DISCUSSION

Background: Obesity has emerged as global pandemic.[1] One in eight individuals worldwide is obese with body mass index (BMI) ≥ 30 kg/m^{2}. About 2-6% of the world population is morbidly obese with BMI ≥ 35 kg/m^{2} with at least one obesity-related comorbidity, or with BMI ≥ 40 kg/m^{2}.[2,3] Not all people exposed to lifestyle variables considered as potential risk factors for obesity become obese. This suggests that there are underlying genetic, and epigenetic mechanisms at play. Rate of heritability of BMI is high, and ranges from 40-70%.[3]

Polygenic obesity arises due to simultaneous DNA mutations in multiple genes. As per Hinney et al. (2010),[4] "any of a group of alleles at distinct gene loci that collectively control the inheritance of a quantitative phenotype or modify the expression of a qualitative character are termed 'polygenic' variants." Recent genome-wide association studies (GWAS) have identified more than 200 common genetic variants in polygenic obesity.[5] Thus, the scope for precision medicine herein might be limited. On the other hand, a 'monogene' is defined as a "gene with a strong effect on the phenotype [Mendelian traits or Mendelian (single gene) conditions], giving rise to a (close to) one-to-one relationship between genotype and phenotype."[4] Thus, monogenic obesity arises due to mutations in a single gene. Monogenic obesity is rare, and currently, eleven different forms of it have been recognized.[3] Further, epigenetic effects could lead to additional individual specific differences in BMI, and phenotype in obesity.[6,7]

Pathophysiology: A number of comorbidities are associated with obesity, including metabolic disease, insulin resistance, type 2 diabetes, hypertension, kidney failure, dyslipidemia, stroke, sleep apnea, osteoarthritis, and cardiovascular disease.[8] Obesity entails excess adiposity, and dysregulation in energy-balance. Two sets of neurons in the arcuate nucleus in the mediobasal hypothalamus are central in regulating energy balance. These neurons upon excitation, or inhibition by circulating neuropeptide hormones—regulate food intake, and energy expenditure accordingly.[9] There is increased accumulation of excess lipids, mainly triglycerides, in the adipose tissue. This along with the increased volume of skeletal muscle, liver, and other organs, and tissues leads to increased body mass.[3,6] Such individuals are generally characterized by increased energy expenditure, blood pressure, cardiac output, and pancreatic β-cell mass.[3,10] Excess adipocytes are mostly stored subcutaneously.[11] Most of these adipocytes are white [with deposits of triglycerides], although smaller concentrations of thermogenic brown, and beige adipocytes are also encountered.[12] Another storage site for lipids is visceral adipose tissue.