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REVIEW ARTICLE

Nutrition and cellular senescence in obesity-related disorders

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Abstract

Adequate nutrition is vital for immune homeostasis. However, the incidence of obesity is increasing worldwide due to the adoption of the Western diet and a sedentary lifestyle. Obesity is associated with chronic inflammation which alters the function of adipose tissue, liver, pancreas, and the nervous system. Inflammation is related to cellular senescence, distinguished by irreversible cell cycle arrest. Senescent cells secrete the senescence-associated secretory phenotype (SASP) which contains pro-inflammatory factors. Targeting processes in senescence might have a salutary approach to obesity. The present review highlights the impact of an unhealthy diet on tissues affected by obesity, and the mechanisms that promote the consequent inflammation and senescence.

Keywords: aging; diet; inflammation; microbiota obesity; senescence.

Abbreviation: ATM, ataxia-telangiectasia mutated; BDR4, bromodomain-containing protein 4; CDK, cyclin-dependent kinase; CDKN1A or p21, cyclin-dependent kinase inhibitor 1A; CR, calorie restriction; CRP, C-reactive protein; C/EBPβ, CCAAT/enhancer-binding protein-β; CNS, central nervous system; DBC1, deleted in breast cancer 1; DNA, deoxyribonucleic acid; E2FI, E2F Transcription Factor 1; EHMT2 or G9a, euchromatic histone-lysine N-methyltransferase 2; GFAP, glial fibrillary acidic protein; GATA-4, GATA binding protein 4; GLP, G9a-like protein; HCC, hepatocellular carcinoma; HSCs, hepatic stellate cells; HFD, high-fat diet; HMGB2, high-mobility group box 2; IL-10, interleukin 10; IL-6, interleukin 6; IL-1β, interleukin-1β; IL-22, interleukin 22; IGF, insulin-like growth factor; γ-H2A.X, phosphorylated histone variant H2AX; LPS, lipopolysaccharide; mTOR, mammalian target of rapamycin; MLL1, mixed lineage leukemia protein-1; MCP-1, monocyte chemoattractant protein-1; NAFLD, non-alcoholic fatty liver disease; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NASH, nonalcoholic steatohepatitis; OPN, osteopontin; OXPHOS, oxidative Phosphorylation System; PPARγ, peroxisome proliferator-activated receptor gamma; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PD-1, programmed cell death protein 1; pAMPK, phospho-AMP-activated protein kinase; PP, polypeptide cells; PFOXO3, phospho-forkhead box O3; p-IκBα, phosphorylated IκBα; p53, tumor protein p53; p16, cyclin-dependent kinase inhibitor p16; $P16^{INK4a}$, cyclin-dependent kinase inhibitor 2A; ROS, reactive oxygen species; SPP1, secreted phosphoprotein 1; SAMP8, senescence-accelerated mouse-prone 8; SAMP10, senescence-accelerated mouse prone 10; SAMR1, senescence-accelerated-resistant mice; SASP, senescence-associated secretory phenotype; SA-β-gal, senescence-associated β-galactosidase; SMP30, senescence marker protein; SGK-1, serum- and glucocorticoid-inducible kinase homolog 1; SIRT1, Sirtuin1; TGF-b, transforming growth factor-b; TORC2, target of rapamycin complex-2; TRF1, telomeric repeat factor 1; TNF-α, tumor necrosis factor-α; TWEAK, tumor necrosis factor-like weak inducer of apoptosis; T1DM, type 1 *diabetes mellitus*; T2DM, type 2 *diabetes mellitus*; YAP, yes-associated protein; ZNF521, zinc Finger Protein 521.

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1. Introduction

Chronic over-nutrition, distinguished by an extended positive energy variance that facilitates obesity, is a risk factor for the development of multiple health problems (i.e., diabetes, non-alcoholic fatty liver disease (NAFLD), leaky gut, neuropsychiatric disorders, cancer, etc.) [1-5]**.** The World Health Organization defines overweight and obesity as abnormal or excessive fat accumulation that may harm health. Additionally, the prevalence and increase of people with obesity have led to consider it as a dangerous disease worldwide [6]. Although the causes of obesity are multifactorial, it is well established that diet is a key player in the equation. Indeed, current lifestyle changes with a more sedentary lifestyle and the consumption of highly processed foods, and food with high fat and low water content or poor in nutrients, encourage fat accumulation and the development of overweight and obesity [7]. By contrast, the consumption of a healthy diet reduces the risk of overweight/obesity while the consumption of simple carbohydrate-rich food (e.g., sugar-sweetened beverages) is often associated with increased obesity risk [8,9]. Obesity is involved in chronic inflammation and inflammation is also related to cellular senescence, a cell state distinguished by an extended and generally irreversible cell cycle arrest triggered by multiple stimuli [10,11]. Paradoxically, the presence of senescent cells also has beneficial effects on the organism. Senescence is involved in physiological processes such as embryological development [10,11], wound healing, or tissue regeneration [12,13]. Besides, senescence has been described as a mechanism to eliminate aberrant cells and can be considered as an alternative to apoptosis [14]. Hence, taking into account the important effect of diet on obesity, targeting processes involved in inflammation, such as senescence, through changes in diet or dietary supplementation could be a promising approach to alleviate related disorders. Herein, we highlight molecular mechanisms that promote and perpetuate cellular senescence in obesity. We also describe the physiopathological diet-induced obesity effects on the liver, pancreas, or central nervous system (CNS) and the involvement of senescence as well as dietary approaches to managing these effects.

2. Nutrition and immunity

One of the most energy expending cell systems in the body is the immune system. Consequently, it is influenced by nutrient variance, establishing a close link between nutrition and immunity [15]. Several studies have recognized a relation between nutrition and macrophages [16,17]. Accordingly, diet acts as a critical regulatory factor in the immune response: (1) malnutrition can lead to immunosuppression due to a susceptibility to infection; and (2) over-nutrition can lead to immune activation or directly to resistance or to an inflammatory condition. Contrarily, any disparity in the consumption of nutrients and nutritional state can induce unfavorable consequences. On the other hand, severe under-nutrition or starvation produces gradual weight loss, a reduction in energy expenditure and, a diminished metabolic rate and survival [18].

Concerning dietary patterns, a high-fat diet (HFD) promotes weight gain by generating excess fat that leads to an increase in adipose tissue, inducing hypothalamic inflammation and deregulating homeostasis, and producing insulin resistance, glucose intolerance and obesity [19]. It is also known that a HFD creates excessive body fat accumulation and impairs the immune system. Indeed, fatty acids such as polyunsaturated, saturated, and trans-fatty acids are of interest for their effects on inflammatory status [15]. Other authors have reported that some vitamins and minerals present favorable effects on oxidative stress and immune responses. Moreover, cross-sectional and interventional studies have consistently exhibited that vitamins and minerals are related to several inflammatory markers [C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α)] [15]. By contrast, calorie restriction (CR) promotes health-span, and a plethora of CR mimetics have been used to imitate its helpful effects by regulating mitochondrial metabolism or autophagic flux, suppressing inflammatory processes, protecting intestinal barrier function, and reducing both inflammation and neuroinflammation [20].

In conclusion, optimal nutrition is vital for healthy immune homeostasis, however, dietary patterns such as HDF, unbalanced diet, or over-nutrition are related to inflammation and may lead to obesity.

3. Inflammation and senescence

Cellular senescence is a cellular state presenting extended and generally irreversible cell cycle arrest triggered by multiple stimuli [21,22]. Importantly, once cells become senescent, they produce and secrete the so-called senescence-associated secretory phenotype (SASP). Broadly, SASP is composed of pro-inflammatory cytokines and chemokines, growth factors, proteases, and angiogenic factors that can act in a paracrine and autocrine manner to spread and strengthen senescence [23,24]. The presence of SASP-producing senescence cells can have negative long-term effects such a chronic inflammation, which can produce tissue dysfunction and/or carcinogenesis [25,26].

Senescence is a dynamic process with multiple steps [27]. The initiation of senescence is characterized by early signals that are sufficient to initiate processes such as oncogene activation or DNA damage. In early senescence, the chromatin of senescent cells is gradually altered and there is a loss of Lamin B1, changes in lysosomal activity and autophagy. These senescent cells develop SASP and the distinguished senescence-associated β-galactosidase (SA-β-gal) activity to enter into a final step of full senescence. Senescent cells that persist in the aforementioned step for long periods can be classified in a final step called late senescence, in which the senescent phenotype adapts and progresses with chronic inflammation [26] (Fig. 1).

SASP is regulated by a wide range of elements, such as signaling molecules [p38, mammalian target of rapamycin (mTOR), and Notch], transcription factors [nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), CCAAT/enhancer-binding protein-β (c/EBP-β), GATA binding protein 4 (GATA4), and epigenetic regulators (euchromatic histone-lysine N-methyltransferase 2 (EHMT2 or G9a), G9a-like protein (GLP), MacroH2A, high-mobility group box 2 (HMGB2), mixed lineage leukemia protein-1 (MLL1), bromodomain-containing protein 4 (BRD4), H2A.J] [28]. Cell cycle withdrawal and subsequent entry into senescence can be mediated by many molecular pathways, depending on the senescence stimulus, but all of the pathways seem to converge in the activation of the cyclin-dependent kinase (CDK) inhibitor $P21^{WAF1/Cip1}$ [29].

In summary, inflammation is intrinsically related to cellular senescence mainly through the pro-inflammatory factors of SASP. Thus, senescence might contribute to inflammation related to obesity, and targeting senescent cells might be a therapeutic approach to reducing pro-inflammatory responses in obesity-related disorders.

4. Obesity and senescence

Obesity and obesity-associated hyperglycemia and metabolic stress can trigger senescence of a plethora of cell types. Importantly, HFD-associated hyperglycemia and dyslipidemia can also induce senescence [30,31]. Accordingly, the mean telomere length, a

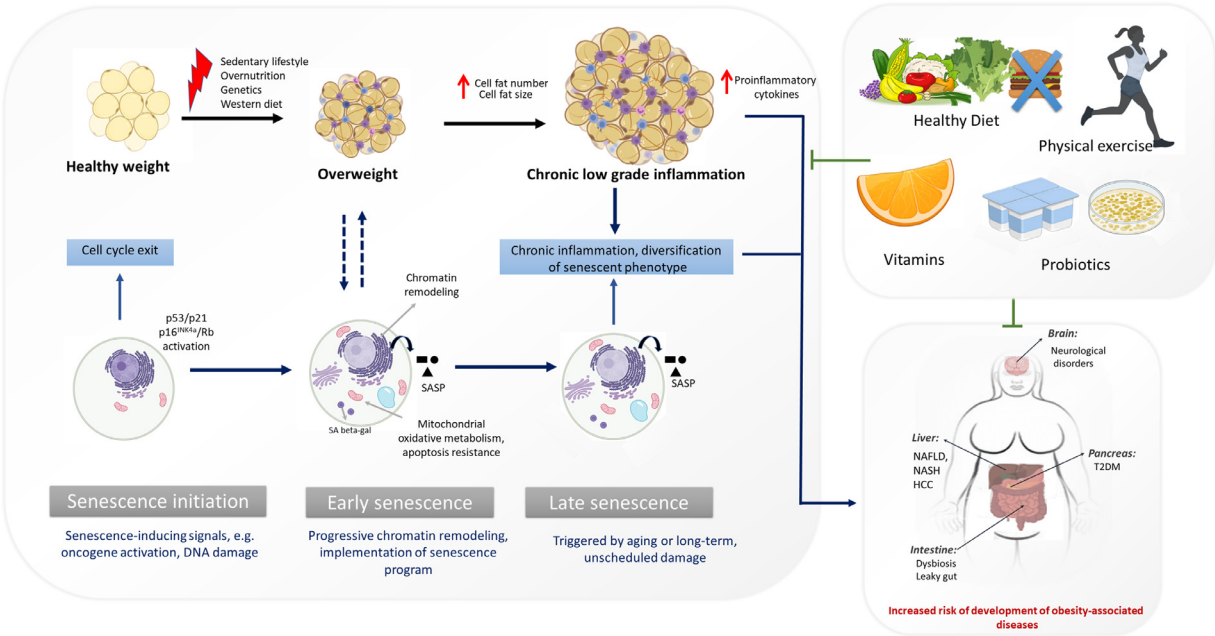

Fig. 1. Physiopathological diet-induced obesity effects on the liver, pancreas, and central nervous system and the involvement of senescence as well as main approaches to managing their impact on health. Abbreviations: DNA, deoxyribonucleic acid; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SASP, senescence-associated secretory phenotype; T2DM, type 2 *diabetes mellitus*.

marker of cellular senescence, was reduced up to 30% in cardiomyocytes of older (normal-weight and obese) and younger obese subjects, showing the shortest telomeres in the older obese group [32]. Thus, individuals with higher total and abdominal adiposity have lower telomere length [32,33]. Adults with severe or morbid obesity present shorter telomeres compared with eutrophic subjects, mainly due to telomeric repeat factor 1 (TRF1), one of the components of the shelterin complex also known as telosome (a protein complex known to protect telomeres in many eukaryotes from DNA repair mechanisms and the regulation of telomerase activity [34], and insufficient antioxidant adaptive responses to compensate for oxidative stress and telomeres attrition. Additionally, the obesity status of para-inflammation might promote an increased rate of proliferation of hematopoietic precursors in the bone marrow, expansion and proliferation of leukocytes in peripheral sites prompting leukocyte senescence and, finally, a reduction in telomeres [35].

Obesity is a complex disorder and a major risk element for many diseases and several health problems. Based on the current data, senescent cell clearance might be a suitable tool to treat obesity-related disorders.

5. Gut microbiota, diet and senescence

The gut microbiota (a complex dynamic population of microorganisms including viruses, bacteria, archaea, fungi or protists) is of relevance for research related to diet and metabolic health. A body of evidence has described the gut microbiota as a mediator of dietary impact on host metabolic status [36] taking into account that: (1) diet is considered to be one of the main modulators of the gut microbiota; (2) intestinal bacteria are crucial for maintaining immune and metabolic homeostasis, and (3) the gut microbiota plays a protective role against pathogens [37].

In this regard, some dietary compounds affect aging through modification of the gut microbiota. For example, fiber decreases inflammation, hypertension and obesity, while saturated fats increase inflammation, atherosclerosis and obesity, and polyphenols reduce inflammation and have antioxidant effects. These outcomes are the consequences of changes in the bacterial composition of the microbiota [38].

An altered intestinal microbial (dysbiosis) profile produces intestinal permeability and is associated with the pathogenesis of numerous inflammatory diseases and infections [37]. In this respect, the mature intestine renews quickly along life being the principal factor for intestinal epithelium self-renewal the Wnt-mediated signaling pathway [39].

Remarkably, the gut microbiota can influence senescence in various organs [40] and both genetic and nutritional obesity steer variations in the composition of the gut microbiota, accompanied by alterations in intestinal physiology, metabolites, and endocrine factors [41,42]. In this regard, it has been reported that methylglyoxal, a bacteria-derived metabolite, accelerated cellular senescence in human dermal fibroblasts and regulated longevity of *Caenorhabditis elegans* by targeting rapamycin complex-2/serum- and glucocorticoid-inducible kinase homolog 1 (TORC2/SGK-1) inhibition and DAF-16 activation [43]. In a model of liver cancer in obese mice, obesity-induced imbalance of the intestinal microbiota led to higher levels of the microbiota-derived secondary bile acid deoxycholic acid and Gram-positive gut microbial component, lipoteichoic acid. These compounds induced senescence of hepatic stellate cells (HSCs) and the secretion of pro-inflammatory SASP, creating a pro-tumorigenic microenvironment [44,45].

To summarize, the gut microbiome exerts a critical influence on several facets of human health including metabolic regulation, energetic homeostasis, immune response, or gut barrier integrity, although the interrelation between the complex triad formed by diet, senescence and the microbiota is still un-deciphered. Research about the impact of microbiota profiles in cellular senescence is mandatory.

6. Diet, aging and senescence

Cellular senescence is a hallmark of aging [46]. In turn, aging is affected by diet, as well as genetic and psychological factors [47]. It

has been suggested that many foods and dietary compounds promote or impede healthy aging, i.e., longevity accompanied by the quality of life what highlights the idea that the maintenance of a healthy diet is a key strategy to improve lifespan and health-span.

The Mediterranean dietary pattern (typical in countries such as Spain, Italy and Greece) considered as a whole, as well as by specific components, including olive oil, fruits, vegetables, tomatoes, fish or fish oil, nuts, red wine, folate and polyphenols, positively affects all the hallmarks of aging [48]. Since aging is related to an increase in oxidative stress and the subsequent production of reactive oxygen species (ROS), an increment in the intake of dietary antioxidants, such as adaptogens, anthocyanins, isoflavones and vitamins A, D, C and E (which are found in high quantities in plants) delays the aging process [49]. Vitamin D and calcium [50], as well as dietary phosphorus [51] support bone health, and therefore, healthy aging. Furthermore, vitamin C, vitamin E, carotenoids (vitamin A, β-carotene, astaxanthin and retinol), vitamin F, polyphenols (mostly found in fruits and plant-derived foods), ubiquinol (coenzyme Q10), prebiotics and probiotics protect against skin aging [52]. In addition, specific dietary compounds, including antioxidant trace elements (zinc and selenium), insulin sensitizers (chromium and zinc) and polyphenols, have been shown to prevent brain aging [53].

On the other hand, low dietary protein intake seems to induce loss of muscle mass and accelerates aging [54]. Whether branched-chain amino acids (leucine, valine and isoleucine) have a positive or negative influence on the aging process is not clear, and may be due to the fact that they act as signaling molecules, leading to different outcomes in different biological contexts [55].

6.1. Fatty acid composition of the diet and aging

Concerning the relation to aging and the type of dietary fat, not all types of fat would have the same effect. For instance, a study carried out on animals showed that consumption of HFD is associated with accelerated aging, unfortunately, the authors did not specify the type of fat consumed [56]. By contrast, the consumption of a Mediterranean diet rich in monounsaturated fats had a protective effect on cellular senescence compared to diets with a high content of saturated fats [57]. Also, the type of fat modulated the response to aging in several tissues. A study carried out in rats found that consumption of sunflower oil resulted in higher levels of cytochrome b (associated with increased aging) compared to olive oil consumption [58]. Concerning the brain, preclinical models have shown that this organ could be negatively affected by saturated and trans-fat [59–61]. It has been reported that maintaining a balance between docosahexaenoic acid (DHA) and polyunsaturated fatty acid (PUFA) n-6 arachidonic acid (20:4n-6) in the brain membrane is crucial for normal CNS function [62–64]. Likewise, dietary supplementation with arachidonic and DHA can improve aging-related cognitive dysfunction [65], and dietary n-3 PUFA has been associated with delayed cognitive decline in a senescence-accelerated prone 8 mouse model (SAMP8) [66]. Conversely, a study carried out by Inoue et al. revealed that the consumption of fatty acids such as palmitic acid-induced cellular senescence and lipid accumulation in hepatocytes [67]. Further, the consumption of fish oil rich in ω-3 polyunsaturated fatty acids may promote aging and oxidative stress in the SAMP8 mouse model [68]. Nonetheless, fish oil consumption was associated with an increase in lifespan (higher than 40%) in females (NZB x NZW)F(1) a mouse model prone to autoimmunity [69-71]. In the same line, the study carried out by García-Esquinas et al. in a cohort of 1,592 individuals older than 60 years showed that the increment of bluefish consumption was negatively associated with unhealthy aging, and the intake of eicosapentaenoic acid (EPA) and DHA led to a protective effect in age-related deficits [72].

Altogether it is important to remark that the fat source, and its composition, may influence senescence and, in consequence, the aging process.

6.2. The relevance of calorie restriction (CR) in overweight and obesity from the point of view of aging

CR is understood as a decrease in caloric intake without leading to malnutrition. In the present section, we remark on some studies and results in this regard.

Monkeys subjected to 30% CR for more than 20 years found contradictory results in terms of lifespan extension. These conflicting results might be explained by the different monkey breeds used and the type of feeding [73,74]. Another study by Liao et al. performed in 41 recombinant strains of mice subjected to a CR regimen of 40% suggested a greater reduction in adiposity and shorter lifespan in these animals [75]. However, the authors did not include an assessment of health indicators, causes of death, or other underlying mechanisms that could be involved. By contrast, several studies have shown that a reduction in caloric intake of 20–40%, prevents age-related diseases and increases lifespan and/or health [76]. Unfortunately, no data in humans on the relationship between CR and longevity, so surrogate measures have to be used. In this line, CR for 6 months, with or without exercise, in overweight, non-obese (body mass index, 25 – 30) men and women reduced 2 biomarkers of longevity (fasting insulin level and body temperature) [77]. Besides, CR by diet alone or with exercise reversed lipid deposition in visceral and hepatic tissues in a study conducted in 48 overweight volunteers [78]. Importantly, D Ard et al. found that a moderate CR (reduction of 500 Kcal/day) reduced total body fat and cardiometabolic risk factors without significant adverse events and lean mass loss in obese adults [79].

In C57Bl/6 (ICRFa) mice subjected to CR the authors observed a positive change in senescence and inflammation markers [80]. Remarkably, Harrison et al. found that obese mice subjected to CR lived longer than lean mice fed ad libitum [81]. These results could be a consequence of a reduction of the energy imbalances and the effect of a higher fat accumulation in obese mice compared to lean ones [82]. Notwithstanding due to the molecular mechanisms linking adipose tissue and longevity are not yet fully understood it is difficult to separate CR-associated benefits and those from reduced adipose tissue mass and leanness. In this regard, some studies show that weight loss increases mortality compared with its maintenance [83–85]. This might be likely explained given that losing weight is not the same as losing body fat. Selective fat loss is associated with reduced mortality [86], whereas loss of fat-free mass is deleterious and responsible for the excess mortality following weight loss [87].

In conclusion, CR could be considered as a solid and effective tool to delay aging and its harmful consequences. However, reported studies in this regard show inconclusive data.

7. Obesity-associated tissue and organ disorders and senescence

Obesity is connected to alterations in the function of several organs such as adipose tissue, liver, pancreas, or the nervous system. This section summarizes studies describing the relationship between these organs and senescence in the context of obesity as well as the effect of some dietary patterns.

7.1. Adipose tissue

The adipocytes and immune cells, including macrophages and T cells, secrete a large spectrum of inflammatory mediators favoring a local inflammatory niche in adipose tissue that contributes to low-level systemic inflammation [88]. However, while it is not completely understood how obesity triggers inflammation, one hypothesis proposes that the overburden of nutrients in adipocytes promotes intracellular stress resulting in the activation of inflammatory cascades [15,89].

The concept that adipose tissue is a simple fat storage space has changed over the last years towards its present consideration as an organ with multifunctional secretory function [90]. Mature adipocytes are required in endocrine, paracrine, and autocrine regulatory processes by the secretion of several multifunctional molecules known as adipokines. Adipokines can modify physiological processes, such as hematopoiesis, reproduction, and feeding behavior, and may mediate the genesis of a wide number of pathologies related to an expanded fat mass [91].

Concerning senescence, in obesity, there is an accumulation of senescent cells in a mouse model [92]. Fat tissue is rich in progenitors able to produce pro-inflammatory factors susceptible to cellular senescence. Possibly, senescence is an alternative cell fate that has much in common with pro-inflammatory stress-activated states. Consequently, inflammatory processes related to cellular senescence in fat tissue may be crucial [93].

The presence of senescent cell markers in adipose tissue is associated with detrimental effects. Thus, the presence of an elevated burden of senescent cell biomarker cyclin-dependent kinase inhibitor $p16^{INK4a}$, within adipose tissue, leads to detrimental effects associated with poorer physical function in older persons [94]. The pro-inflammatory state associated with cellular senescence is more evident in omental than subcutaneous fat-derived endothelial cells, perhaps contributing to regional differences in fat tissue functions in obese adults [95]. These changes involve long-term activation of the protein kinase Akt in mice [96]. Although senescence is associated with aging [97,98] and dysregulated activation of fat tissue in obesity, immune responses might lead to the same metabolic dysfunction in a mouse model [92].

Obesity-associated bone fragility can be related to improved insulin signaling and enhancement of adipocytic progenitor cells in the bone marrow. These variations lead to augmented glucose use and an improved mitochondrial oxidative phosphorylation system (OXPHOS), generating ROS and producing bone marrow stromal stem cells exhaustion as well as the creation of a senescent bone marrow microenvironment conducive to bone fragility in a mouse model and bone marrow stromal stem cells from lean, overweight, and obese subjects [92,99]. In mice, reduced senescence was observed in obesity and was related to adipogenesis and decreased adipose tissue dysfunction showing that a reduction in senescent cell burden in obese mice led to alleviating important elements of obesity-related metabolic dysfunction, such as improved glucose tolerance, enhanced insulin sensitivity, lowered circulating inflammatory mediators, and the promotion of adipogenesis [100]. Additionally, zinc finger protein 521 (ZNF521), a transcription cofactor with recognized regulatory functions in human hematopoietic, osteo-adipogenic, and neural progenitor cells, seems to be vital in the regulation of cell cycle [101], and knockdown embryonic fibroblast mouse cell line 3T3-L1 deleted in breast cancer 1 (DBC-1) gene (a gene related to senescence) showed increased senescence-related markers in adipose tissue [102].

Senescence also activates peroxisome pro-liferator-activated receptor gamma (PPAR-γ), a crucial regulator of primary human adipose tissue endothelial cell function including fatty acids, driving inflammatory response which might impact adipose tissue function in human adipose tissue samples [103]. Finally, human obesity causes premature senescence in adipose tissue-derived mesenchymal stem cells. Thus, the obesity-induced cellular injury might alter the efficacy of this endogenous repair system and hamper the feasibility of autologous transplantation in obese individuals [104]. In Table 1 we summarize findings in the literature about adipose tissue and senescence.

A HFD produces preferential enlargement and accumulation of $CD44^{hi}CD62L^{lo}CD4+$ T cells that constitutively express cell death protein 1 (PD-1) and CD153 in a B cell-dependent manner in murine visceral adipose tissue [105]. These cells possess characteristics of cellular senescence and demonstrate high activation of secreted phosphoprotein 1 (Spp1) (encoding osteopontin [OPN]) in visceral adipose tissue [105].

In addition, certain dietary patterns are able to decrease lipopolysaccharide (LPS) activity in humans [106]. In turn, LPS decreases adipogenesis through disrupting preadipocyte differentiation that is independent of LPS stimulation of the NF-κB pathway and cytokine production in murine adipose tissue [107]. On the other hand, mesenchymal stem cells from obese subjects revealed a lower proliferative function compared to those from non-obese individuals. The senescent cell phenotype was characterized by up-regulation of p16, p53, IL-6, and MCP-1 gene expression in obese subjects. The body mass index corresponds directly with the p16, p21, and IL-6 expression cyclin-dependent kinase inhibitor p16 (p16), p53, IL-6, and monocyte chemoattractant protein-1 (MCP-1) gene expression in obese subjects. Body mass index corresponds directly with the p16, cyclin-dependent kinase inhibitor 1A (CDKN1A or p21) [104]. Embryonic rat osteogenic calvarial cells from HFD obese dams and human umbilical cord mesenchymal cells showed overexpression of p53/p21-mediated cell senescence signaling but reduced glucose metabolism [108]. Senescence-like changes were observed in lysosomal dysfunction with changes in inflammasome activation in white adipose tissue of obese mice [109]. Female growth hormone receptor antagonist transgenic mice displayed decreased age-related lipid redistribution and enhanced insulin sensitivity, but no variation in cellular senescence was observed [110].

The above suggests the potential role of cellular senescence on systemic metabolism and health-span through its effects on fat tissue. Certain dietary patterns may induce senesce signaling in adipose tissue, which in turn influences other organs disrupting homeostasis and leading to several disorders. However, we believe that there continues to be much debate on the role of senescence in adipose tissue and its possible relationship with obesity.

7.2. Liver

The liver is an accessory digestive organ, meaning that it is not part of the digestive tract but rather secretes substances into it. The liver synthesizes and secretes many molecules that have exocrine (digestive), endocrine, and clotting functions, and it is a key metabolic organ [111]. It is composed of hepatocytes, HSCs, cholangiocytes, liver sinusoidal endothelial cells, and resident immune cells [112]. Hepatocytes (as shown in human samples [113]), HSCs (as shown in murine HSCs[114]), cholangiocytes (as shown in human cholangiotes [115]) and liver sinusoidal endothelial cells (as shown in a rat model [116]) can enter senescence under certain conditions. On the contrary, mammalian immune cells are involved in the clearance of senescent cells [114,117]. Many mechanisms have been proposed as inductors of HSCs senescence, including IL-22 in mice [118], the anti-inflammatory cytokine IL-10 through the STAT3-p53 pathway in rats [119], inhibition of Yes-associated protein (YAP) signaling and subsequent expression of p53 in rodents [120], increased activity of p27 promoter and E2F Transcription

Table 1
Reported studies about adipose tissue and senescence.

Senescent cell type	Model	Effects	References
Senescent cell burden in obese mice	Mice heterozygous for transgenes on a C57BL/6 background maintained on a 60% (by calorie) fat diet. *N*= 8 mice per group	Elimination of senescent cells prevented the migration of transplanted monocytes into intra-abdominal adipose tissue and reduced the number of macrophages	Palmer et al. [100]
Subcutaneous adipose tissue stromal vascular fractions were CD45+ hematopoietic cells, followed by CD34+/CD105− cells and only a few CD105+/CD34− mesenchymal stem cells	Human *N*=44 (29 healthy controls and 15 were type 2 diabetes and first-degree relatives) Abdominal subcutaneous adipose tissue biopsies	Increased progenitor cell senescence, reduced adipogenesis and hypertrophic expansion of the subcutaneous adipose tissue cells in first-degree relatives and established type 2 diabetes.	Gustafson, et al. [101]
Embryonic fibroblast mouse cell line 3T3-L1	Human 31 subcutaneous and 32 omental adipose tissue samples from morbidly obese subjects and 38 subcutaneous and 42 visceral adipose tissue samples from participants with different degrees of obesity were studied. *In vitro*: 3T3-L1 cell line	inhibition of Sirt1 activity was associated with human adipose tissue senescence in morbidly obese subject DBC1 increased the NF-κB expression in fully differentiated 3T3-L1 adipocytes, possibly by the inhibition of Sirt1 activity,	Moreno-Navarrete, et al. [102]
Isolated primary microvascular endothelial cells from human adipose tissue	Human: *N*=67 Subcutaneous abdominal adipose tissue samples from nonobese and obese subjects	Accelerated aging is likely to participate in adipose tissue dysfunction and the redistribution of lipids.	Briot, et al. [103]
Mesenchymal stromal/stem cells	Human *N*=44 Mesenchymal stromal/stem cells harvested from abdominal subcutaneous fat from obese and age-matched non-obese subjects during bariatric or kidney donation surgeries	Human obesity triggers an early senescence program in adipose tissue-derived mesenchymal stromal/stem cells	Conley, et al. [104]
Stromal vascular cells, T and B cells and macrophages	Mice C57BL/6 (B6) *N*=6 mice per group	A distinct T cell population that accumulates in the visceral adipose tissue of HFD fed obese mice caused inflammation of visceral adipose tissue by producing large amounts of osteopontin	Shirakawa, et al. [105]
Adipocyte	Mice, Inguinal adipose tissue of C57BL/6	Lipopolysaccharide induces premature senescence of adipocyte progenitors	Zhao, et al. [107]
Embryonic rat osteogenic calvarial cells, and umbilical cord human mesenchymal stem cells	Rats, female Sprague-Dawley rats *N*=6 rats per group. *In vitro*: Umbilical cord human mesenchymal stem cells from pregnant women	Overexpression of p53 linked increased cell senescence signaling and decreased glucose metabolism in fetal osteo-progenitors from obese rats and humans	Chen, et al. [108]

(*continued on next page*)

Table 1 (*continued*)

Senescent cell type	Model	Effects	References
Adipose tissue	Male C57BL/6 mice and 3T3-L1 cells, *N*=6 mice per group	Lysosomal abnormalities in adipose tissue, including deteriorated cathepsin L function and compensatory activation of cathepsin B, caused cellular senescence and inflammasome activation	Mizunoe, et al. [109]
Adipose tissue	Different types of adipose tissue from transgenic mice (*N*=37), inguinal subcutaneous, subscapular, paraovarian, retroperitoneal and mesenteric.	None protection against the generation of senescent cells afforded by decreased growth hormone action, low insulin-like growth factor 1 and/or improved insulin sensitivity was observed	Comisford, et al. [110]

Abbreviations: DBC1, deleted in breast cancer 1; HFD, high-fat diet; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells. N means the number of subjects.

Factor 1 (E2F1) in human cell lines [121] and regulation of the tumor necrosis factor-like weak inducer of apoptosis TWEAK-SIRT1-p53 axis in human cell lines and primary murine cells [122] or the insulin-like growth factor IGF-I-p53 axis in mice [123]. Dietary compounds, such as epigallocatechin gallate (present in green tea) [124] or curcumin [125], can also induce HSC senescence when administrated to rats, although the molecular mechanisms are not fully understood. Furthermore, natural killer cells [114] and B lymphocytes [126] limit HSC senescence in murine models, with the subsequent negative impact on fibrosis resolution. Nevertheless, one study has described a decrease in carbon tetrachloride (CCl_4)-induced liver fibrosis in HSC-specific senescence marker protein 30 (SMP30) KO mice [127].

Hepatocyte senescence is related to a bad prognosis in patients with NAFLD [113] and alcoholic liver disease [128]. NAFLD is a growing cause of chronic liver disease associated with obesity and metabolic conditions including hypertension, dyslipidemia, and type 2 *diabetes mellitus* (T2DM). In obese individuals, exceeded storage capacity and dysfunctionality of the adipose tissue lead to the accumulation of lipids in the liver and the development of NAFLD [129,130]. Aravinthan et al. described a positive interrelation between the quantity of $P21^{WAF1/Cip1}$-positive hepatocytes and fibrosis stage, and hepatocyte telomere length and the grade of steatosis in NAFLD patients. During the follow-up period, the percentage of $P21^{WAF1/Cip1}$-positive hepatocytes decreased in patients with reversed fibrosis but increased in those with worsened fibrosis. Additionally, patients with more $P21^{WAF1/Cip1}$-positive hepatocytes, shorter hepatocyte telomere length and a higher hepatocyte nuclear area (indicators of senescence) had an increased probability of having an unfavorable liver-related outcome [113]. Accordingly, Ogrodnik et al. found that $P21^{WAF1/Cip1}$-positive hepatocytes and foci of telomere-associated DNA damage correlate with the severity of NAFLD [131].

Concerning diet, a study performed in rats described the presence of hepatic senescence in the animals that developed obesity and steatosis on receiving a HFD with 45% kcal from fat, and high quantities of sugar, including sucrose and maltodextrin [132]. Ogrodnik et al. showed that long-term *ad libitum* feeding provoked hepatic fat increment and hepatocyte senescence in mice. A reduction in the liver fat deposition was achieved by the elimination of cyclin-dependent kinase inhibitor 2A ($P16^{INK4a}$) expressing senescent cells in INK-ATTAC transgenic mice fed with a HFD plus AP20187 treatment and by the administration of a senolytic cocktail containing dasatinib and quercetin. The effect was attained by the clearance of senescent cells in obese mice carrying a mutation in the leptin receptor. Furthermore, DNA damage-induced hepatocyte senescence reduced steatosis *in vivo* and *in vitro* by causing mitochondrial dysfunction and reducing fatty acid oxidation capacity [131]. Additionally, accumulating evidence from human and animal studies suggests that senescence-related proteins, including ataxia-telangiectasia mutated (ATM) *in vitro* [133], and senescence marker protein (SMP30) in mice [134], and molecular mechanisms, such as changes in DNA methylation patterns, genomic instability, and telomere shortening, might be involved in the development of steatosis, NAFLD, and non-alcoholic steatohepatitis [135].

On the other hand, nutraceutical intake and other diet supplements, such as vitamin D, attenuated the initiation and progression of NAFLD in HFD fed mice. Inhibition of senescence, quantified by a decrease in hepatocyte senescence-associated β-galactosidase (SaβG) staining and in P53, P21, and P16 protein levels, was observed in animals fed a HFD and treated with vitamin D, compared to HFD non-treated mice, indicating that vitamin D affects cellular senescence [136]. The senescence-accelerated mouse-prone 8 (SAMP8) model was used to test the efficacy of supplementation with IF dipeptide from potato extract hydrolysate. The results of this study indicated that swimming exercise training combined with IF administration in HFD fed SAMP8 mice protected against the effects of the HFD. This protection included lower hepatic steatosis possibly mediated by the up-regulation of the phospho-AMP-activated protein kinase (pAMPK)/SIRT1/ peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)/ phospho-forkhead box O3 (pFOXO3) pathway [137].

In hepatic cancer, vitamin C supplementation showed hepatoprotective effects in both wild type and SMP30 (involved in vitamin C biosynthesis) knockout mice treated with diethylnitrosamine, a widely used liver carcinogen [138]. Using this animal model of hepatocellular carcinoma Duan et al., described the protective effects of CR [139]. In humans, the natural alkaloid berberine (found in many plants such as the tumeric tree) reduced cell proliferation in hepatocarcinoma cells in synergy with X-rays, by inducing cellular senescence of tumor cells [140].

The liver is also an organ affected by cellular senescence in the context of obesity. Unbalanced diets might promote senescence in liver cells, initiating or worsening the prognosis of related diseases.

Table 2
Reported studies about liver cellular senescence and related disorders.

Senescent cell type	Model	Effects	References
Hepatocyte	Human, NAFLD *N*=70	Hepatocyte senescence related to bad prognosis in NAFLD	Aravinthan et al. [113]
Hepatocyte	Mice, C57Bl/6 *N*=9	Hepatocyte senescence related to bad prognosis in NAFLD	Ogrodnik et al. [131]
Hepatocyte	Human, alcoholic liver disease *N*=42	Hepatocyte senescence related to bad prognosis alcoholic liver disease	Aravinthan et al. [128]
HSC	Rats, Wistar *N*=8	Epigallocatechin Gallate (green tea) promoted hepatic stellate cells senescence resulting in chemopreventive and antifibrotic effects	Sojoodi et al. [124]
HSC	Rats, Sprague Dawley *N*=6	Curcumin induced hepatic stellate cells senescence	Jin et al. [125]
HSC	Mice, C57/BL6 *N*=12	Obesity-induced intestinal dysbiosis induced senescence of HSCs and the secretion of pro-inflammatory SASP	Loo et al. [44], Yoshimoto et al. [45]
Hepatocyte	Rats, *N*=8	HFD induced obesity and steatosis led to Hepatocyte senescence	Zhang et al. [132]
Hepatocyte	Mice, *N*=5	Vitamin D decreased HFD-induced cellular senescence	Liu et al. [136]
Hepatocyte	Mice, SAMP8 *N*=6	IF dipeptide from potato extract hydrolysate protected against HFD effects	Asokan et al. [137]
Hepatocyte	Mice, SAMP8 *N*=15	Vitamin C protected against cancer even in the absence of SMP30	Son et al. [138]
Hepatocyte	*In vitro*, human HSC cell line	Calorie restriction protected against cancer	Duan et al. [121]
Hepatocyte	*In vitro*, Hepatocellular carcinoma cell line (HepG2)	Berberine (tree turmeric) induced tumor senescence	Ramesh et al. [140]

Abbreviations: HFD; high-fat diet, HSC; hepatic stellate cell, NAFLD; non-alcoholic fatty liver disease, SASP; senescence-associated secretory phenotype, SMP30; senescence marker protein-30. N means the number of subjects.

Table 2 summarizes studies about liver cellular senescence and related disorders.

7.3. Pancreas

The islets of Langerhans are scattered throughout the acinar parenchyma and perform endocrine functions. Each islet consists of a core of β cells that produce insulin, surrounded by α cells, δ cells, ε cells, and polypeptide (PP) cells that secrete glucagon, somatostatin, ghrelin, and pancreatic polypeptide, respectively [141,142]. Loss of functional β cell mass produces diabetes, being Type 1 (T1DM) and T2DM the main types. T1DM is an autoimmune disease while T2DM is mediated by metabolic mechanisms, including obesity. In T2DM excessive lipid storage leads to insulin resistance and systemic inflammation contributing to its development [129,143].

In humans, T2DM donors present a higher percentage of SA-β-gal-positive senescent cells in the islets [144]. In rodents, Sone et al. showed that long-term diabetes induced by HFD reduced proliferating β cells, decreased insulin production, and increased pancreatic senescence [145]. Moreover, mice subjected to metabolic stress, i.e. hyperglycemia and hyperinsulinemia caused by treatment with an insulin receptor antagonist, displayed increased $P16^{INK4a}$ islet expression [146]. Importantly, these murine senescent β cells synthesized and produced SASP. In turn, $P16^{INK4a}$ seems to hamper the regenerative potential of pancreatic islets in this murine model [147]. Islets senescent clearance improved glucose tolerance and β cell functionality in HFD fed mice [144]. Notably, T2DM and obesity are important risk elements for pancreatic cancer [148], although the role of senescence in their development is unclear [149].

A high intake of red and processed meat, sugar, and artificially-sweetened drinks accelerate the onset of T2DM, while diets enriched in dietary fiber, olive oil, whole grain, low-fat dairy products, magnesium, and flavonoids, among others, as well as specific dietary patterns such as the Mediterranean can prevent its appearance [150]. In addition, serum 25-hydroxyvitamin D levels may be linked to increased fat mass and impaired glucose metabolism in a healthy aged population [151]. Results from Cheng et al. in mice indicated that CR could be a potential treatment for both T1DM and

Table 3
Reported studies about pancreas cellular senescence and related disorders.

Senescent cell type	Model	Effects	References
B cells	Human, T2DM, *N*=49 Mice, C57BL/6 *N*=4	Increased SA-β-gal-positive senescent cells in T2DM Better β cell functionality in HFD fed mice after clearance of senescent cells	Aguayo-Mazzucato et al. [144]
B cells	Human, T2DM, *N*=49 Mice, C57BL/6 *N*=4	Hyperglycemia and hyperinsulinemia increased β cells senescence	Aguayo-Mazzucato et al.[146]
Whole islets of Langerhans	Mice, C57BL/6J *N*=8	HFD-induced diabetes increased pancreatic senescence	Sone and Kagawa [145]
Whole islets of Langerhans	Mice *N*=7-23	Senescence diminished the regenerative potential of pancreatic islets	Krishnamurthy et al. [147]
Whole islets of Langerhans	Mice, SMP30 KO, *N*=7	Altered insulin release patterns after glucose stimulation	Senmaru et al.[153]

Abbreviations: HFD, high-fat diet; KO, knockout; SA-β-gal, senescence-associated beta-galactosidase; SMP30, senescence marker protein-30; T2DM, Type 2 diabetes. N means the number of subjects.

Table 4
Reported studies about CNS cellular senescence and related disorders.

Senescent cell type/Place	Model	Effects	References
Astrocytes	*In vivo*: Rats, Wistar *N*=4	Acidic fibrillary protein (GFAP)-positive: flat morphology with aging	Mansour et al [164]
Astrocytes	*In vivo*: Rats, Wistar *N*=4	Acidic fibrillary protein (GFAP)-positive: flat morphology with aging	Mansour et al [164]
Microglia	*In vitro*: Microglia from newborn rats (Specie = NI)	Telomere shortening with advancing age	Flanary et al. [165]
Astrocytes	*In vitro*: Human and mouse astrocyte (Specie = NI)	Cellular senescence in response to stressors	Bitto et al. [166]
Neuron-glia	*In vitro*: Primary mesencephalic neuron-glia from C57BL/6 mouse embryos	Environmental paraquat and iron exposure might induce senescence	Peng et al. [167]
Glial cells	*In vivo*: Mice, C57BL/6 *N*=6	Senescent glial cells favored the excess of fat deposits accumulation	Ogrodnik et al. [92]
Paraventricular nucleus	*In vivo*: Mice, C57BL/6 *N*=4	Obesity-related senescence induction	Subramanian et al. [168]
Hypothalamus	*In vivo*: Mice, INK-ATTAC N = 5-6	HFD increased senescent cells number	Ogrodnik et al. [92]
Hippocampus	*In vivo*: Mice, C57BL/6 *N* =11	HFD/high-fructose promoted cell senescence	Jang et al. [177]
Astrocytes	*In vitro*: Astrocyte from 2-d-old SAMP8 and SAMR1 mice	CR decreased senescence	García Matas et al. [182]
Brain slices	*In vivo*: Zebrafish *N* =10	SA-β-gal level was not modified by diet	Arslan-Ergul et al. [183]
Cerebrum	*In vivo*: Mice, SAMP10 *N* = 7-11	35 mg/kg/day green tea catechin suppressed the level of oxidative damage to DNA,	Unno et al. [186]

Abbreviations: CR, calorie restriction; HFD, high-fat diet; GFAP, glial fibrillary acidic protein; SA-β-gal, senescence-associated β-galactosidase; SAMR1, senescence-accelerated-resistant mice; SAMP8, senescence-accelerated mouse-prone 8; SAMP10, senescence-accelerated mouse prone 10. N means the number of subjects; NI: not indicated.

T2DM [152]. However, to date, none of these foods and diets has been related to a decrease in cellular senescence in the pancreas, although it has been shown that islets from SMP30 knockout mice present different insulin release patterns after glucose stimulation. Nevertheless, further research is needed to evaluate the implication of cellular senescence in this pathology [153]. In Table 3 we summarize studies about pancreas cellular senescence and related disorders.

The above-mentioned studies indicate that diabetes is likely to be a risk factor for the production of senescent cells and should be taken into account as a key player in regulating their development. In addition, certain diets seem to have a protective role in the development of diabetes, which, in turn, could be a barrier to the appearance of senescent cells. However, more studies are needed to address this issue.

7.4. The central nervous system (CNS)

Among other systems, the CNS is involved in the organic control of dietary intake and participates in short- and long-term energy balance by receiving signals from the body's energy state [154]. Various factors act at the CNS level to stimulate or inhibit food intake such as leptin, insulin, or glucagon-like peptide 1 [155]. The hypothalamus integrates peripheral signals which modulate food intake and energy expenditure arising from the arcuate nucleus, the paraventricular nucleus, the lateral hypothalamic area (considered to be the center of appetite), the ventromedial nucleus (center of satiety), and the dorsomedial nucleus [156]. Thus, lesions caused in these regions can modify food intake producing obesity and hyperphagia [157].

The CNS is composed of the brain and the spinal cord. The first coordinates a multitude of functions, ranging from physical movement to hormone secretion, whereas the spinal cord runs along the back of the body and carries information between the brain and the body, among other functions [158–160]. Currently, the study of senescence in the CNS is an innovative concept focused on its role as a contributor to neurodegenerative diseases. Although the mechanisms underlying cellular senescence in the brain remain unclear, it has been demonstrated that different types of CNS cells can become senescent [161,162]. One of the most studied cell type is astrocytes. It has been reported that in an experimental *in vitro* ageing model in which astrocyte-enriched primary cultures were established from 2-day-old Fischer 344 rat brain cortical tissue rats, cultured astrocytes stained positive for the senescence marker senescence-associated beta-galactosidase (SA-Bgal) 3 months later [163]. Moreover, results from an *in vivo* experimental model in which astrocytes were analyzed in retinal whole-mount preparations from Wistar rats aged 3 months (young adult) to 18 months (aged), showed that ageing is associated with glial fibrillary acidic acidic protein (GFAP)-positive astrocytic cells, showing a flat morphology typical of senescent cells [164]. Concerning microglia, some observe that with advancing age, telomere shortening occurs, and this can lead to senescence. In this study using an *in vitro* model of microglia isolated from the brains of newborn rats, authors observed that telomere shortening in microglia is accompanied by their progression towards senescence by 32 days of its *in vitro* cultured [165]. Not only aging but also other factors are related to senescence in the CNS, as senescence in human and mouse astrocytes occurs in response to several stressors as showed this study using an *in vitro* model of human astrocytes and primary cultures of astrocytes prepared from forebrains of 3-day-old mice [166], whereas environmental paraquat and iron exposure could induce senescence in neuron-glia culture cells (in this case were used primary mesencephalic neuron-glia cultures from embryonic gestation day 14–15 C57BL/6 mouse embryos) [167]. The CNS is also closely related to obesity and senescence [131], and it has been suggested that obesity might induce senescence in the paraventricular nucleus [168].

Additionally, an *in vivo* study carried out by Ogrodnik et al. [92] in a model of C57Bl/6 mice fed with HFD showed an accumulation of senescent glial cells with an excess of fat deposits next to the lateral ventricle, generating obesity-induced anxiety [92]. Palmer et al. [169] suggest that there may be a link between the increased risk of cognitive impairment caused by diabetes and senescence in the brain, but there are no studies on this aspect. On the other hand, elevated p53 and ROS values have been observed in obese mice and in patients with Parkinson's disease [170–172]. Since the activation of p53 produced by a transitory stop of the cell cycle is due to the beginning of senescence as a consequence of a cell insult [173], it has been suggested that obesity may increase the risk of developing this disease [170–172]. Nonetheless, more studies are required to determine if increased p53 activation as a consequence of obesity increases cell senescence and finally leads to Parkinson's disease.

As far as diet is concerned, an unbalanced diet according to calories ingested with an intake that exceeds caloric expenditure, resulted in the reduction of oxygen to the superoxide ion [174]. ROS production can induce premature senescence causing persistent DNA damage which can injure neurons [175]. In this regard, a significant increase in senescent cells was observed in the hypothalamus of an *in vivo* model of INK-ATTAC mice fed with HFD [92]. As suggested by Golde et al. [176], the environment caused by these kinds of diets would generate senescent changes in neuroglial stem cells, the glia, as well as endothelial and smooth muscle cells that form the cerebrovasculature. In this line, Jang et al. [177] determined in an *in vivo* study that a HFD/high-fructose diet promoted cell senescence in the hippocampus in female C57BL/6 mice. On the contrary, endurance exercise entirely reversed cell senescence in a group subjected to the same diet. These authors also showed a reduction in interleukin-1β (IL-1β) and TNF-α levels induced by the diet plus the endurance exercise. Despite these promising results, more studies are necessary to confirm the mechanisms by which HFDs advance neuronal senescence.

On the other hand, CR has anti-inflammatory properties such as pro-inflammatory mediator suppressors (i.e. NF-κB, IL-1β, IL-6, TNF, cyclooxygenase 2, and inducible nitric oxide synthase) delaying brain senescence and preventing neurodegeneration [178–180]. CR also can suppress oxidative stress and damage. An *in vivo* study carried out in rhesus macaques (*Macaca mulatta*), reported that CR could promote health and delay the progression of neuronal aging in several brain areas [181]. The effect of CR on astrocyte senescence has also been studied using a CR *in vitro* model as of primary cultures enriched in astrocytes obtained from cerebral cortical tissue from 2-d-old SAMP8 and SAMR1 mice and cultured during 21 d, revealing decreased senescent astrocytes due to CR and a reduction in β-galactosidase activity related to replicative-type senescence [182]. In contrast, the *in vivo* study in young and older adult zebrafish (wild-type AB strain) carried out by Arslan-Ergul et al. [183] concluded that diet did not change the signal levels of the senescence marker SA-β-gal in brain slices.

It is widely known that diets with high saturated fats, trans fats, or refined sugars produce pro-inflammatory substances and promote the development of chronic inflammatory diseases [184,185]. The use of green tea catechin (35 mg/kg/d, similar to 10 cups of green tea per day by person) in an *in vivo* male mouse model of accelerated senescence (SAMP10), suppressed the level of oxidative damage to DNA, indicating that dietary antioxidants could be an important key to arresting or mitigating the effects of senescence in the brain [186]. Finally, dietary antioxidants have shown preventative effects on oxidative stress [187,188]. In Table 4 we summarize studies about CNS cellular senescence and related disorders.

Further studies are needed to elucidate the mechanism of action by which senescence occurs in the CNS, but it seems that obesity may play an important role not only in the development of senescent cells but also in neurodegenerative diseases. In addition, the CNS controls food intake, and damage caused by senescence could mean that increased food intake leads to fat accumulation and obesity.

8. Conclusions

Nowadays, a sedentary lifestyle and the progressive adoption of the Western diet are enhancing the development of obesity. Senescence status and obesity share a pro-inflammatory activated state that promotes alterations in the physiology of several organs and tissues promoting an unhealthy status. SASP is compound by pro-inflammatory factors that overlap with those secreted by adipose tissue.

The above mentioned studies suggest that dietary-mediated senescence is involved in liver disease, diabetes, CNS disorders and intestinal dysbiosis, suggesting that cellular senescence may be an alternative circumstance in pro-inflammatory responses and might be used for therapeutic purposes. In this line, nutraceutical supplementation (e.g., vitamins or plant-derived compounds) as well as CR, have been adopted as effective interventions for obesity treatment and related pathologies, albeit with contradictory results. We believe that there are still many controversies related to the role of senescence in adipose tissue and its relationship with obesity, and the medical literature is fraught with problems of uncontrolled observations in nutrition. Unfortunately, to date, the role of senescence in obesity is far from clear.

Thereby, to contrast the contradictory reported results it is mandatory to characterize the precise processes associated with cellular senescence and also the implication of diet and obesity so as to assist within the development of therapies and dietary interventions for the treatment of obesity and connected diseases.

8.1. Closing remarks

In the present review, we highlight recent literature regarding nutrition and cellular senescence in obesity-related disorders covering studies conducted *in vitro*, humans and animal models. We discuss the impact of an unhealthy diet on tissues affected by obesity, and the mechanisms that promote inflammation and senescence.

Some aspects seem clear and the scientific community has reached a consensus on them. Namely: (1) optimal nutrition is vital for healthy immune homeostasis; (2) dietary patterns such as HDF, unbalanced diet, or over-nutrition are related to inflammation and obesity; (3) inflammation is linked to cellular senescence through the pro-inflammatory factors of SASP; (4) senescence is associated with aging.

However, many controversies and contradictory results have not been elucidated yet. In our view aging, senescence, response to nutrients, immunity, and inflammation present differences not only between species but also because of the stimulus that triggers it and the used model in the study (in the case of animal models or *in vitro* approaches). In consequence, differences in the modulation of signaling and related pathways are expected which would explain at least partly discrepancies and controversial results. Further, it exists a wide heterogeneity in the human population (e.g., sex, location, age, ethnicity or weight) that together with factors such as environment, psychological stress factors, or genetics should be also considered to evaluate results and extract conclusions.

In addition to the mentioned factors, senescence and/or immunity response can be induced by many other different intrinsic and extrinsic insults, such as oncogenic activation, oxidative and genotoxic stress, mitochondrial dysfunction, irradiation or chemotherapeutic agents, even microbiota profile need to be considered due to several studies suggest that it is unique to each individual. Having these into account, overall, animal models are very helpful to overcome, difficulties from human studies. Other advantages of studies performed in animals are their reproducibility, reliability or their, affordable and technical availability. However, we should only compare those studies carried out with similar animal models and standardized protocols, as well as those that mimic the clinical scenario as much as possible.

Author Contributions

T.R.-T., A.R.-R., J.P.-D., and A.I.Á.-M. participated in the bibliographic search, discussion, and writing of the manuscript. T.R.-T. and A.I.Á.-M. designed the work. A.I.Á.-M. revised the manuscript. All authors have read and agreed with the published version of the manuscript.

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Declaration of Competing Interest

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