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## Review Article

Indian J Med Res 149, May 2019, pp 610-615

DOI: 10.4103/ijmr.IJMR\_2120\_18

# ‘Obesageing’: Linking obesity & ageing

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Received November 20, 2018

**Obesity is one of the leading causes of preventable mortalities in many parts of the globe. The rise in geriatric population due to better treatment opportunities has also emerged as a major public health challenge. Both of these health challenges have impacted developed as well as developing countries. Obesity is attributed as a powerful risk factor of a variety of health problems such as cardiovascular diseases, hypertension, type 2 diabetes, dementia, neuropsychiatric diseases and many more. On the other hand, ageing is a natural process involving a gradual decline in physiological functions and is associated with similar co-morbidities as obesity. This review discusses about the commonalities (termed as ‘Obesageing’) between the pathological phenomenon of obesity and normal physiological process of ageing. A unique rodent model of obesageing has been developed (WNIN/Ob) that has characteristics of morbid obesity as well as premature ageing. Such a novel animal model would facilitate the understanding of the complex interplay of different mechanisms that are common to obesity and ageing and help to devise strategies in future to tackle the growing burden of obesity and ageing.**

**Key words** Accelerated ageing - cognitive decline - dementia - inflammation - nicotinamide adenine dinucleotide - oxidative stress - Wistar of National Institute of Nutrition obese rat

## Introduction

The increase in the aged population and obesity has emerged as major public health issues globally. On one hand, the geriatric population is increasing at a rapid rate, with an estimation that by 2050, there will be more than two billion people above 60 yr of age<sup>1,2</sup>. On the other hand, obesity and its associated co-morbidities have already become an epidemic in most of the developed and developing countries, causing more than four million deaths annually<sup>3</sup>. Both ageing and obesity are associated with an array

of co-morbidities such as cardiovascular diseases, type 2 diabetes mellitus (T2DM) and certain types of cancer<sup>4-6</sup>. Further, normal physiological ageing and the pathological condition obesity have biological similarities in being complex multifactorial processes with the involvement of chronic inflammation, insulin resistance, oxidative stress and DNA damage<sup>7-9</sup>.

It is evident that obesity and its associated metabolic disturbances can speed up the rate of ageing and lead to early mortality<sup>10-12</sup>. With the alarming increase in the incidence of obesity and related co-morbidities,

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improving the quality of life in the geriatric population remains a challenging task<sup>13</sup>. Hence, understanding the complex interplay between obesity and ageing will help in deciphering the pathophysiology of obesity-induced accelerated ageing. This in turn, will eventually lead to the development of newer strategies to improve the quality of life in the geriatric population to reduce the disease burden. In this review, the concept of 'Obesageing' has been proposed to explain the overlap between obesity and ageing.

### **Obesity and longevity**

Diverse approaches have been tried in the past, and others continue to be under trial to increase longevity, and to promote healthy ageing. In the list of avoidable causes of demise, obesity beats all the other health conditions. This makes it one of the most serious health concerns of the 21<sup>st</sup> century<sup>14</sup>. The excess accumulated body fat causes obesity leading to reduced longevity in humans and other animals<sup>6,7</sup>. Factors influencing the lifespan of an individual include different genetic conditions, chronic disorders and lifestyle-related disorders such as obesity, cardiovascular diseases and T2DM<sup>10,15</sup>. Many studies have linked obesity to reduced longevity and accelerated ageing<sup>10,16-19</sup>. Studies show that maternal deficiency of micronutrients such as vitamin B12 predisposes the mother as well as the next generation to obesity and various behavioural anomalies including depression that are known to incite hyperphagia<sup>20-22</sup>. Hence, populations in which the deficiency of micronutrients exists, the possibility of obesity and its co-morbidities increases significantly. Chronic inflammation caused by altered adipokine signalling<sup>23</sup> and oxidative stress<sup>24</sup> is considered to be the probable underlying mechanism in obesageing. Further, the degree of ageing in various tissues is also associated with augmented oxidative stress<sup>25,26</sup>. To understand how obesity affects different tissues and organs to accelerate the ageing process and the complex interplay of obesity and ageing, it is of utmost importance to develop appropriate animal models.

### **Unique rodent model of obesageing**

At the ICMR-National Institute of Nutrition, Hyderabad, researchers have developed the Wistar of National Institute of Nutrition obese (WNIN/Ob) rat strain from WNIN rats using the selective backcrossing. This rat model showed morbid obesity<sup>27</sup> and considerably decreased longevity (1½ yr as compared to approximately three years in normal WNIN rats). This is the first known obese and inbred mutant rat

model with body weight up to 1.47 kg. They exhibit a typical 1:2:1 Mendelian ratio in the distribution of phenotypes (+/+lean, ±carrier and -/-obese)<sup>27</sup>. The mode of inheritance in these rats is autosomal incomplete dominance. These rats are euglycaemic and show characteristic features of metabolic syndrome such as insulin resistance, hyperinsulinaemia, hyperleptinaemia, hypertriglyceridaemia and hypercholesterolaemia. They are hyperphagic and show polydipsia, proteinuria, and polyuria along with other secondary complexities associated with metabolic syndrome. These rats also exhibit leptin resistance, but the coding sequence of leptin and its receptor remains unchanged<sup>28</sup>. Experiments on WNIN/Ob rats revealed the existence of a mutation in the 4.3 cM region with flanking markers - D5Rat256 and D5Wox37 on chromosome 5 upstream of leptin receptor<sup>28</sup>. Leptin gene promoter methylation was found to be impaired in these WNIN/Ob rats<sup>29</sup>. In addition, these rats exhibit numerous health issues that are often associated with ageing such as infertility, compromised immunity, cataract, retinal degeneration, polycystic ovaries and various kinds of tumours<sup>30-32</sup>. Altered ubiquitin-proteasome system, existence of endoplasmic reticulum stress, upregulation of apoptosis and its markers have also been reported in the cerebral cortex of WNIN/Ob rats<sup>33</sup>. All these studies demonstrated WNIN/Ob rats to be an appropriate model of obesageing.

### **Common underlying mechanisms in ageing and obesity**

Both ageing and obesity are characterized by a gradual decline of function of various organs that eventually disrupt homeostasis<sup>34,35</sup>. Excessive reactive oxygen species (ROS) production underlies both ageing and obesity. ROS is well known to shorten telomere length<sup>36,37</sup> and increase oxidative damage to macromolecules leading to cell death<sup>38</sup>. Further, accumulation of DNA damage is the common hallmark of both ageing and obesity<sup>7,39</sup>. DNA damage is caused by several factors such as oxidative damage, telomere attrition, stress, *etc*<sup>40</sup> all of which are involved in the pathogenesis of obesity- and ageing-related disorders.

Obesity is considered to be an inflammatory condition represented by elevated levels of inflammatory cytokines<sup>41</sup>. Similarly, chronic low-grade inflammation is common in ageing<sup>42</sup>. As ageing is characterized by a progressive increase in the proinflammatory status, it is also referred to as 'inflammageing'<sup>43</sup>. In aged individuals with obesity, elevated levels of inflammatory markers such as

C-reactive protein, interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF- $\alpha$ ) have been reported<sup>44,45</sup>. Adipokines play a significant role in metabolic regulation during ageing and obesity. In obese individuals, the adiponectin levels are found to be at low concentrations<sup>46,47</sup>. In such a scenario, the anti-inflammatory and insulin sensitivity benefits rendered by adiponectin are diminished. On the other hand, centenarians are privileged to have higher levels of adiponectin, thereby establishing its protective role in healthy ageing<sup>48</sup>.

The decline in the stem cell population is yet another characteristic of ageing<sup>49</sup>. Once stem cells start declining in number and efficiency, the regenerative capacity of that organ decreases substantially. Likewise, in obesity, mesenchymal stem cells derived from adipose tissue are immensely affected<sup>50</sup>. Further, there is evidence that in obese individuals, these stem cells have upregulated inflammatory genes and impaired angiogenic and adipogenic differentiation<sup>51,52</sup>. Animal studies in the WNIN/Ob rats also show that adipose tissue and bone marrow-derived mesenchymal stem cells present features of enhanced inflammation<sup>53,54</sup>.

Recent studies have elucidated the influence of nicotinamide adenine dinucleotide (NAD) in the processes of ageing and obesity. NAD is well established to play a key role in cellular signalling and brain energy metabolism. During chronological ageing, the NAD levels decline significantly, which negatively affects mitochondrial function and sirtuin activity<sup>55</sup>. Studies show when the levels of NAD are augmented using its precursors such as nicotinamide mononucleotide and nicotinamide riboside, it relieves age-associated physiological decline and enhances longevity<sup>55</sup>. Further, there is evidence that obesity is associated with reduced functioning of NAD and sirtuin pathway in adipose tissue<sup>56</sup>. Therefore, more research is advocated using NAD precursors in obesageing as it holds promises for addressing obesity-related problems and facilitating healthy ageing.

### **Brain health in obesity and ageing**

Obesity characterized by central adiposity is associated with not only white matter changes but also increased risk of dementia and Alzheimer's disease<sup>57</sup>. Obesity and overweight in middle age dramatically increase the risk of dementia by 74 and 35 per cent, respectively, independent of socio-demographic factors<sup>58</sup>. Obese individuals are known to have decreased brain volume as compared to healthy middle-aged

adults<sup>59</sup>. Central obesity is also associated with brain atrophy and reduced hippocampal volume<sup>60</sup>. There is evidence that in obesity, increased levels of adipokines secreted from visceral adipose tissue are accompanied by impaired cognitive processes<sup>61</sup>. Increased levels of pro-inflammatory molecules such as TNF- $\alpha$  in close collaboration with IL-6 have been implicated in obesity-associated dementia. Such association has been established probably because increased inflammation produces a harmful microenvironment that negatively impacts brain functions such as synaptic plasticity and neurogenesis<sup>57,62-65</sup>. In line with this, increased peripheral inflammation, as estimated by blood IL-6, is associated with overall cognitive decline in non-demented geriatric population<sup>66</sup>. This further shows a mechanistic similarity between obesity and ageing.

One of the common consequences of ageing is deterioration of cognitive functions. This cognitive dysfunction is known to significantly affect the capacity of learning and memory, perception and problem-solving<sup>67</sup>. Most cases of age-related cognitive decline are associated with amyloid- $\beta$  (A $\beta$ ) deposition. Accumulation of A $\beta$  is known to enhance the process of neurodegeneration<sup>68</sup>. Similarly, in obesity, leptin crosses the blood-brain barrier and has been implicated in A $\beta$  deposition and neurodegeneration<sup>69</sup>. Obesity as well as ageing is associated with increased risks of hypertension and T2DM<sup>70-73</sup>. Both hypertension and T2DM are known to impair cognitive function<sup>74,75</sup>. Hypertension alters the cerebral microvasculature and raises the risk of dementia and Alzheimer's disease<sup>76</sup>. There is also some evidence that antihypertensive drugs offer protection against dementia<sup>77</sup>. Similarly, T2DM also doubles the susceptibility to developing Alzheimer's disease<sup>78</sup>. As discussed above for leptin, insulin is also implicated to increase the A $\beta$  accumulation and tau protein hyperphosphorylation<sup>79</sup>. This makes hyperinsulinaemia as one of the factors of dementia and cognitive dysfunction during ageing (especially in the elderly). The decrease in the level of brain-derived neurotrophic factor (BDNF) has been associated with neurodegeneration and cognitive dysfunction<sup>80-83</sup>. BDNF helps in the generation of new neurons, proliferation and their survival throughout the life. BDNF level is known to decrease in both ageing and obesity. In obesity, the macromolecular damage in brain increases in hippocampus, which results in cognitive dysfunction and neurodegeneration. Therefore, obesity is also associated with accelerated ageing<sup>7</sup>.

## Conclusions

Due to increased research and awareness programme, the knowledge and understanding of obesity have augmented significantly. Similar is the case with age-related disorders, which has helped in early detection and initiation of treatment paradigms. However, one of the impediments in this area is fragmented understanding of the mechanisms connecting obesity and ageing or obesageing. Attention towards this is the need of the hour. WNIN/Ob rat model is one of the best animal models to investigate and unravel different pathways that get erred during obesageing. Interventions that can rescue decreased SIRT-1 expression and NAD<sup>+</sup> levels and increased inflammation and altered epigenetic processes<sup>84</sup> would be good strategies to handle this growing burden of obesageing. Considering the protective role of adiponectin, translational research unravelling the therapeutic potential of adiponectin and its mimetics also can prove to be helpful.

**Financial support & sponsorship:** The study was financially supported by the Indian Council of Medical Research, New Delhi.

**Conflicts of Interest:** None.

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