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Review

Metabolic regulation and the anti-obesity perspectives of brown adipose tissue (BAT); a systematic review

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ABSTRACT

Background: Obesity is a disease that body energy intake is more than energy expenditure. In rodents and humans, there are two types of adipose tissue: White adipose tissue and Brown adipose tissue. Whereas WAT stores excess energy as triacylglycerols, BAT is specialized in the production of heat.
Methods: PubMed and Cochrane databases were searched using the related keywords to find related documents published until August 2019. In total, 115 published reports were reviewed in the study.
Results: Obesity associated with different diseases such as type 2 diabetes, cardiovascular disease, hypertension, stroke, arthritis, and various types of cancer. Until recent years, it treated in various ways, such as diet, physical activity, using medications, and surgical procedures. In recent years, Brown adipose tissue has been recognized as a way to combat obesity and metabolic regulation.
Conclusions: Recent years are challenging times for all those working in the field of obesity and the pace of discovery about obesity than ever before. During the last decades, many notable discoveries resulting from the active research into the pathophysiological mechanisms controlling food intake, energy expenditure, and body fat mass have been produced. Potential new avenues are opened for the future treatment of obesity by the recent findings and its related disorders, although finding practical solutions to the problems posed by obesity could ultimately depend as much on clever science and good clinical practice as on actively engaging the individual and society alike to change everyday lifestyle.

1. Introduction

Obesity as the same as other metabolic disorders is a global problem and it is a disease that body energy intake is more than energy expenditure. Thus it can be treated by reducing food intake and/or increasing energy expenditure (EE)(Kajimura and Saito, 2014). A large portion of the resting energy expenditure is spent on thermoregulation (Lee and Greenfield, 2015).

Adipose tissue is a central metabolic organ that controls energy homeostasis and it can be subcategorized into WAT and BAT. WAT stores excess energy as triglycerides (TG) and mobilizes it into free fatty acid upon systemic demands. On other hand, BAT is a specialized thermoregulatory organ that generates heat through uncoupling protein 1 (UCP1)-dependent non-shivering thermogenesis (cannon and Nedergaard, 2004). Thus, activation of brown adipocyte metabolic activity has been investigated as a potential therapeutic target to increase energy expenditure, and ultimately, to counteract obesity and its related metabolic diseases (Chondronikola et al., 2016).

This study, based on previous research in this area, will introduce obesity, adipose tissue, its variants and the impact of BAT and obesity.

2. Methods

Two authors (Milad Dodangeh and Masoud Dodangeh) independently performed a search of PubMed and the Cochrane Database of Systematic Reviews through August 2019. Search terms were Obesity, Adipose tissue, White adipose tissue (WAT), Brown adipose tissue (BAT) and the search was limited to publications in English. We searched the keywords, both as free terms and in combination with MeSH (medical subject headings) in PubMed.

Titles and abstracts of the resulting articles were examined, and full-text articles were retrieved after excluding non-eligible ones. Bibliographic references of recovered articles were examined to look for additional studies.

3. Results

A total of 1158 observational studies were retrieved electronically

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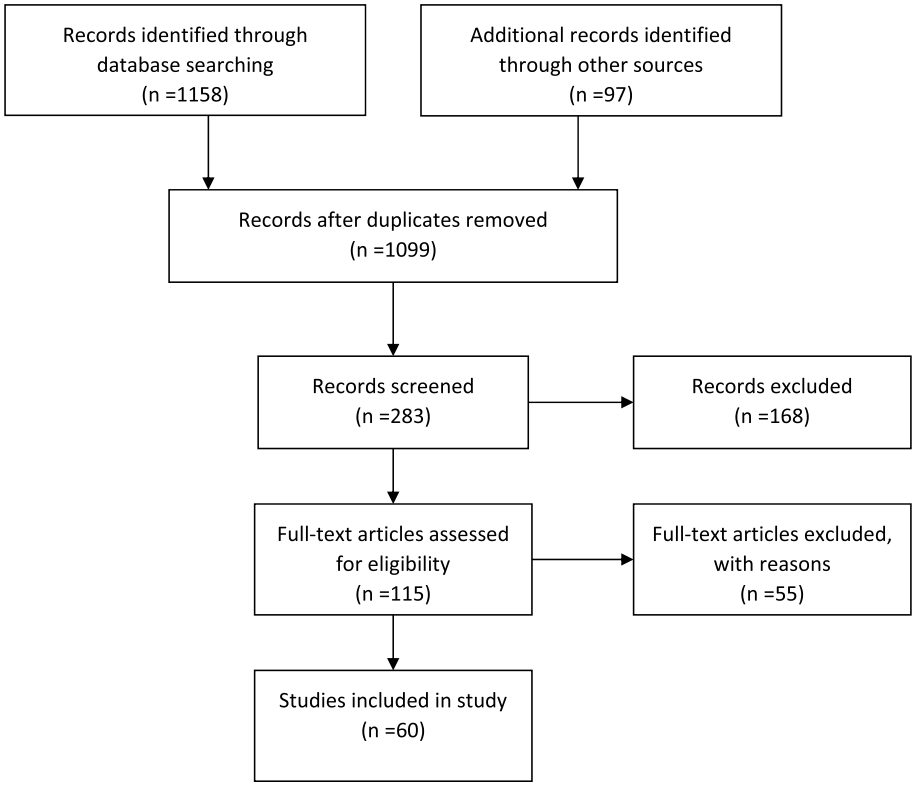

Fig. 1. Follow diagram of search results.

from PubMed and Cochrane, and 97 studies were identified by other sources. Endnote software was used to screen the references for duplication and 156 references were deleted. 283 articles were selected for abstract assessment based on titles. After an abstract assessment, we selected 115 studies for further evaluation by full-text assessment. (Fig. 1)

4. Manuscript

4.1. Obesity

Although obesity has been recognized as significant global health, social and economic problem for many years, the obesity epidemic is continuing without signs of abatement (James, 2008). The obesity epidemic is increasing sharply at an alarming rate; thus the pandemic of obesity and overweight poses a severe threat to global public health and nations (Kelly et al., 2008). Literature demonstrated that over 50% of the world's population is in the overweight or obese category (Kelly et al., 2008). In 1995, there were an estimated 200 million obese adults worldwide. However, by the year 2000, the number had grown to 300 million and has continued to increase since then (Agha and Agha, 2017). In 2018, The prevalence of overweight and obesity in Iran was 34.5% and 21.5% (Kolahi et al., 2018).

Energy intake is more than energy expenditure in obese people. Thus, Obesity and overweight caused by 1)High-calorie food 2) Sedentary life (Cohen and Spiegelman, 2016; Scherer et al., 1995; Stanford et al., 2013; Thomou et al., 2017). Accumulation of excess dysfunctional adipose tissue is pathological. Obesity is a major biomedical challenge with its associated diseases, particularly for type 2 diabetes, cardiovascular disease, hypertension, stroke, arthritis, and various types of cancer, imposing a substantial and increasing burden on healthcare systems (Bray and Bellanger, 2006) and Governments spend a great deal on the treatment of these diseases and these costs increase sharply every year. The obesity and overweight treat simply, if energy expenditure exceeds energy intake; thus reducing high-calorie food and increasing exercise helps to combat obesity.

Although many years have been known that the metabolic impact of sex hormones (estrogen, testosterone) effect on obesity, the hormonal role of BAT related to male or female gender has only recently been suggested.

4.2. Adipose tissue

Adipose tissue includes various cell types. The most important cell types are adipocytes, adipose-derived stem cells (ADSC's), preadipocytes, and immune cells. Increasing the size of existing mature adipocytes (hypertrophy) and to some extent increasing in preadipocyte and adipocyte numbers (adipogenesis) is the cause of adipose tissue expands during periods of chronic positive energy imbalance (Prins and O'rahilly, 1997; Rosen and Spiegelman, 2000).

There are two types of adipose tissue in rodents and humans (Frayn, 2010):

1) White adipose tissue (WAT)
2) Brown adipose tissue (BAT)

Whereas WAT stores excess energy as triacylglycerols, BAT is specialized in the production of heat (Frühbeck et al., 2009). WAT or BAT has a unique developmental gene that is independent of the nutritional state (Yamamoto et al., 2010).

4.2.1. White adipose tissue (WAT)

WAT stores energy in the form of triglycerides and releases energy when the body needs energy such as during physical activity or fasting (Frayn, 2010). WAT is characterized by various features, such as large unilocular lipid droplets, limited mitochondria and is innervated by the sympathetic and parasympathetic nervous systems (Bamshad et al., 1998; Bartness and Bamshad, 1998; Bowers et al., 2004; Youngstrom and Bartness, 1995). WAT exists in multiple locations in the body and

two major subtypes are visceral and subcutaneous. Visceral WAT (vWAT) accommodates around the internal organs and visceral WAT is associated with insulin resistance, increased incidences of atherosclerosis, altered lipid profile, increased risk for type 2 diabetes, and overall mortality (Carey et al., 1997; Nicklas et al., 2006; Ross et al., 2008; Wang et al., 2005).

Subcutaneous WAT (scWAT) is like a peripherally located depot that associate with increased insulin sensitivity and decreasing rates of type 2 diabetes, atherosclerosis, and dyslipidemia (Misra et al., 1997; Snijder et al., 2003; Tankó et al., 2003).

4.2.2. Brown adipose tissue (BAT)

In 1551, Gessner identified Brown Adipose Tissue (BAT) in the inter-scapular area of marmots (Smith and Horwitz, 1969). In rodents, BAT is found primarily in the inter-scapular region and the axillae, whereas minor amounts are found near to the thymus and in the dorsal midline region of the thorax and abdomen. In the human neonates, BAT is found in conspicuous depots mainly in the neck, mediastinum, surrounding the great vessels and around the kidneys (Nedergaard et al., 2007). BAT is more prominent in females and younger people and subjects. With age, BAT declines disproportionately more in males. In newborn infants about 5 percent of the body mass is BAT. BAT is very essential for infants to avoid critical body cold (Kozak, 2010; Ravussin and Kozak, 2009).

The initial theory was that it was linked to hibernation, reflecting the fact that marmots are hibernating animals. Sequentially this theory was followed by the view that BAT was a part of the thymus (1670–1817), an endocrine gland active in the formation of blood (1817–1863), a modified form of fat tissue providing a reservoir for food substances (1863–1902), and again as an endocrine gland (1902–1961). In 1961, the effecter of non-shivering thermogenesis (NST) and the “metabolic power” of brown adipocytes finally identified (Smith and Horwitz, 1969).

There were three situations where BAT was understood to be highly active (Smith and Horwitz, 1969):

1) During arousal from hibernation
2) In response to cold-exposure of certain adult mammals
3) In cold-stressed mammalian neonates

BAT is characterized by high levels of mitochondria (Cannon and Nedergaard, 2004), multilocular lipid droplets (Rothwell and Stock, 1983), a high degree of vascularization (Fawcett, 1952), and sympathetic innervation (Cannon and Nedergaard, 2004). UCP1 creates a ‘leaky’ proton channel (Matthias et al., 2000) in the mitochondria that uncouples mitochondrial proton pumping from ATP production, resulting in increased release of heat as part of the process of non-shivering thermogenesis. Activated BAT increases sympathetic signaling through norepinephrine, which stimulates β3-adrenergic receptors and initiates lipolytic processes to liberate free fatty acids in the cytosol (Bieber et al., 1975; Cannon and Nedergaard, 2004; Kuusela et al., 1986).

4.3. Evidence for anti-obesity functions of BAT

Although many years have been known that the metabolic impact of sex hormones (estrogen, testosterone) effect on obesity, the hormonal role of BAT related to male or female gender has only recently been suggested (Pfannenberg et al., 2010).

In rodents the early scientific evidence to ascribe BAT anti-obesity functions came from experiments in which the surgical denervation or excision of inter-scapular BAT was followed by an abnormal increase in the amounts of WAT in those animals (Hansen and Kristiansen, 2006). Targeted disruption of Cidea (cell-death inducing DFF45-like effector A), which inhibits the uncoupling activity of the UCP1 protein, results in lean mice that are resistant to diet-induced obesity (Zhou et al., 2003). Additional examples of the relevance of BAT against the development of obesity come from genetically obese mouse models like the ob/ob and db/db strains where BAT is dysfunctional (Hansen and Kristiansen, 2006). Finally, in most rodent models proneness to obesity reportedly correlates with decreased BAT activity, whereas resistance to obesity correlates with increased BAT function or the induction of brown-adipocyte-like gene expression in WAT(Cannon and Nedergaard, 2004; Hansen and Kristiansen, 2006; Kozak and Anunciado-Koza, 2008). Adipocytes in culture, glucose uptake is directly adrenergically stimulated, whereas stimulated thermogenesis is a prerequisite for FDG uptake in BAT in vivo (Nedergaard et al., 2007).

The treatment of obesity is one of the thorniest issues in obesity. Until recent years, BAT was an under-researched area in humans. Given the current worldwide concern posed by the obesity epidemic, it is exciting to contemplate translational applications related to a BAT-derived increase in energy expenditure in obese individuals as a therapeutic alternative based on a new conceptual strategy (Hanssen et al., 2016, 2015).

The latest findings in humans provide evidence that defined regions of BAT can be quantified noninvasively by FDG–PET/CT in adults (Cypess et al., 2009; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009). Until recent years it was assumed that only vestigial amount of BAT was present in adulthood. Thus, stimulating BAT had generally been discarded as a pharmacological option for human obesity therapy. However, recently [^{18}F]-2-fluoro-D-2-deoxy-D-glucose (FDG) positron emission tomography (PET) has clearly shown that BAT is present mainly in cervical, supraclavicular, axillary and paravertebral regions of adult humans and might, thus, be considered to be both a physiological and pharmaceutical target (Hany et al., 2002; Nedergaard et al., 2007; Wijers et al., 2009).

The acute stimulatory effects of cold on BAT and prolonged cold exposure produce not only BAT hyperplasia but also a remarkable induction of beige adipocytes, both of them contribute to increased EE (Saito, 2015; van Marken Lichtenbelt and Daanen, 2003). Van Ooijen et al.(Vanooijen et al., 2004) showed that, during cold exposure, non-shivering thermogenesis in winter is significantly higher compared with summer, in the same volunteers. Moreover, subjects without BAT activity show significantly lower non-shivering thermogenesis (Vijgen et al., 2011; Yoneshiro et al., 2011). A study in healthy humans using indirect calorimetry and stable isotopes showed that cold exposure increased the resting metabolic rate of 14% in subjects who had detectable BAT levels and that this increase was fueled by both plasma-derived glucose (30%) and free fatty acid oxidation (70%)(Chondronikola et al., 2014). However, the relatively small contribution of fully active BAT in average whole-body energy consumption does not make it a viable weight loss goal.

In overweight and obese individuals BAT activity is reportedly lower than in lean subjects (van Marken Lichtenbelt et al., 2009). Literature demonstrated that BMI and body fat percentage showed an inverse correlation with BAT, resting metabolic rate exhibited a positive correlation with BAT activity and higher levels of BAT might protect against age-related obesity (Cypess et al., 2009). In overweight and obesity treatment any intervention that causes a negative energy balance is guaranteed to be effective in producing weight loss. It has been calculated that affecting energy balance by as little as 50–100 kcal/day, an easily attainable target, could prevent weight gain in most of the population (Hill et al., 2003). Even more, evidence-based guidelines have recognized the clinical benefits of moderate 5–10% weight loss (Hainer et al., 2008).

There are two strategies for generating functional adipose tissue:

1) The first one based on autologous BAT transplantation proved ineffective. But free fat transplants rarely achieve sufficient functional tissue because of deficient neovascularization and cell necrosis (Tanzi and Farè, 2009).

2) The second one is fat tissue bioengineering, the use of adult mesenchymal cells and preadipocytes that appears to be more promising (Tseng et al., 2010).

BAT is a potential therapeutic target to improve the comorbidities associated with obesity due to its inherent thermogenic capacity and its ability to improve glucose metabolism (White et al., 2019).

5. Conclusions

Recent years are challenging times for all those working in the field of obesity and the pace of discovery about obesity than ever before. The next decade will be crucial for testing our collective ability to limit the spread and impact of obesity. During the last decades, many notable discoveries resulting from the active research into the pathophysiological mechanisms controlling food intake, energy expenditure, and body fat mass have been produced. In the next years, new candidate signals are sure to be identified. In this context, it is difficult to envision that in given clinical situations an ultimate all-powerful controller of energy balance, able to over-ride all other regulatory systems, will be found to be applied with therapeutic purposes. Noteworthy, from a teleological perspective, the co-existence of numerous systems that are designed to come into play under particular circumstances to control specific aspects of feeding behavior and energy balance seems to prevail over a single top-down hierarchy. It remains to be seen whether these parallel mechanisms, which have evolved to protect energy stores that are essential for survival and reproduction, can be counterbalanced and superseded by a surplus of induced energy expenditure via BAT manipulation. Moreover, the benefit and full value of these new findings will only be translated into practice if they can be integrated with the everyday scenario of human obesity and if the acquired knowledge can be usefully exploited in individuals. This is particularly challenging in humans, where further layers of complexity are added by the numerous psychological, social and cultural factors that shape eating behavior and physical activity. Undoubtedly, the recent findings open potential new avenues for the future treatment of obesity and its related disorders, although finding practical solutions to the problems posed by obesity could ultimately depend as much on clever science and good clinical practice as on actively engaging the individual and society alike to change everyday lifestyle.

Declaration of competing interest

Not Applicable.

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List of abbreviations:

EE	Energy expenditure
TG	Triglycerides
UCP1	Uncoupling protein 1
WAT	White adipose tissue
BAT	Brown adipose tissue
MeSH	Medical subject headings
ADSC's	Adipose-derived stem cells
vWAT	Visceral WAT
scWAT	Subcutaneous WAT
FDG	[^{18}F]-2-fluoro-D-2-deoxy-D-glucose
PET	Positron emission tomography
Cidea	Cell-death inducing DFF45-like effector A

Ethics approval and consent to participate

Not Applicable.

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Availability of data and material

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Authors' contributions

Both authors wrote the manuscript and contributed equally. Also, both authors read and approved the final manuscript.

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