Despite the fact that obesity is a major risk factor for the development of type 2 diabetes and cardiovascular disease, it has now been recognized that a proportion of obese individuals display a healthy cardiometabolic profile. In contrast, a proportion of lean individuals have been shown to portray an increased risk for cardiometabolic complications. These distinct sub-phenotypes of obese and lean individuals are referred to as metabolically healthy obese (MHO) and the metabolically obese, non-obese (MONO) phenotypes. We have shown that the MONO phenotypes are characterized by increased levels of pro-inflammatory mediators and reduced levels of anti-inflammatory adipokine adiponectin. The clinical relevance of these sub-phenotypes of obesity and the issues related to the categorization of metabolic obesity are also discussed in this research highlight. The health outcomes related to these phenotypes and their differential response to interventions should also be characterized.

Keywords: Metabolically obese but normal weight; metabolically healthy obese; inflammation; oxidative stress; cardiovascular risk

healthy, but obese subjects demonstrated lower levels of lipid parameters, fasting blood glucose and glycosylated hemoglobin levels compared to metabolically healthy non-obese (MHN0) individuals. Since adipose tissue is an important player in terms of exerting metabolic and endocrine control in the pathogenesis of insulin resistance, the subjects were categorized based on the presence of metabolic abnormalities and BMI. Since the dysregulated secretion of adipokines is one of the primary adipose tissue defects in obesity, we looked at the levels of the adipokines adiponectin, resistin, visfatin, hs-CRP, TNF-alpha, IL-6, MCP-1 and oxidized LDL in the various body phenotypes. The study showed reduced levels of, whereas, the pro-inflammatory adipokines showed an increasing trend from the MHO to the MONO phenotype and were highest in the MOO group. We speculate that fat-accumulation leading to adipocyte hypertrophy causes the release of increased levels of pro-inflammatory cytokines [7]. This in turn probably promotes the infiltration of immune cells that exacerbate the inflammatory process [8] thus leading to increased cardiometabolic risk. It is possible that the altered secretory profile of adipokines and the parallel increase in the acute-phase reactants could be one of the critical mediators in the transition from a metabolically healthy phenotype to a metabolically obese phenotype.

More studies are needed on whether the metabolically healthy obese individuals possess any epigenetic or genetic predisposition to maintain their insulin sensitivity. It could also be possible that this phenotype is unstable and can progress gradually to an insulin resistant state. Conversely, it can also be argued that metabolically obese, non-obese (MONO) phenotype can become metabolically obese, obese (MOO) phenotypes. In a recent report by Appleton et al [9], over 67% of the MHO phenotype were found to be stable over a duration of 10 years. This shows that a proportion of MHO individuals demonstrate a long term protection towards the development of metabolic diseases like T2DM. In depth studies on the metabolically healthy but obese individuals would unravel novel pathways and information on how their unique anatomical and molecular characteristics confer protection against type 2 diabetes and cardiovascular disease. In this context, it is of interest that mouse models of metabolically healthy obesity are being developed which show a favorable metabolic profile despite being obese [10, 11].

There are several issues related to the categorization of metabolic obesity that remain unresolved. The molecular and physiological mechanisms underlying these unique subgroups have not been clarified. Moreover, the stability of the metabolic phenotypes with the passage of time is still a contentious issue. The health outcomes related to these phenotypes and their differential response to interventions are yet to be characterized. Another challenge is the lack of consensus on the clinical or biochemical parameters required to categorize subjects into these phenotypes.

In conclusion, the use of BMI alone to define obesity appears to be inadequate as there is a category of people with a metabolically healthy but obese phenotype. More research is needed on the role adipocytes play in health and obesity and how inflammatory mediators act as signaling molecules in this process. Thus, there is an urgent need for a new definition of obesity on the basis of anatomical location of fat rather than just its volume. Further refinement of the term “metabolic obesity” could lead to the better identification of cardiovascular risk that these various phenotypes represent and this can only be assessed through longitudinal follow up studies with clear clinical endpoints. The ultimate goal of the treatment strategies should not only be to promote weight loss in obese individuals, but also to control the adverse metabolic risk factors in normal weight individuals so that their cardiovascular risk can also be categorized.

Conflict of Interests

The authors have declared that no competing interests exist.

References

