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Literature Review

Metabesity: expert panel recommendation for taking up the challenge by a multidisciplinary approach

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Abstract

Metabesity refers to metabolic aberrations associated with obesity. These include low-grade inflammation, mitochondrial dysfunction, and changes in gut microbiome. Along with a genetic component, the phenotypes in metabesity are largely the result of sedentary lifestyle and unhealthy eating habits. Metabesity is

associated with several co-morbidities including an increased risk for cardiovascular conditions like hypertension, heart failure, myocardial infarction, stroke, and sudden death. Insulin resistance, high blood pressure and glucose levels, visceral adiposity, progressive atherosclerosis, dyslipidaemia and fatty liver are common in obese individuals. Obesity increases the risk for and overall mortality due to cancer. Metabesity adversely impacts endocrine balances in the body and increases the risk of degenerative conditions like dementia. Metabesity is an impending epidemic of huge public health implications with enormous clinical, socioeconomic, and humanistic burden. Interventions to combat sedentary lifestyle and unhealthy eating should be introduced early in life to prevent the onset and progression of metabesity. This review also summarizes the experts' recommendation from Pakistan to manage the rising metabesity concern in their geography based on the literature evidences.

Key words: Metabesity, Obesity, metabolism, cancer, diabetes, insulin resistance.

Introduction

Obesity is currently a major public health problem. Obesity is associated with several chronic diseases such as hypertension, diabetes mellitus, cardiovascular (CV) diseases, atherosclerosis, non-alcoholic fatty liver disease (NAFLD), cancer, and others. Independently and with the accompanying co-morbidities, obesity is a common cause of mortality, unhealthy ageing, and adverse outcomes in adult life. Obesity and its associated disorders share metabolic pathologies. This spectrum of conditions can be referred to as 'metabesity' which involves mechanisms ranging from mitochondrial dysfunction, inflammation, and microbiome to drugs and environmental factors [1].

Metabolic abnormalities like insulin resistance are common in obese individuals and usually improve after weight loss. Though majority of the individuals with

insulin resistance are overweight, not all obese individuals develop insulin resistance. Obesity and insulin resistance represent a metabolic cluster of abnormalities like glucose intolerance, hyperinsulinism, dyslipidaemia, and increased C-reactive protein in plasma [2]. Obesity and insulin resistance are key elements that describe the 'metabolic syndrome' (MS) which is an independent risk factor for increased risk for disorders like diabetes and CV disease. MS also includes criteria of dyslipidaemia including high triglycerides and low high-density cholesterol and elevated blood pressure (BP).

Metabesity and genetics

Obesity has also been described as a genetic trait with specific markers for increased body mass index (BMI), fat distribution, and metabolic syndromes. Genetic traits associated with obesity include mutations or polymorphisms in the fat mass and obesity associated (FTO) gene, melanocortin-4 receptor (MC4R) gene, and the gastric inhibitory polypeptide receptor (GIPR) gene [3]. Genetic determinants of fat distribution include loci near TFAP2B, MSRA, and LYPLAL1 that have been associated with waist circumference and waist hip ratio. In addition, the FTO and neurexin 3 (NRXN3) genes are also associated with waist circumference (WC) and Body Mass Index (BMI) [4]. Parental obesity is an important risk factor for obesity in children. Genome-wide association studies have described more than hundred genetic variants that are associated with an increased risk for obesity [5].

A complex interplay of genes and behavioural and environmental conditions influence the development of obesity [6]. Sedentary lifestyle along with excessive calorie intake is the most common cause of increased weight and cardiovascular risk.

BMI and waist circumference are the most common parameters used to describe obesity[7]. According to the World Health Organization (WHO), individuals with BMI of 15.5-24.9 kg/m² are classified as normal weight whereas those with BMI of 25.0-29.9 kg/m² and ≥ 30 kg/m² are said to be overweight and obese, respectively. Extreme obesity is defined as BMI of BMI ≥ 40 kg/m². Overweight individuals have an increased risk and obese individuals have high risk for diseases such as diabetes, hypertension, and cardiovascular disease. This classification applies to the Caucasian population[8]. Asian populations have a predominance of central fat distribution and larger waist circumference. This predisposes Asians to an increased risk of diabetes and hypertension at lower BMI when compared to the non-Asian populations. Thus, the WHO has suggested lower cutoff points for therapeutic intervention in Asians: a BMI of 18.5 to 23 kg/m² represents acceptable risk, 23 to 27.5 kg/m² confers increased risk, and 27.5 kg/m² or higher represents high risk [9]. Ethnicity is an important determinant of fat distribution. Visceral adipose tissue is reported to be more in Whites when compared to African Americans [10]. There is also evidence that African American youth have more abdominal subcutaneous adipose tissue (SAT) than White youth[11].

Cardiovascular implications of metabesity

Obesity is a significant and independent risk factor for CV diseases such as hypertension, heart failure, myocardial infarction, stroke, and sudden cardiac death. The underlying mechanisms include a quick progression of atherosclerosis, increased inflammatory mediators, and changes in vascular homeostasis and ventricular remodeling [12]. Obesity causes derangements in metabolic parameters such as dyslipidaemia, hyperglycaemia, and systemic inflammation which promote the development and progression of cardiovascular disease (CVD).

In the Framingham study, 23% of coronary heart disease (CHD) in men and 15% of CHD in women was attributable to excess adiposity [13]. In a long-term follow up of the Framingham cohort, all-cause mortality increased with the increase in duration of obesity; CVD mortality increased by 7% for every 2 years in succession with obesity [14].

It is important to check the onset and progression of obesity as adverse CV outcomes are known to increase with the duration of obesity [15]. Exercise, dietary modifications, and cardiac rehabilitation can improve CV outcomes in obesity. Exercise reduces total body fat and improves metabolic parameters like insulin sensitivity and lipid levels. Improvement in cardiorespiratory fitness can decrease inflammation, lower the risk for metabolic syndrome and counter the accumulation of visceral fat [16]. Exercise, tailored to individual health and abilities, can prevent metabolic and CV risks in obese people. Physical activity of moderate intensity for at least 30 minutes is recommended for beneficial health effects [17].

Weight loss is associated with improvement in metabolic and CV health in obese individuals. It results in reduction of obesity-related co-morbidities like hypertension, hyperglycaemia, and dyslipidaemia and improves the overall quality of life [18]. In adults with obesity, reduction of weight reduces premature all-cause mortality. In a meta-analysis of 54 randomized controlled studies, weight loss in obese adults decreased all-cause (34 trials; n=685 events; risk ratio: 0.82; 95% CI: 0.71 to 0.95) and CV (8 trials; n=134 events; risk ratio: 0.93, 95% CI: 0.67 to 1.31) mortality. There was also a reduction in mortality due to cancer (8 trials; n=34 events; risk ratio: 0.58, 95% CI: 0.30 to 1.11)[19]. Risks for CVD are lower in fit obese individuals than in the unfit lean [17].

Obesity and diabetes

Type 2 diabetes is a common co-morbidity in obese individuals. Metabolic derangements and physical inactivity predispose obese individuals to insulin resistance and high glucose levels. Further, therapy for other co-morbidities such as dyslipidaemia and CV disease may increase the risk for diabetes in obese individuals. Patients with dyslipidaemia and CVD are treated with statins to decrease plasma cholesterol levels [20]. However, statin therapy is reported to negatively influence glucose metabolism and result in an increased risk for development of diabetes [21]. Endocrine abnormalities like polycystic ovarian disease can increase the risk of obesity, diabetes, metabolic syndrome, and CV disease [22]. Weight loss in obese individuals can help to regulate the metabolic aberrations including insulin resistance. Physical activity of at least 150 min/week can delay or prevent diabetes in individuals who are at risk or those who are pre-diabetic [23].

Metabolic implications of obesity

Non Alcoholic Fatty Liver Disease (NAFLD) is associated with visceral adiposity, progressive atherosclerosis, insulin resistance, high blood glucose, hypertension, and dyslipidaemia. Characterized by fatty changes, hepatocyte necrosis, lobular inflammation, and perisinusoidal fibrosis, this condition is essentially the hepatic manifestation of metabolic syndrome. In an observational study, a prevalence of 67% was reported for MS (National Cholesterol Education Program-Adult Treatment Panel III 2001 criteria) in 356 non-diabetic adults with NAFLD[24].

NAFLD is a chronic systemic inflammation that increases the risk of several cardio-metabolic and renal diseases. NAFLD is associated with chronic kidney disease (CKD) and albuminuria. The prevalence of CKD in NAFLD is reported to range from 20% to 55%. This is approximately twice as high when compared to

the prevalence of CKD in patients without NAFLD. The risk and severity of CKD and impaired renal function increases with the severity of NAFLD. Patients with NAFLD should be screened for cardiac and renal function [25].

Gut microbiome may play an important role in the development of NAFLD by increasing hepatic lipogenesis and production of reactive oxygen species and creating a pro-inflammatory milieu leading to hepatic injury, necrosis, and fibrosis. The ‘gut, diet, and liver’ are closely related due to the anatomic and functional association through the portal system. Dysbiosis and inflammasome deficiency are component to the pathophysiology of NAFLD. Alteration and manipulation of microbiota is said to change the severity of NAFLD [26]. In early stages, NAFLD can be reversed with lifestyle modifications and weight reduction. Treatment of underlying conditions can improve the outcomes and quality of life in NAFLD.

Obesity and risks for cancer

Obesity and MS are associated with a higher risk, onset, and progression of cancer. The underlying factors include an increase in visceral adiposity, insulin and insulin like growth factor 1, lipid levels, growth factors, sex hormones, and inflammatory mediators. The resultant increase in insulin resistance, serum cholesterol, and cyclo-oxygenase expression increases the intracellular and intercellular signaling, intratumour steroidogenesis, and angiogenesis. Chronic low-grade inflammation in obesity is an important mechanism linking it to the increased risk and progression of cancer. Obesity is a risk factor for several cancers including the prostate and breast cancers which are the leading cause of death in men and women, respectively. Restriction of calorie intake and loss of weight counters the tumourigenic properties of obesity. Besides this, the treatment of comorbidities in obesity reduces the risk, occurrence, and mortality of cancer. Above all, the reduction of obesity helps to decrease the all-cause mortality in cancer [27].

Several non-biologic mechanisms contribute to the link between obesity and cancer. Obese individuals are likely to have a delayed diagnosis and inadequate treatment of cancer which can impact survival in obesity-related cancers. Obese individuals are less likely to undergo screening and may face technical difficulties during screening and treatment of cancer. The comorbidities of obesity impact the association, treatment, and outcomes of cancer. Weight loss is a key cancer preventive strategy in obese individuals. Obesity, being a modifiable factor, is a significant possible intervention for the prevention and management of cancer.

The risk of obesity-related cancers is progressively increasing in younger individuals. The early onset of colorectal cancer reflects the increase in obesity in young adults. Data from 25 population-based registries in the USA (1995 to 2014), reported a total of 14 672 409 incident cases of 30 cancer types including 20 most common cancers and 12 obesity-related cancers. Among young adults (25-49 years), there was a significant increase in incidence of 6 of the 12 obesity-related cancers, i.e. multiple myeloma, colorectal, uterine corpus, gallbladder, kidney, and pancreatic cancer. The rise was steep in the younger individuals with an annual rise ranging from 1.44% (95% CI: -0.60 to 3.53) for multiple myeloma to 6.23% (95% CI: 5.32-7.14) for kidney cancer in individuals aged 25-29 years [28].

Metabesity including high body weight is a potential risk factor for several cancers including colorectal, renal, pancreatic, and breast cancers. Visceral adipose tissue plays a crucial role in the pathogenesis of several cancers, possibly by release of cytokines such as tumour necrosis factor (TNF α) and interleukin-6 (IL-6) which induce pro-inflammatory effects with links to tumourigenic pathways. A meta-analysis of 12 prospective cohort studies (n=22,728,674) explored the dose-response relationship between BMI and breast cancer. This meta-analysis reported a linear association between BMI and risk for breast cancer. With an increase of every 5 kg/m² of BMI, the risk for breast cancer increased by 2%. The increase in

risk was specifically high in the postmenopausal women. On the other hand, BMI emerged as a potential protective factor for the risk of breast cancer in premenopausal women. the increase in risk can potentially be explained by the larger fat reserves acting as sites for aromatization of androstenedione to produce more estrogen [29]. There is evidence suggestive of the association of metabolic syndrome with prostate cancer, in particular, the more aggressive forms of this cancer. General adiposity has a positive association with advanced prostate cancer. The components of metabesity that are associated with the increased risk include hyperinsulinaemia, abdominal fat distribution, obesity, increased waist-hip ratio, elevations in systolic and diastolic BP, and low HDL-cholesterol. In addition, androgen deprivation therapy, a widely used treatment option for prostate cancer, is known to adversely change the body composition. Some of the changes induced by androgen deprivation include decreased insulin sensitivity, increased triglycerides and total cholesterol, increased fat mass, and increased proinflammatory markers and endothelial dysfunction. Obesity is associated with decline in testosterone levels. There is a linear inverse relation between BMI and testosterone levels. The hypogonadism associated with obesity may be a contributor to the risk of prostate cancer in men[30]. Similarly, renal cancer which is fundamentally a metabolic disease, has an association with MS. Several of the genes associated with kidney cancer, for example MET, FLCN, fumarate hydratase, VHL, succinate dehydrogenase B, and succinate dehydrogenase D, are also involved in cellular mechanisms relating to use of oxygen, processing of nutrients, and generation of energy. This metabolic basis of renal cancer is a potential future target for novel therapies [31].

Other implications of obesity

The inflammatory mechanisms underlying metabesity increase the risk for vascular and degenerative conditions. MS increases the rate of ageing and accelerates

degeneration by increasing the risk for age-mediated cell death. Obesity has an association with degenerative diseases like osteoarthritis, dementia, and cardiovascular changes. In a population-based study, 3458 individuals (aged between 40 to 80 years) from the Taiwanese Survey on Prevalence of Hypertension, Hyperglycaemia, and Hyperlipidaemia (TwSHHH), were classified as persistent (n=407), non-persistent (n=715), and no MS (n=2336). During the 10 year follow-up period, risk for dementia was higher in individuals with persistent (crude HR: 2.37; 95% CI: 1.23–4.60; $P=0.010$) and non-persistent (crude HR: 3.37; 95% CI: 2.07–5.51; $P<0.001$) MS than in those without MS. Overall, with 31,741 person-years of follow-up, 76 individuals developed dementia. In this study, the risk of dementia increased with the worsening of MS. This supports the early detection and treatment of MS to reduce the risk of dementia [32].

Metabesity is associated with endocrine adaptations including changes in vitamin D metabolism. Deficiency and sub-optimal levels of vitamin D, defined by 25-hydroxyvitamin D (25(OH)D) levels of <25-30 nmol/L and <50-100 nmol/L, respectively, are associated with adverse metabolic phenotypes including insulin resistance, diabetes, and cardiovascular disease. These conditions are also closely linked with obesity. Changes in vitamin D status and metabolism in obesity can be explained by increased sequestration of the fat-soluble vitamin in adipose tissues, volumetric dilution, and negative feedback mechanisms due to increased levels of circulating 1,25-dihydroxyvitmain D3. Further, the sedentary lifestyle of obese individuals may decrease their exposure to the sun, thus impairing the adequate synthesis of vitamin D [33].

Metabesity adversely impacts learning and development in children and adolescents. Obesity has an association with intellectual disability in children and young adults. Factors that may lead to this compromise in developing children include the increased intake of medications, having syndromes associated with

obesity, and malicious food habits[34]. These collectively compromise the quality of life in children. Introduction of physical activity and improvement in eating habits in early childhood can improve the overall health and wellbeing of children who are obese or are at an increased risk for obesity.

There is an emerging need for targeting the chronic low-grade inflammation in metabesity. Drugs that decrease body weight are potentially of use as these can help to reduce the levels of adipose tissue macrophages which have a key role in obesity-related inflammation. The widely used oral hypoglycaemic agent, metformin, is reported to have an anti-inflammatory action. Experiments in mice suggest that metformin decreases the serum level of the pro-inflammatory cytokines like TNF- α and IL-6. In addition, metformin is reported to lower the expression of the M1 macrophage markers CD11c and MCP-1 in adipose tissues. Alterations in macrophage polarization are the key underlying mechanism for improvement in obesity-related inflammation [35]. Further, it is also hypothesized that metformin helps to combat obesity by altering the composition of the gut microbiome [36].

Strategies to overcome the challenges of metabesity

Metabesity is an impending epidemic that can have several deleterious effects on not alone the physical wellbeing but also the psychological and emotional wellbeing. Obesity, independently and with its comorbidities, increases the risk for psychiatric disorders like depression, anxiety, loneliness, and social withdrawal. Metabesity imposes a huge socioeconomic burden. The increase in comorbidities with metabesity can complicate the management of the condition. This can amplify the direct and indirect costs associated with metabesity. Metabesity is a huge challenge for healthcare systems. Prevention of obesity can go a long way in preventing the loss of productivity due to obesity in both patients as well as

caregivers. Measures to prevent metabesity need to be introduced at individual, family, as well as society levels. Population-based interventions are key to increase the awareness about risk factors for metabesity and a rational approach to its treatment. Above all, measures should be introduced to reduce and eliminate the risk of metabesity. This includes education of individuals and society to adopt healthier lifestyle and eating habits. There should be nationwide and global regulations to control the composition and availability of food. Restaurants and food joints should partner with public to encourage healthy eating. There is an urgent need for public health measures to prevent metabesity to save societal resources.

The medical management of metabesity should include a holistic approach to lifestyle changes, changes in food habits, and treatment of any associated comorbidities like hypertension and hyperglycaemia. There are no drugs in specific for MS. Aggressive interventions in diet and physical activity are a mandate for obese individuals. This may include options in alternate medicine like chia seeds, flax seeds, cinnamon, and some detox diets. There are not many drugs that target the component inflammation in metabesity. Bariatric surgery has been used in individuals where it is not possible to reduce weight by diet and exercise. However, this aggressive measure cannot be introduced at population levels. It should only be offered to the right patients after evaluation of nutritional status and segmental body composition. After any extreme dietary or surgical intervention, efforts should be made to sustain the attained loss in weight. The prevention of metabesity should begin early in life and healthy eating habits and physical activity should be part of routine for children and young adults. Individuals, families, society, and governments should come together to collaborate for reducing the constantly increasing burden of metabesity. Research should continue to focus on

and explore key pathways in metabesity and identify risk factors including genetic targets and gut microbiomes.

Expert recommendations

Topic of Metabesity was also discussed in focus groups as below:

Risk Factors of Obesity: Group discussed major risk factors and pointed out following as outliers:

Psycho Social Aspect: Group discussed and recognized the impact of Metabesity on Body Image (Bad impression/image of Obese person), Social Pressure (Socially disconnected and bullied) and possibility of Less opportunity for Job and growth for obese persons.

Weight Loss with Alternative Medicines: Group discussed use of alternative methods of weight loss, but could not recommend due to lack of randomized clinical trials. Group discussed regimens often asked for included Water therapy, Lemon + Honey (Warm Water), Detox (Infusion Water), Thyme /Oregano /Cumin / Turmeric /Ginger /Ginseng / Chia Seeds / Nigella Seeds / (Blacks Seeds, Kalonji, Caraway), Apple Cider Vinegar, Cinnamon, Fenugreek and Ginger. Due to lack of clinical evidence group thought it is difficult to suggest if any of these have a clear benefit.

Physical Activity: Group discussed the epidemic of decreased physical activity, Lack of opportunity for physical activity. Group suggested focusing on modalities to help build Playground/Parks, Awareness campaign at School Level / Workplaces / Media for public, overcoming cultural barriers against female cultural restriction for outdoor activities and Promote Physical Activity.

Nutrition: Group discussed and pointed out easy access of Junk Food, increased use of Sugar, increased intake of Sodium, Decreased intake of Fiber.

Bariatric Surgery: This Group emphasized the difficulties in finding the right Patient: as was advised to assess patient candidates for bariatric surgery

Weight Maintenance after Intervention: Expert group suggested Important measures in weight maintenance phase which included Motivation, Eating Behaviours modifications, Public Awareness, etc. Healthy Lifestyle for Young and Health Education at Schools and Home, Sport activities at School and Home, Public Awareness Workshops on health Hazards of Metabesity, Public parks with Sports Activities for Youth)

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