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Normal Weight Obesity: An Underrecognized Problem in Individuals of South Asian Descent

Nitin Kapoor, MD(Medicine), DM(Endocrine)[1,2]; John Furler, MBBS, PhD[3]; Thomas V. Paul, MD(Medicine), DNB(Endocrine), PhD[1]; Nihal Thomas, MD(Medicine), FRCP, PhD[1]; and Brian Oldenburg, MPsychol, PhD[2]

[1]Department of Endocrinology, Diabetes and Metabolism, Christian Medical College & Hospital, Vellore, Tamil Nadu, India; [2]Melbourne School of Population and Global Health, Faculty of Medicine, Dentistry and Health Science, The University of Melbourne, Melbourne, Australia; and [3]Department of General Practice, Faculty of Medicine, Dentistry and Health Science, The University of Melbourne, Melbourne, Australia

ABSTRACT

Purpose: Obesity has attained pandemic proportions across the world, and its prevalence in developing countries is also on the rise. Nevertheless, there is still a large gap in understanding the reasons behind a disproportionately high prevalence of diabetes as opposed to a lesser degree of obesity seen in individuals of South Asian origin. This research letter highlights the importance of identifying individuals with normal weight obesity, which may partially bridge this knowledge gap.

Methods: We reviewed recently published evidence on normal weight obesity.

Findings: Normal weight obesity is a common public health problem and may be prevalent in up to one-third of individuals of certain Asian ethnicities. Literature is emerging on its pathophysiology and association with metabolic diseases, such as type 2 diabetes mellitus, hypertension, and dyslipidemia. More recently, normal weight obesity was also identified as an independent strong predictor of cardiovascular mortality. However, evidence is particularly lacking on its appropriate management.

Implications: Normal weight obesity is an underrecognized yet widely prevalent problem in individuals of Asian descent. Further research on pathogenic mechanisms, diagnostic modalities, and therapeutic options in individuals with normal weight obesity is needed to appropriately manage this condition. (*Clin Ther*. xxxx;xxx:xxx) © 2019 Published by Elsevier Inc.

Keywords: Cardiovascular mortality, Normal weight obesity, Obesity, South Asian population.

INTRODUCTION

Obesity has attained pandemic proportions across the world, and its prevalence in developing countries is also on the rise.[1] Nevertheless, there is still a large gap in understanding the reasons behind a disproportionately high prevalence of diabetes as opposed to a lesser degree of obesity seen in individuals of South Asian origin.[2] This high prevalence may be partly explained by a unique phenotype known as normal weight obesity (NWO) harbored by some of these individuals; however, data regarding NWO are sparse in the Indian population.[3] This research letter provides further insights following the call made by Mukhra et al[4] in this journal on the problem of obesity in countries such as India. We reviewed recently published evidence on NWO. This study was conducted according to the guidelines laid down in the Declaration of Helsinki.

Mukhra et al[4] noted that the prevalence of obesity in Indian adolescents and adults is 11% to 20%. Although this is an important finding, in keeping with previously published literature, another pertinent aspect should be considered before

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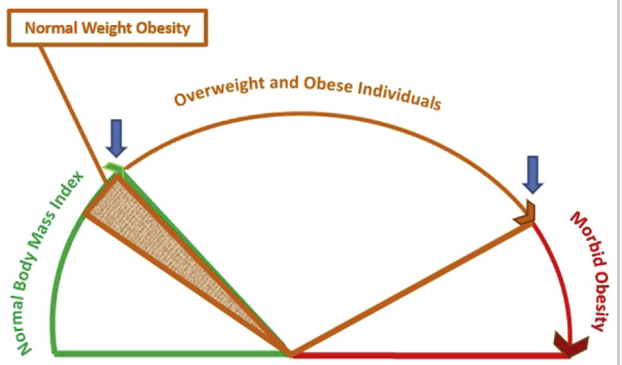

Figure. Spectrum of obesity in any community. The blue arrow indicates the relevance of the threshold used for any obesity indicator, in determining the prevalence of obesity in the community.

projecting this information more widely to academicians and policymakers in the field. The spectrum of obesity in any ethnicity can range from apparently thin-looking individuals with NWO to people with severe obesity (Figure). The proportion of individuals in each obesity group is determined by genetic background, lifestyle, environmental factors, and, importantly, the obesity indicator used to classify individuals.[5] Diabetes and other related metabolic disorders are frequently observed among those who with obesity as measured by body mass index (BMI). However, compared with white populations, India has a high prevalence of diabetes and other metabolic abnormalities despite a relatively lower proportion of obese individuals as measured by BMI. This disparity may be explained by differences in body composition and distribution of body fat in the otherwise apparently lean Asian phenotype.[6] This finding was first described by De Lorenzo et al[7] in 2006, who coined the term *NWO* and suggested an association between high body fat content (despite normal weight) and cardiometabolic disorders.

The NWO phenotype is often described in people of Asian origin, but limited awareness and consolidated literature are available on this topic.[6] In this article, we highlight the current understanding, clinical importance, and implications for clinical and public health of this important phenomenon. We identify important research gaps, particularly in the areas of pathogenesis, diagnosis, and effective therapies.

The term *NWO* is defined as a body mass index $\leq$25 kg/m^2 but with an increased body fat percentage. The cutoffs used for body fat percentage have varied, depending on the study population and sex and ethnicity of the studied populations. The American Society of Endocrinologists[8] defines obesity by body fat percentage as $\geq$35% in women and $\geq$25% in men. The cutoffs derived for individuals of Asia Pacific origin are lower ($\geq$33.4% in women and $\geq$20.6% in men).[9]

Recent estimates suggest that approximately 30 million Americans are affected by NWO, and its prevalence is increasing in younger individuals (23–25 years old).[9] However, there is a wide variation in the results of similar studies in other populations published to date. Among the Asian population, Kim et al[10] found an NWO prevalence of 36% in men and approximately 29% in women in a Korean population, including 5313 men and 6904 women >20 years of age. In another recently published Chinese study of 23,748 individuals (9633 males and 14,115 females), the prevalence of NWO was 9.5% among men and 6.06% for women.[11] There is paucity of published literature among people of South Asian and other ethnicities.

This variation is predominantly attributed to ethnicity-related variation but also importantly to the methods used to quantify body fat and the diverse cutoff points used for its diagnosis. Direct measurement of adipose tissue using standard methods such as water-displacement plethysmography or magnetic resonance imaging is too expensive and impractical for day-to-day use in clinical practice. However, methods such as air-displacement plethysmography, dual-energy X-ray absorptiometry (DXA), or bioelectrical impedance, have been reported to be valid and cost-effective. Among these, DXA is emerging as one of the most efficient, accurate, and valuable tools to estimate body fat, largely because of its additional capacity for estimating visceral adipose tissue.[12] In resource-limited settings, anthropometric measures, such as waist circumference and waist-hip ratio, are often used by clinicians as a proxy measure of visceral adipose tissue, but DXA now offers the possibility to allow a low-cost way of more accurately characterizing the epidemic of NWO in these populations.

There is emerging evidence to suggest that individuals with NWO can develop a low-grade proinflammatory state, insulin resistance, enhanced oxidative stress, and dyslipidemia, which may predispose them to a high risk of cardiometabolic disease processes and related complications.[13] There is also evidence to suggest that women with NWO have a significantly higher risk of all components of the metabolic syndrome compared with their BMI-matched leaner counterparts.[11,14] Inanother longitudinal analysis of 6171 people with normal BMI from the National Health and Nutrition Examination Survey III database, women with NWO had an independent association with cardiovascular mortality.[15] The increased cardiovascular mortality in NWO individuals could also be attributed to the poor left ventricular systolic and diastolic function that has been found in these patients secondary to increased abdominal fat deposition, a profibrotic state, increased insulin resistance, and higher inflammatory markers. This initial preclinical myocardial dysfunction may then gradually progress to overt cardiomyopathy.[16]

Moreover, data from a recently published nationwide Chinese study,[11] suggest that individuals with NWO had significantly higher cardiometabolic risks. They found the risk of type 2 diabetes mellitus (odds ratio [OR] = 1.519; 95% CI, 1.262−1.828), Framingham risk score ≥10% (OR = 1.973; 95% CI, 1.596−2.439), hypertension (OR = 1.525; 95% CI, 1.333−1.745), and metabolic syndrome (OR = 2.175; 95% CI, 1.920−2.463) significantly increased in the NWO group compared with the individuals with normal weight. Furthermore, the association of increased cardiometabolic risks in the NWO population persisted after statistically excluding the effect of abdominal obesity. This study suggests that NWO may provide more information about the cardiometabolic risks compared with traditional obesity indicators.[11]

Although most literature on this subject suggests that the poor cardiometabolic outcomes in individuals with NWO are due to increased body fat and consequent elevated circulating fatty acids, thereby leading to increased inflammation, insulin resistance, and atherosclerosis, another underrecognized feature in these people is their reduced lean muscle mass (sarcopenia).[16] Related to this, there is emerging literature on the antiatherosclerotic role of irisin and similar myokines secreted by the skeletal muscle. These myokines may be a useful future therapeutic target in patients with NWO.

An additional obvious pitfall for people with NWO is the reduced focus on obesity management by their health care practitioner because of their apparently normal-appearing body habitus. This problem is further compounded by a lack of self-awareness of their predisposition to increased cardiovascular risk. These pitfalls could be reduced if body fat estimation was used more commonly by physicians to determine the magnitude of obesity in these individuals. Individuals with normal-appearing body habitus may be predisposed to an even a higher cardiovascular disease risk than their obese counterparts as reported in the study by Sahakyan et al[17] in which women with NWO had a higher mortality risk than not only those with similar BMI without central obesity (hazard ratio = 1.48; 95% CI, 1.35−1.62) but also those who were obese according to BMI alone (hazard ratio = 1.32; 95% CI, 1.15−1.51).

The increased cardiometabolic risk in Asian Indian individuals born with low birth weight is also associated with NWO and may be an important risk factor for future development of this phenotype and its related consequences.[18] This finding is in line with the Barker hypothesis, and a history of low birth weight may help in early identification and intervention of at risk individuals to prevent development of NWO.[18]

Timely identification followed by appropriate intervention through intense lifestyle modifications that aim at reducing body fat content and periodic follow-up may prevent the projected cardiovascular morbidity and mortality in these at risk individuals.[15] However, there is limited literature on which intervention would work better in these metabolically unique individuals. A recent study[19] among university students found poorer physical fitness and lower skeletal muscle mass in students with NWO and proposed increased isometric exercises in these individuals. Until further evidence is generated on the effect of physical activity and dietary-based interventions in this cohort, conventional principals should be used for the management of obesity.

DISCUSSION

Given that body composition analysis is not usually assessed in routine outpatient practice, it is important

to provide further clarity to health care professionals about the definition, prevalence, assessment, and clinical implications that characterize the NWO phenotype, especially for individuals of Asian Indian ethnicity. Such clarity will enable early identification and appropriate management of these high-risk individuals.

Currently, there is a paucity of information regarding the key determinants of NWO in the general population. Even though environmental factors are implicated in the origin of central NWO, the role played by underlying genetic factors cannot be totally excluded. Furthermore, the response to conventional treatment of obesity and associated comorbidities needs to be evaluated, and specific evidence-based guidelines for management of this condition are warranted.

In light of these emerging concepts, it is likely that in the future the diagnosis of obesity will warrant information on body fat content and distribution to predict occurrence of cardiometabolic disorders. The decision about the diagnostic threshold of these parameters will depend on optimal cutoffs derived from long-term epidemiologic studies with accurate information not only on related comorbidities but also on a hard end point, such as mortality.

In conclusions, additional epidemiologic studies are needed to assess the etiology, prevalence, phenotypic characterization, and therapeutic response of NWO among individuals of different ethnic origins. In addition, genotype-phenotype characterization of these individuals will elucidate the potential role of genetic markers in the understanding the NWO phenotype.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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Address correspondence to: Nitin Kapoor, MBBS, MD(Med), DM(Endo), Department of Endocrinology, Diabetes, and Metabolism, Christian Medical College, Vellore, TN, 632004, India. E-mail: nitin.kapoor@cmcvellore.ac.in

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