its primary cause. Metabolic obese normal weight is very rarely recognised in clinical practice.

On the basis of NHANES data from 1999-2004 the prevalence of MONW in the USA is estimated at 23.5% of adults by Wildman *et al.* [1]. While in Korea, MONW was diagnosed in 8.7% of adults [2]. In Poland, the prevalence of MONW among subjects aged 20-40 years was estimated at 15.8% among women and 7.8% among men [3]. In the EGIS study the frequency of MONW in the European population was estimated at 10% [4]. However, it should be noted that these data are difficult to compare due to the use of different diagnostic criteria.

Characteristics and diagnostic criteria of metabolic obese normal weight

Metabolic obese normal weight was first described by Ruderman as the coexistence hyperinsulinaemia, insulin resistance, hypertriglyceridaemia, low HDL cholesterol level, and predisposition to subsequent development of type 2 diabetes and coronary artery disease in subjects with normal BMI [5,6]. Visceral fat obesity and elevated blood pressure have also been shown in MONW. There are eight diagnostic criteria of MONW, which differ in both BMI values recognised as normal weight (< 26.3 kg/m^2 [7], < 25 kg/m^2 [8-11], < 27 kg/m^2 [12,13], 18-25 kg/m^2 [14]), as well as additionally accepted diagnostic parameters (glucose utilization < 8 mg/min/kg fat free mass during euglycaemic clamp [7], visceral fat area in CT > 100 cm^2 [8], HOMA-IR values > 1.69 [9], meeting the diagnostic criteria for metabolic syndrome or upper quartile of HOMA-IR [10], impaired glucose tolerance found in the oral glucose load [11], fasting insulin levels > 84 pmol/l [12], meeting the criteria for diagnosis of metabolic syndrome NCEP-ATP III [13], and the percentage of fat mass assessed by densitometry > 30% [14]). Numerous studies have defined MONW as three or more metabolic derangements [8-14]. Recently, the TyG index – a product of the fasting blood glucose and triglyceride levels – was proposed as an additional MONW diagnostic criterion [15]. However, some studies defined MONW as two or more metabolic abnormalities [16]. It should be stressed that MONW is associated with increased waist circumference and body fat percentage and utilising BMI in definitions limited in some

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cases diagnosis of visceral obesity or obesity based on body fat percentage in subjects with MONW [7]. Thus, identification of consistent MONW diagnostic criteria is very important to better recognise its prevalence, factors predisposing to its development, and implementation of appropriate treatment.

To assess the body fat percentage in clinical practice a bioimpedance method is commonly used (analysers or scales). This method is based on differential current conduction in various body tissues. Due to different water content in the various tissues varying resistance is generated, and based on this fat and lean mass is calculated [17]. However, this method does not allow an assessment of body fat distribution. Identifying an area of visceral fat is possible using densitometry, computed tomography, and magnetic resonance imaging [18,19]. Based on these methods, excessive visceral fat deposit was considered > 100 cm^2 [8]. It should be noted that these methods are expensive and not widely available. Therefore, in daily clinical practice, as an indirect method of assessment, the waist circumference measurement is used for the visceral fat area. For Europeans, Caucasians cut-off point for visceral obesity is ≥ 80 cm for women and ≥ 94 cm for men [20]. However, it was suggested that the risk of metabolic disturbances increases with waist circumference > 70 cm for women and 86 cm for men [5,6].

It seems that in clinical practice MONW should be diagnosed in subjects with BMI 18.5-24.9 kg/m^2, waist circumference > 70 cm for women and > 86 cm for men, and two of the following factors: systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg, fasting glucose level ≥ 100 mg/dl, fasting triglycerides level ≥ 150 mg/dl and HDL cholesterol level < 50 mg/dl for women and < 40 mg for men.

Risk factor of metabolic obese normal weight development

Initially, genetic predisposition to MONW development was suggested [5], but this has not been confirmed by other studies [7-9]. Also, the effect of low birth weight (< 2.5 kg) is inconclusive [5,10].

In addition, psychogenic stress is considered as a risk factor of MONW development. The pathogenic links between stress and MONW are chronic hypothalamus-pituitary-adrenal axis activity and increased expression of 11 beta-hydroxysteroid dehydrogenase type 1 in liver and visceral fat [21].

An important factor participating in MONW development seems to be low physical activity level [5,7,9,12]. This is also confirmed by an interventional study that showed decreased visceral fat accumulation and increased insulin sensitivity of peripheral tissue after regular aerobic physical activity [22,23]. The low physical activity and a diet rich in simple carbohydrates are factors predisposing to fat accumulation in muscle and liver and consequent insulin resistant development [22,23]. In addition, higher intake of saturated fat and lower fibre intake was associated with MONW in women [24]. Recently it was shown that higher meat consumption is a risk factor of MONW development in men [25]. In addition, decreased exercise energy expenditure and lower maximum threshold oxygen (VO_{2max}) was shown [9]. However, other studies have not confirmed these observations [7]. Further studies are necessary to explain the probably complex factors participating in MONW development, but the role of lifestyle seems to be key.

Metabolic obese normal weight as a cardiovascular and type 2 diabetes risk factor

In MONW, similar to obesity, the main link between insulin resistance and hyperinsulinaemia development is excessive visceral fat depot. This is confirmed by a study that showed higher circulating TNF-α, IL-6, and leptin levels and lower adiponectin levels in women with than without MONW [24]. It is known that insulin resistance is a main cause of metabolic disturbance development in MONW. Moreover, systemic chronic microinflammation is the second link of pathogenesis of cardiovascular risk in MONW, partially directly and partially indirectly by participation in insulin resistance development [26,27]. The additional cardiovascular risk factors in MONW are lipid disturbances associated with insulin resistance. However, it should be noted that increased triglyceride levels and decreased HDL cholesterol levels were observed in women but not in men with MONW [3,8,14]. In contrast, in the Qazvin Metabolic Diseases study triglyceride levels were significantly increased in both women and men with MONW [28]. Furthermore, the cardiovascular risk in MONW is increased by higher blood pressure levels [5,7,13]. It should be noted that the relative risk of developing cardiovascular disease is 2-3 times higher in subjects with than without MONW [9]. In addition, MONW is an important risk factor of type 2 diabetes development. The risk of type 2 diabetes development was more than 2.5-times higher among subjects with than without MONW during seven years of follow-up [10]. However, a recently published study has shown that MONW among normal-weight type 2 diabetes subjects affects 1 in 10 [29].

There is a lack of studies assessing the impact of MONW on fertility. However, it seems that insulin resistance related to MONW may be a cause of some cases of PCOS in women with BMI < 25 kg/m^2.

Metabolic obese normal weight treatment

The mainstay of MONW treatment is lifestyle change, especially regular aerobic physical activity. It is reasonable to use of metformin not only in subjects with prediabetes and type 2 diabetes, because metformin helps decrease the visceral fat area and liver steatosis [30-32]. In the case of insufficient efficacy of lifestyle changes, pharmacotherapy of lipid disturbances and hypertension can be used [33,34].

In summary, subjects with MONW have increased cardiovascular risk. However, MONW is not diagnosed in clinical practice. The lack of diagnosis and treatment causes a risk of cardiovascular events at a younger age. Therefore, waist circumference measurement should be included in physical examination and in subjects with this value above cut-off, blood pressure measurement and biochemical analysis should be performed.

Disclosure

Authors report no conflict of interest.

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