Metabolism Clinical and Experimental 92 (2019) 1–5

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Obesity: seize the day, fight the fat

ARTICLE INFO

Article history:
Received 28 December 2018
Accepted 29 December 2018

Keywords:
Adipocyte
Adipokines
Adipose Tissue
Obesity
Metabolic Syndrome
Treatment

1. Introduction

Obesity is the global epidemic of the 21st century: about 1.5 billion adults worldwide are overweight, and among them, about 200 million men and 300 million women are obese [1]. In some countries, the prevalence of obesity has exceeded 50%, as in Tonga (men), and in Kuwait, Kiribati, Micronesia, Libya, Qatar, Tonga and Samoa (women) [2]. The prevalence of overweight and obesity are also increasing in children and adolescents in developed (about 25%) and in developing countries (about 13%) [2]. Obesity has been associated with many comorbidities, including type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease (NAFLD), hypertension, chronic kidney disease, cardiovascular disease (CVD), and malignancies, leading to increased mortality observed in obese individuals [3]. Overweight and obesity were estimated to be associated worldwide with 3.4 million deaths, which could also be expressed as 4% of disability-adjusted life-years lost (DALYs) [4]. It is also alarming that children with severe obesity are apparently at increased risk of premature death [5].

Although devastating in its breadth and depth, timely recognition and appropriate management of obesity may, at least in part, limit or fully eliminate the obesity associated increased morbidity and mortality [6]. Apart from the morbidity and life expectancy, obesity is a significant burden to any healthcare system. Medical costs have been estimated to be 30% higher for obese than normal weight individuals [7] and the total health-care costs related to obesity have been predicted to be doubling every decade [8].

This special issue of "*Metabolism*" is devoted to obesity, a timely topic, given the important individual, social and economic burden related to obesity. The aims of this special issue are to provide a current overview of the entire spectrum of obesity, from genetics, to pathophysiology to therapeutics, and to provide necessary evidence to support the daily clinical practice of physicians, and to motivate scientists to perform more advanced research in the field, which will continue elucidating our understanding and improving the quality of life, as well as the morbidity and mortality of obese individuals.

2. Reviews in this Special Issue of "Metabolism"

Many experts in the field of obesity have accepted to contribute to this special issue of "*Metabolism*". They have all put together outstanding pieces of work, combining the presentation of established knowledge with novel evidence, thus providing expert opinion and generating questions for further research in the field of obesity.

Chooi et al. reviewed the epidemiology of obesity. They provided current trends demonstrating that worldwide prevalence of overweight and obesity has doubled since 1980 and that about one third of the world population is nowadays overweight or obese [9]. The prevalence of overweight and obesity remained greater in women than in men throughout this period and increases with age. Despite variability among countries, obesity trends were relatively uniform worldwide [9]. Chooi et al. also challenged the World Health Organization (WHO) definition of obesity, which is based on body mass index (BMI) cut-off points, because BMI has high inter-racial and inter-individual variability, i.e., the percent body fat differs among individuals of the same BMI [9]. As a classic example, Asians have more abdominal fat than

Abbreviations: ABOM, American Board of Obesity Medicine, ACA, American College of Cardiology, AHA, American Heart Association, BMI, body mass index, CVD, cardiovascular disease, DALYs, disability-adjusted life-years, GLP, glucagon-like peptide, MHO, metabolically healthy obesity, MUO, metabolically unhealthy obesity, NAFLD, nonalcoholic fatty liver disease, NASH, nonalcoholic steatohepatitis, OMEC, Obesity Medicine Education Collaborative, PCOS, polycystic ovary syndrome, PCSK, proprotein convertase subtilisin/kexin type, SCOPE, Strategic Centre for Obesity Professional Education, SGLT, sodium-glucose cotransporter, T2DM, type 2 diabetes mellitus, TOS, The Obesity Society, WHO, World Health Organization.

https://doi.org/10.1016/j.metabol.2018.12.011
0026-0495/

Caucasians of the same BMI. Newer and more precise definitions will certainly help the field move forward.

Chapelot and Charlot provided a masterful overview of the physiology of energy homeostasis and the cross-talk of hormonal and homeostatic with non-homeostatic processes linked to environmental inputs processed in cognitive and reward centers of the brain to control energy homeostasis. Obesity (or leanness) thus presents the integrated hormonal, neuronal and metabolic response to energy intake and energy expenditure [10]. These authors also focused on the failure of homeostatic responses to energy challenges, including cafeteria diet, overfeeding and diet-induced weight loss. Last but not least, they supported that the set-point theory is currently being challenged and that other models, e.g., energy allostasis, seem more relevant to experimental reports and life preservation [10].

Oussaad et al. subsequently summarized current evidence on the pathogenesis of obesity [11]. They presented established knowledge, e.g., that obesity results as a chronic positive energy balance (relative decrease in energy expenditure and increase in energy intake), but they also reviewed state of the art evidence on central and peripheral mechanisms regulating energy homeostasis [11].

Rohde et al. summarized current knowledge on the genetic and epigenetic underpinnings of monogenic and common obesity, with the latter highlighting the recent advances on how epigenetic modifications may affect the pathogenesis of obesity [12]. Although the rare cases of monogenic obesity expand our understanding on the hypothalamic circuits regulating homeostatic systems and the brain-peripheral organs axes interactions, common obesity is largely multifactorial, thereby resulting from the interplay of genetic, epigenetic and environmental factors, which are integrated in brain centers higher than the hypothalamus. In this regard, multiple genetic variants are linked to the genetic predisposition to human obesity, but each of them adds a little on BMI variability. Non-genetic factors, including social norms, environmental inputs, eating behavior and physical activity significantly modulate the individual risk of obesity, by building upon genetic predisposition for obesity, and interacting with epigenetic modifications [12].

Iacobini et al. compared metabolically unhealthy obesity (MUO) with metabolically healthy obesity (MHO), the latter being a highly debated concept, possibly lying between metabolically healthy normal weight and MUO, when considering the spectrum of cardiometabolic risk [13]. The authors contrasted MHO with MUO regarding the distinct genetic and behavioral factors contributing to each one, as well as their clinical implications. Special emphasis was given on the role of adipose tissue, specifically in determinants of body fat distribution, depot-specific fat metabolism and adipogenesis [13]. Better understanding of the transition from MUO to MHO and a deeper knowledge of the determinants of MHO may possibly allow practices promoting shifting obesity from MUO towards this favorable condition, especially in obese individuals not able to achieve major weight loss.

Nimptsch et al. provided an overview of biomarkers currently available in research and/or clinical practice of obesity [14]. Based on the above limitations of BMI to measure abnormal or excessive fat accumulation, they propose the use of waist circumference in clinical practice as a simple measure that may improve the prediction of abdominal obesity. Imaging, including magnetic resonance imaging, provides a more accurate information on body fat distribution, but is not readily available in routine clinical practice, has high cost and is impaired by the lack of specific cut-offs for cardiometabolic risk [14]. There is also accumulating information on biomarkers reflecting underlying mechanisms, characterizing the distinct phenotypes of obesity and being studied as predictors of risk. Adipokines (e.g. leptin, adiponectin, resistin), molecules of insulin/insulin-like growth factor axis and indices of chronic low-grade inflammation are only some of the proposed biomarkers, which are expected to classify better obese individuals in the near future, thus possibly providing the base for a more personalized management [14].

Vekic et al. addressed the major mechanisms of obesity-induced dyslipidemia and the main characteristics of dyslipidemia in obesity [15]. Noteworthy, the authors reviewed evidence on novel lipid biomarkers in obesity, including microRNAs, proprotein convertase subtilisin/kexin type 9 (PCSK9), the key molecule regulating metabolism of low-density lipoproteins, and sphingosine-1-phosphate, a significant mediator of the function of high-density lipoproteins [15]. Importantly, the authors provided their considerations in the field of obesity-related dyslipidemia warranting further research, thus possibly providing new tools for the prevention and management of obesity-related dyslipidemia and cardiometabolic risk in the future [15].

Polyzos et al. reviewed the association between obesity and NAFLD in terms of epidemiology, pathophysiology and treatment [16]. Obesity has been linked to simple hepatic steatosis, but also with advanced disease, i.e., nonalcoholic steatohepatitis (NASH), NASH-related cirrhosis and hepatocellular carcinoma. This does not simply represent an epidemiologic observation, but has clinical implications, since obesity increases liver-specific mortality in NAFLD patients [16]. Since there is currently no approved medication for NAFLD, targeting obesity is a rational option for the management of NAFLD, proposed by all guidelines. Lifestyle modification (diet and exercise) is strongly recommended, but it is difficult to achieve and sustain. In this regard, several anti-obesity medications have been investigated in NAFLD (e.g., orlistat, glucagon-like peptide [GLP]-1 analogs) with encouraging results. However, there are more medications (e.g., lorcaserin, phentermine hydrochloric, phentermine/topiramate and naltrexone/bupropion), whose anti-obesity effect warrants further investigation specifically in NAFLD patients. If the combination of lifestyle modification and pharmacotherapy also fails, then bariatric surgery may be considered in selected morbidly obese individuals with NAFLD [16].

Koliaki et al. critically updated the traditional and novel pathophysiological links between obesity and CVD, including hypertension, coronary heart disease, atrial fibrillation, heart failure, stroke and sudden cardiac death, but also the impact of weight loss interventions on CVD [17]. They supported that obesity may directly augment CVD risk through adipokine alterations, thereby affecting vascular homeostasis and inflammation, but also through structural and functional adaptations of the cardiovascular system to excess body weight. Obesity may also indirectly increase CVD risk, by affecting related factors, including insulin resistance, blood pressure, glucose and lipid metabolism [17]. In this regard, CVD may represent a maladaptive response to adipose tissue expansion and impaired function, observed in obesity [17].

Glueck and Goldenberg reviewed the association between obesity and polycystic ovary syndrome (PCOS) [18]. In particular, the authors recapitulated how visceral adiposity amplifies and worsens metabolic and reproductive outcomes in PCOS, how obesity sensitizes thecal cells to luteinizing hormone stimulation and how it upregulates ovarian androgen production, thus amplifying functional ovarian hyperandrogenism. They also underlined adipokines as a mediator among obesity, insulin resistance and adipogenesis [18]. Lifestyle modification (diet and exercise) is a key in the management of PCOS in obese individuals, which, however, is commonly followed by the addition of pharmacologic therapy. Bariatric surgery may be also required for selective morbidly obese women with PCOS, who are unresponsive to lifestyle and pharmacologic management [18].

Avgerinos et al. summarized epidemiologic evidence linking obesity with malignancies, including esophageal, pancreatic, renal and endometrial adenocarcinomas, gastric, colorectal, postmenopausal breast, ovarian, gallbladder and thyroid cancers, hepatocellular carcinoma, and multiple myeloma, underlying that about 12–13% of the global cancer burden is attributed to obesity [19]. The authors also focused on potential interplaying mechanisms between obesity and malignancies, on the role of weight gain and weight loss in the modulation of cancer risk, and on future perspectives regarding prevention and management of cancer by targeting obesity [19].

López-Suárez addressed a similar topic from another scientific angle: the dynamic interplay between obesity and T2DM, and their synergistic effect on cancer risk [20]. The author reported epidemiologic risk factors affecting the triangle of obesity, T2DM and cancer, such as

physical inactivity, unhealthy diet and excessive alcohol intake, and suggested education as a longitudinal investment to promote public health, thus reducing the burden of obesity and T2DM related cancer and reducing their economic burden to health systems [20].

Weihrauch-Blüher et al. highlighted the increasing prevalence of childhood obesity worldwide (that has been more than doubled since 1980), its complex underlying factors (that may be similar, but also distinct from those in adults) and its concomitant diseases [21]. Noteworthy, the authors provided their expert opinion on the prevention and management of childhood obesity, including lifestyle modification, behavioral intervention, but also measures to limit the effect of obesogenic environment [21]. They underscored the importance of normalization of body weight before the onset of puberty, so as to reduce the risk of obesity, T2DM, CVD and malignancies, such as leukemia, Hodgkin's disease, colorectal cancer and breast cancer, in adulthood [21].

Yannakoulia et al. critically summarized evidence on dietary schemes for weight loss and weight maintenance published after 2013 [22], when the obesity management guidelines of the American Heart Association (AHA), American College of Cardiology (ACC) and The Obesity Society (TOS) recommended that any dietary scheme is effective for weight loss, as long as it can induce a sustainable energy deficit [23]. The authors supported that this principle has not essentially changed since then, given that evidence continuous to favor that mainly energy deficit and not a specific dietary scheme, i.e., based on nutrient, food group or dietary pattern, is the main driving mechanism for achieving weight loss [22]. Although there are less data for dietary interventions achieving weight loss maintenance, it seems that limited data also favor that the major driving is similarly energy deficit rather than diet composition. However, we should hereby highlight that, apart from the weight loss effect, diet composition may affect cardiovascular and metabolic parameters; in this regard, Mediterranean diet is to-date the only diet that has shown beneficial metabolic and cardiovascular effects, ranging from basic research to epidemiological and to clinical trials in Europe, albeit it remains to be shown in other regions of the world [24]. Notably, there is to-date no randomized controlled trial to investigate the combination of Mediterranean diet with anti-obesity medications, especially in populations with high prevalence of obesity, such as the US population.

Petridou et al. highlighted evidence on regular exercise for weight loss and weight loss maintenance, the latter being a greater challenge. The authors supported that ideal exercise programs should target on negative energy balance, long-term adherence and beneficial effects on health and well-being, emphasizing that exercise is valuable in obesity, even in the absence of weight loss, apparently due to its fat loss effect [25]. The association between higher levels of physical activity and greater weight loss maintenance is regarded as established, but there are also distinct roles for endurance, resistance training and high-intensity interval training for weight loss and weight loss maintenance [25]. Interestingly, the authors also provided their expert opinion on the potential misuse of exercise in obese individuals and the potential adverse effects, when more exercise than needed is provided [25].

Pilitsi et al. reviewed extensively the pharmacological management of obesity, which is valuable when lifestyle and behavioral modifications fail to achieve or maintain the predefined target on weight loss [26]. It seems that current anti-obesity medications, including orlistat, lorcaserin, liraglutide and the combinations of phentermine/topiramate and naltrexone/bupropion lead to an additional weight loss of 3–8%, when added onto lifestyle modifications, which however may be translated into multiple metabolic and cardiovascular benefits [26]. Of note, the authors also summarized evidence on emerging anti-obesity medications, including those approved for other related diseases, e.g., GLP-1 analogs and sodium-glucose cotransporter (SGLT)-2 inhibitors approved as anti-diabetic medications, but also those being under investigation in phase 1–3 clinical trials [26].

Bassatne et al. systematically reviewed the randomized controlled trials on oral vitamin D administration in obese individuals (with or without weight loss), as well as in morbidly obese individuals subjected to bariatric surgery [27]. The authors reported that mean baseline 25-hydroxyvitamin D levels were < 30 ng/ml in all studies, being below the appropriate cut-off proposed by the Endocrine Society guidelines [28]. Based on their systematic review, the authors recommended that vitamin D (cholecalciferol) administration ≥1600 IU/d may be needed in obese and ≥ 2000 IU/d in severely obese individuals subjected to bariatric surgery to increase 25-hydroxyvitamin D levels >30 ng/ml [27]. Nevertheless, vitamin D administration had no effect on weight loss, and its effect on weight loss-induced bone loss, low-energy fractures, glycemic and vascular indices in obesity currently remains inconsistent, thus warranting further well-designed randomized controlled trials [27].

Nudel and Sanchez focused on common (sleeve gastrectomy and Roux-en-Y gastric bypass are the most common procedures) and emerging (e.g., endoscopic interventions) bariatric surgery procedures, their comparative benefits and risks in severely obese individuals, as well as the criteria to select the appropriate procedure for each candidate [29]. The authors also outlined the major mechanism through which bariatric surgery induces weight loss and metabolic benefits on obesity-related morbidity, including T2DM, NAFLD and CVD. Importantly, the increasing need for weight loss revision surgery is also discussed [29]. Finally, the authors underlined that bariatric surgery is under-utilized and suggested an improvement in access and delivery of severely obese candidates to surgical centers with significant expertise [29]; it has been estimated that <1% of eligible patients meeting the National Institutes of Health criteria for bariatric surgery actually undergo surgery [30]. However, since metabolic improvement following bariatric surgery helps us to elucidate underlying mechanisms in obesity, this deeper knowledge may possibly lead to the development of novel therapeutics that would eventually and progressively limit the use of bariatric surgery.

3. Closing Remarks

The obesity epidemic has been remaining an important public health issue for at least five decades and is apparent in almost all countries. An even more alarming issue is the escalading prevalence of childhood obesity, which may imply that obesity and its short and long-term individual, social and economic consequences will be there in the future [31], possibly even more enlarged, if preventive measures are not be globally applied.

Managing obesity is hard and usually disappointing for both patients and physicians. Weight loss is difficult to achieve and even more difficult to sustain in the long-term [26]. When lifestyle modifications fails to achieve the predefined target, anti-obesity medications may be added on, as recommended by all relevant guidelines, including those of the Endocrine Society [32] and recent guidelines for obese with diabetes [33]. However, anti-obesity medications, most of which have not been approved for long-term use, usually result in weight loss <10% and then reach a plateau. Moreover the discontinuation of anti-obesity medications leads to weight regain in the most patients [26]. Especially in obese with T2DM, which are commonly encountered in daily practice, most recent guidelines underlined the importance of weight loss and recommended the necessity of intensive lifestyle management, including food substitution, increasing physical activity and sustained counseling (12–26 individual counseling sessions over 6–12 months) [33]. At a second stage, food substitution should be followed by gradual reintroduction of food [33]. It should be also highlighted that many medications prescribed in daily practice for diabetes, depression and other chronic diseases may either promote weight gain (e.g., insulin, sulfonylureas, thiazolidinediones, tricyclic antidepressants, glucocorticoids) or produce weight loss (e.g., GLP-1 analogs, SGLT-2 inhibitors, bupropion, zonisamide, methylphenidate) [32]. Whenever possible, prescribing these medications should be directed towards those favoring weight loss and avoiding weight gain in overweight/obese individuals [32,33].

Although more efficient medications may be released in the future, fighting obesity should be redirected towards its prevention, which is a complex issue requiring the long-term will and collaboration of the international agencies, governments, industry and, most importantly, each one citizen, so as to start building a less obesogenic future [34]. WHO has introduced a voluntary framework (Global Strategy on Diet, Physical Activity and Health: A framework to monitor and evaluate implementation; http://apps.who.int/iris/bitstream/handle/10665/43524/9789241594547_eng.pdf;jsessionid=5E1254DB86E64E7D430D0D447202F4BD?sequence=1) for action on children and adult obesity, targeting to stop the rise in obesity by 2025 [34]. This framework includes a wide range of health service policies, health promotion programs, food-related environments, physical activity and socioeconomic determinants of health, and is linked to WHO strategies for the prevention of non-communicable diseases [34]. Of course, federal and local governments need to lead obesity prevention. There are sporadic efforts towards this direction. For example, there are initiatives trying to support local implementation and data collection, analysis and reporting at local and state levels, such as the Healthy Children Initiative, having been delivered in New South Wales, Australia since 2011, to support implementation of childhood obesity prevention programs at scale [35]. Other examples are the attempts towards the nutritional quality of products sold in elementary schools [36] or universities [37]. More ambitiously, cities need to be re-designed towards favoring less obesogenic living and education in schools towards a less obesogenic behavior. Nonetheless, governmental policies may be complicated by the fact that preventive obesity measures may possibly need decades to be fruitful, whereas many governments are looking for actions producing shorter-term results.

Scientific evidence on preventive measures for obesity is currently limited. Beyond health benefits, the prevention of obesity should be more spherically projected, since monitoring of obesity trends worldwide, distinct social and economic environments, policy changes and cost should be taken into consideration. In this regard, advanced mathematical modelling currently provides important insights into comparative cost-effectiveness, thus program analyses have indicated that several models may be cost-effective for obesity prevention [34]. Artificial intelligence for integration of multiple converging factors to understand pathophysiology of obesity and then for building predictive models and later diagnostic and therapeutic algorithms has been appeared and seem to be implemented more in the near future [38].

Furthermore, there are some initiatives on obesity education and training deserving mentioning, such as the American Board of Obesity Medicine (ABOM) (https://www.abom.org) and the Strategic Centre for Obesity Professional Education (SCOPE) (https://www.worldobesity.org/training-and-events/training/scope). They both provide up-to-date evidence-based education on obesity, access on relevant resources and certify physicians as having achieved competency in obesity care. Another initiative is the "Obesity Medicine Education Collaborative" (OMEC), which was formed in 2016 and supported by many scientific organization of obesity, including the Obesity Medicine Association, TOS, Endocrine Society, American Association of Clinical Endocrinologists, World Obesity Federation, American Society for Metabolic and Bariatric Surgery (https://obesitymedicine.org/omec/). The aim of OMEC is the promotion and dissemination of comprehensive obesity education across the continuum spanning undergraduate medical education, graduate medical education and fellowship training. For this purpose, a steering committee collaborated to develop 32 obesity-related competencies with specific measurement and assessment benchmarks. After external reviewing by 17 professional societies and organizations, a final document was completed in 2018, which is intended to be used by medical, nursing and physician assistant educators.

This issue of metabolism is devoted to obesity, a globally present disease, with the wish that policymakers will proceed to the appropriate steps to motivate the industry, the scientists, the physicians and the citizens (especially children) towards a less obesogenic lifestyle. In our opinion, education starting from the very early age is probably the most effective, and possibly the unique, preventive measure to a less fatty future. Even speaking with strict economic terms, education should be considered as an investment that will fructify over the next two or three decades in terms of public health and economic burden.

Funding

No sources of financial support for this study.

Disclosure statement

SAP received a consulting fee from InteKrin Therapeutics Inc.; CSM has served as a consultant for Astra Zeneca, Takeda, Coherus, Aegerion and NovoNordisk and is shareholder of Coherus, Pangea Inc. and Novo Nordisk.

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