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Understanding the role of smoking and chronic excess alcohol consumption on reduced caloric intake and the development of sarcopenia

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Abstract

This narrative review provides mechanistic insight into the biological link between smoking and/or chronic excess alcohol consumption, and increased risk of developing sarcopenia. Although the combination of excessive alcohol consumption and smoking is often associated with ectopic adipose deposition, this review is focused on the context of a reduced caloric intake (leading to energy deficit) that also may ensue due to either lifestyle habit. Smoking is a primary cause of periodontitis and chronic obstructive pulmonary disease that both induce swallowing difficulties, inhibit taste and mastication, and are associated with increased risk of muscle atrophy and mitochondrial dysfunction. Smoking may contribute to physical inactivity, energy deficit via reduced caloric intake, and increased systemic inflammation, all of which are factors known to suppress muscle protein synthesis rates. Moreover, chronic excess alcohol consumption may result in gut microbiota dysbiosis and autophagy-induced hyperammonemia, initiating the up-regulation of muscle protein breakdown and down-regulation of muscle protein synthesis via activation of myostatin, AMPK and REDD1, and deactivation of IGF-1. Future research is warranted to explore the link between oral healthcare management and personalised nutrition counselling in light of potential detrimental consequences of chronic smoking on musculoskeletal health outcomes in older adults. Experimental studies should investigate the impact of smoking and chronic excess alcohol consumption on the gut–brain axis, and explore biomarkers of smoking-induced oral disease progression. The implementation of behavioural change interventions and health policies regarding smoking and alcohol intake habits may mitigate the clinical and financial burden of sarcopenia on the healthcare system.

Key words: Smoking: Alcohol: Ageing: Muscle protein metabolism: Undernutrition

Introduction

Smoking and chronic excessive alcohol consumption are lifestyle choices that represent major risk factors for comorbidities in older adults, including heart (fatty liver) disease, cirrhosis, alcoholic hepatitis, chronic obstructive pulmonary disease (COPD), and various forms of cancer[1]. According to latest statistics, 28 % and 14 % of adult men and women in the UK, respectively, consume more than the recommended 14 units of alcohol per week, with 38 % between the ages of 55 and 64 years[2]. Moreover, 14·4 % of adults are classified as smokers and, combined with excessive alcohol consumption, this demographic accounts for >800 000 of hospital admissions per year[3]. Importantly, a higher prevalence of excessive alcohol consumption has been reported in smokers than non-smokers, thus imposing a double burden on public health[1].

The worldwide population over the age of 65 years is rapidly increasing, with figures projected to exceed 2·1 billion by 2050. Age-related morbidities involving the musculoskeletal system are increasingly common, and include type 2 diabetes, cancer cachexia and osteoporosis. These morbidities may be perpetuated by sarcopenia, which describes the age-related decline in skeletal muscle mass and function, and which serves as a precursor for a decrease in independence, frailty and overall mortality during older age[4]. Sarcopenia may begin as early as the fifth decade of life. It is estimated that more than 50 million people worldwide are sarcopenic, and this figure is expected to rise to 200 million by 2050[5]. This trajectory clearly presents an alarming clinical and financial challenge to the healthcare sector[5]. To this end, there is considerable interest in understanding effective lifestyle interventions to promote musculoskeletal health in our ageing population[6]; however, the impact of smoking and/or chronic excessive alcohol consumption on the development of sarcopenia has received relatively limited attention.

The potential link between chronic excessive alcohol consumption and/or systemic smoking and sarcopenia risk is clearly multi-factorial, context-specific and not fully understood.

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Systemic tobacco smoking and alcohol consumption may contribute to ectopic fat accumulation in skeletal muscle[7] and the development of non-alcoholic fatty liver disease, often manifesting in a state of obesity. Accordingly, skeletal muscle fat infiltration (myosteatosis) may increase lipotoxicity and the subsequent release of excess reactive oxygen species (ROS) and low-grade inflammation (i.e. increased interleukin-6 (IL-6) and tumour necrosis factor (TNF)-α secretion), leading to a disruption in glucose homeostasis[8]. Myosteatosis also may interfere with energy metabolism by contributing to skeletal muscle insulin resistance and gut microbiota dysbiosis via intramuscular fat deposition[9]. Moreover, in terms of muscle protein metabolism, systemic inflammation and oxidative stress are associated with muscle fibre atrophy via the impaired stimulation of muscle protein synthesis (MPS) and accelerated rates of muscle protein breakdown (MPB)[10]. In addition, and perhaps paradoxically to the increased risk of ectopic adipose deposition when smoking and excess alcohol intake is combined, both lifestyle choices may indirectly lead to a reduced caloric intake, undernutrition and an energy deficit[11], all of which exhibit detrimental implications for muscle protein metabolism and have the potential to increase risk of sarcopenia[12]. Thus, given that smoking and chronic excess alcohol consumption are lifestyle choices that continue over many years or decades, understanding the impact of both lifestyle habits on muscle protein metabolism is important for maintaining musculoskeletal health across the lifespan.

Multiple physiological mechanisms are understood to underpin sarcopenia, including hypogonadism, altered oral and gastrointestinal health, increased pro-inflammatory cytokines, motor unit impairments and skeletal muscle insulin resistance leading to mitochondrial dysfunction[4]. In addition, muscle anabolic resistance, which describes the age-related impairment in the stimulation of MPS in response to anabolic stimuli (i.e. amino acid provision and exercise/physical activity), alongside the age-related suppression of appetite and reduced energy expenditure[4] all contribute to sarcopenia risk. A key factor that contributes to the development of any catabolic condition is a chronic state of energy deficit[12]. Dietary guidelines for the management of sarcopenia typically target specific macronutrient intakes to support the remodelling of skeletal muscle proteins[13], alongside the emerging roles of dietary fibre[14], omega-3 fatty acids[15] and specific individual amino acids (i.e. leucine)[16] in regulating muscle protein metabolism[17]. More recent interest has focused on the impact of lifestyle factors on sarcopenia risk, with studies measuring changes in muscle protein metabolism in response to physical inactivity[18–20], muscle disuse/immobilisation[21,22] and low protein consumption[23] in older adults. Given the high prevalence rates of smoking and chronic alcohol intake patterns in middle/older adult populations, understanding the metabolic impact of these lifestyle habits (both individually and when combined) on muscle protein metabolism offers an important consideration to combat risk of sarcopenia. While we acknowledge that smoking and chronic excess alcohol consumption are often associated with ectopic adipose deposition[24,25], the primary aim of this narrative review is to critically evaluate the mechanistic link between smoking and chronic excess alcohol consumption and sarcopenia risk in the specific context of a reduced

caloric intake (leading to energy deficit) that also may ensue due to either lifestyle habit. We highlight the direct and indirect biological pathways that underpin the link between smoking and/or chronic excessive alcohol consumption and muscle protein metabolism in this population.

Smoking, undernutrition and sarcopenia

At the metabolic level, a key contributor of skeletal muscle catabolism leading to muscle atrophy is a chronic period of negative energy balance[12]. This metabolic state predisposes a catabolic environment with the loss of both fat and lean tissue mass[26–28]. A negative energy balance has been shown to suppress the activation of insulin-like growth factor 1 (IGF-1) and the mechanistic target of rapamycin complex 1 (mTORC1) cascade, leading to impaired rates of MPS and increased transcription of muscle atrophy-related genes, including myostatin and ubiquitin–proteasome system (UPS) that up-regulate MPB[12]. The stimulation of MPS is an energetically expensive process, and thus, maintenance of muscle mass during an energy deficit is metabolically challenging[12]. Previous studies have revealed associations between smoking and lower body mass index (BMI). Moreover, pre-clinical weight loss studies have demonstrated reductions in BMI to be associated with increased smoking duration[29–32]. Hence, a clinical link appears to exist between smoking status, undernutrition and subsequent risk of sarcopenia.

The causal mechanisms that underpin the impact of smoking on appetite, energy balance and muscle protein metabolism are detailed in Fig. 1. The anorexic effects of smoking primarily relate to the nicotine content of cigarettes[33]. Previous studies demonstrate that food intake is modulated by β2-, β3-, β4-, α3-, α4-, α5-, α6- and α7-nicotinic acetylcholine receptor (nAChR) subtypes[34–38], which act primarily in the arcuate nucleus of the ventral hypothalamus and are responsible for the control of feeding patterns and energy expenditure[39,40]. A change in energy balance with smoking occurs via neurons and appetite-related hormones in the central and peripheral nervous system that are stimulated by nAChR receptor subtypes. Specifically, nicotine administration stimulates pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript[41,42], but down-regulates feeding-promoting neuropeptide Y and Agouti-related protein[43,44]. In addition, decreased food cravings during smoking are associated with lower acetylated ghrelin and enhanced leptin levels as regulatory hormones of energy balance[45–49]. Ghrelin receptors are expressed in the nucleus accumbens and the ventral tegmental area leading to dopamine release, which exhibits reward properties[50,51]. It follows that nAChR receptors decrease the food rewarding properties associated with activation of mesolimbic dopamine neurons, leading to a decreased appetite of sweet and calorically dense foods[52–57]. Although dopamine receptors are stimulated via nicotine administration, studies have demonstrated a reduced nicotine-induced reward in obese individuals, suggesting a greater potential of appetite-suppressive effects on food palatability in leaner individuals[58,59]. Given the addictive properties of nicotine and difficulties associated with long-term smoking abstinence, smoking has the potential to facilitate a chronic period of energy
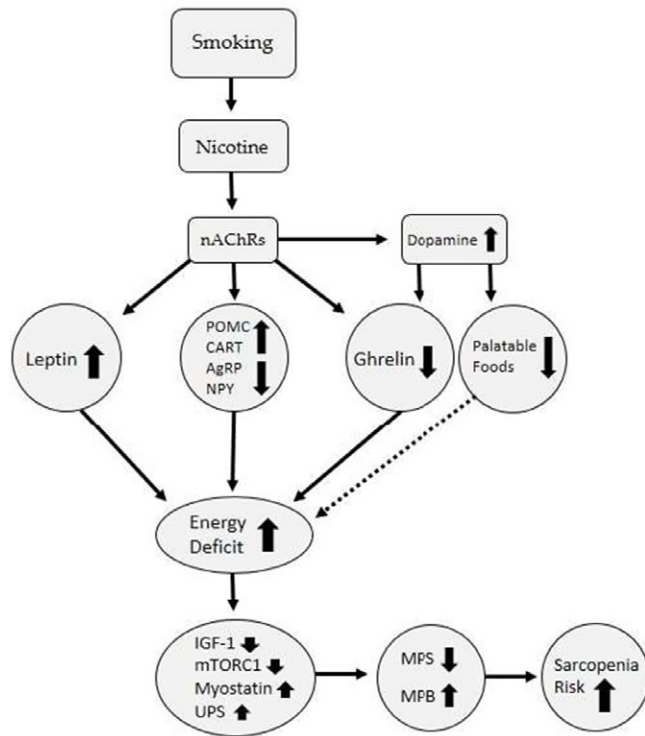
Fig. 1. Proposed mechanisms underpinning the impact of smoking and nicotine administration on appetite and undernutrition. CART, cocaine- and amphetamine-regulated transcript; IGF-1, insulin-like growth factor 1; MPB, muscle protein breakdown; MPS, muscle protein synthesis; mTORC1, mammalian target of rapamycin complex 1; nAChRs, nicotinic acetylcholine receptors; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; UPS, ubiquitin-proteasome system. ↑ Solid arrows denote a direct impact; ⬆ broken arrows denote an indirect impact; ↑ indicates increase; ↓ indicates decrease.

deficit[60]. Therefore, a reduced appetite due to smoking may lead to a negative energy balance, corresponding to a muscle catabolic response and an increased risk of muscle atrophy.

Smoking also has been associated with a decrease in *Bifidobacterium* levels and short-chain fatty acids in the gut microbiota, suggesting that smoking may modify microbial composition[61]. *Bifidobacterium* and short-chain fatty acids are considered beneficial for metabolic health by improving microbiome diversity, insulin sensitivity and the expression of pro-inflammatory cytokines, which are essential for optimal skeletal muscle function[14,62–65]. Accordingly, the interactions between nicotine administration and the gut–brain axis are important in regulating appetite, given that smoking may suppress energy intake and contribute to an energy deficit and subsequent skeletal muscle loss. Also noteworthy is the notion that the gut–brain axis is a complex mechanism that is regulated by multiple factors such as genetics, psychological, social and environmental state, nicotine metabolism, and the gut microbiota. This observation indicates a complex and multifaceted relationship between smoking and suppressed food consumption[66,67]. Moving forward, future human studies are warranted to investigate the relationship between smoking and gastrointestinal hormone regulation to quantify the impact of smoking on muscle protein metabolism and the regulation of muscle mass with advancing age.

Smoking, oral health and muscle loss

The deterioration of oral health and consequential dental implications are restrictive for food choice and mastication, leading to reduced dietary intakes from meat, fruits and vegetables. These commonly consumed food sources are major sources of high-quality protein, vitamins, minerals and dietary fibre[68–72]. Smoking is associated with poor oral health, which may lead to decreased oral function (e.g. swallowing problems, loss of taste) and compromised food intake, both of which may contribute to an increased incidence of sarcopenia and frailty[73–77]. Smoking also may contribute to periodontitis, which manifests as a progressive deterioration of the teeth periodontium leading to chewing difficulties[78]. *In vivo* human studies indicate the relationship between poor oral health and periodontitis[78,79] may lead to increases in mitochondrially derived ROS[80] and lipopolysaccharide (LPS) levels caused by *Porphyromonas gingivalis* bacterial infection[81,82] and has been associated with a substantive decline in handgrip strength[83]. Accordingly, the cumulative response of periodontitis may be exacerbated with age, enhancing the development of sarcopenia through malnutrition, increased oxidative stress and inflammatory cytokine activation involved in the impaired stimulation of MPS[84–90]. In summary, oral health complications associated with smoking may indirectly accelerate the incidence of sarcopenia, highlighting the necessity to maintain oral hygiene during chronic periods of smoking[91]. Moving forward, a multidisciplinary approach, including dental professionals, dietitians, nutritionists and geriatricians, may provide optimal oral health care management (i.e. prosthodontic rehabilitation) and personalised dietary counselling, combined with follow-up treatments[91,92]. Longitudinal studies are required to characterise biomarkers of the progression of periodontitis and understand the risk factors associated with this condition[93].

Smoking, chronic obstructive pulmonary disease and muscle wasting

Smoking is considered the primary cause of COPD, which is characterised by restricted airflow and pulmonary complications[94]. The prevalence of COPD is associated with an increased risk of sarcopenia via systemic inflammation, lower BMI, osteoporosis, cachexia and skeletal muscle weakness[95–100]. Interestingly, COPD may result in limited exercise capacity through enhanced muscle fatigue and may exacerbate lean mass and bone mineral density losses with advancing age[101–103]. Accordingly, previous studies have reported a decline in quadriceps muscle mass and isokinetic muscle function in COPD patients compared with healthy age-matched controls[104–107]. This observation is consistent with previous research that observed reductions in type I and IIA muscle fibres, impaired mitochondrial function and skeletal muscle oxidative capacity in COPD patients, leading to age-related decrements of muscle mass and strength[108–111]. However, it is worth noting that smoking *per se* may not be the causal factor in muscle fibre atrophy and instead may serve to contribute to muscle disuse and its subsequent consequences[112].

Studies also suggest an association between COPD and hypogonadism, which may be attributed to physical inactivity, weight reduction and systemic inflammation[113,114]. The gradual weight loss that is experienced in COPD patients may lead to an increased catabolic response of respiratory muscles and elevated levels of inflammatory cytokines, which exacerbates changes in body composition[115–117]. Although COPD is a potential contributor of sarcopenia, tobacco smoking may independently lead to impaired rates of MPS, increased oxidative stress, myostatin expression and cytokine production in skeletal muscle[118–120]. Consistent with this notion, a series of studies demonstrate an up-regulation of the UPS of MPB, as reflected by increased gene expression of skeletal muscle growth inhibitors such as muscle atrophy F-Box (MAFbx/atrogin-1), muscle RING finger-1 (MuRF1) and myostatin through the deactivation of the Akt pathway in smokers versus non-smokers[119,121,122]. Accordingly, it has been proposed that increased oxidative stress from aldehydes, carbon monoxide, ROS and reactive nitrogen species circulate to the skeletal muscle and activate the p38 and ERK mitogen-activated protein kinase (MAPK), and the nuclear factor κB (NF-κB) signalling pathway[123–125]. This overexpression of MAPK may up-regulate the muscle-specific E3 ubiquitin ligases and lead to a greater inflammatory response and up-regulation of MPB in smokers, thus accelerating risk of sarcopenia[126–128].

Chronic alcohol consumption and skeletal muscle dysfunction

Akin to tobacco smoking, evidence exists that excessive alcohol consumption exacerbates sarcopenia risk via direct and indirect mechanisms related to impaired skeletal muscle protein metabolism[129–131], as depicted in Fig. 2.

The association between excessive alcohol consumption and gut microbiota dysbiosis is supported by studies that reveal hepatic and intestinal inflammation in humans[132–135]. In particular, reduced Bacteroidetes and *Lactobacillus*, and increased Proteobacteria, Fusobacteria and Bacilli species are common in chronic alcoholics versus healthy patients[133,135]. Conversely, positive outcomes in the microbiome also have been highlighted by moderate red wine consumption, potentially due to its polyphenol content and prebiotic benefits[136,137]. Alcohol-induced microbial dysbiosis has the potential to cause or progress liver diseases and facilitate further disruptions in liver metabolism[138–140]. Hepatic damage that results from altered microbial composition, increased intestinal permeability and circulating endotoxins (e.g. LPS) may progressively lead to subsequent systemic inflammation and insulin resistance, which are common in sarcopenic populations[141–145]. Increased circulating LPS levels may lead to greater pro-inflammatory cytokine secretion, inducing muscle atrophy and mitochondrial dysfunction, which is prevalent in muscle-wasting conditions[146]. It follows that skeletal muscle dysfunction may be mediated by a combination of cellular senescence, the up-regulation of UPS, unfolding of MPB regulators, and FoXO1/3 signalling pathways[147].

It has been proposed that a variety of catabolic mechanisms are impacted by chronic exposure to ethanol and contribute to skeletal muscle atrophy[148]. Increased ethanol intake (>40 g/d; 7–14 drinks per week in women–men, respectively) may cause impaired ureagenesis and hepatocyte injury, stimulating high ammonia concentrations[149–155]. This observation may result in hyperammonemia, which dysregulates skeletal muscle proteostasis[156–158]. The increase in skeletal muscle ammonia uptake is suggested to up-regulate autophagy and impair MPS, thus increasing sarcopenia risk[159,160]. Using a rodent model, excess administration of ethanol suppressed protein synthesis rates at the whole-body (−41 %) and skeletal muscle (−75 %) level[161], and resulted in the up-regulation of muscle-specific E3 ligases, atrogin-1 and MuRF1, leading to muscle proteolysis[162]. Furthermore, alcohol consumption following concurrent exercise may impair cellular homeostasis and trigger intramyocellular apoptosis, and subsequently inhibit post-exercise rates of MPS[163]. Similarly, there is evidence that alcohol consumption inhibits MPS and up-regulates UPS and AMP-activated protein kinase (AMPK) phosphorylation during exercise recovery[164–168] and following muscle injury and immobilisation[169,170]. Accordingly, alcohol consumption may inhibit muscle adaptations to resistance training in population groups (i.e. athletes) that aim to enhance muscle mass and function. Importantly, these observations also likely apply to older adult binge drinkers, who are consequently at greater risk of sarcopenia than social drinkers[130,171]. Moreover, the inhibitory effect of systemic inflammation on rates of MPS may be additive when excessive alcohol consumption and smoking are combined. Although human trials are lacking to evaluate the direct effect of combined tobacco and ethanol intake on skeletal muscle protein metabolism, oral flora modifications from aldehydes (i.e. acetaldehyde) via both smoking and alcohol exposure may enhance hyperammonemia and autophagy, and the expression of muscle myostatin, MAFbx and down-regulatory mechanisms of MPS[119,172]. Future work also is necessary to compare the combined impact of excess alcohol consumption and electronic cigarettes (i.e. vaping) or conventional cigarette smoking on muscle protein metabolism and musculoskeletal health outcomes in older adults.

Multiple studies have investigated the impact of chronic alcohol consumption on skeletal muscle metabolism using rodent models, and have observed reduced basal rates of MPS[173–175]. Both *in vivo*[156,176] and *in vitro*[175,177,178] studies have demonstrated that alcohol consumption impairs the muscle protein synthetic machinery via decreased activation of mTORC1, ribosomal protein S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1). This down-regulation of mTORC-1 signalling with chronic alcohol consumption may be initiated via increased AMPK, REDD1 (regulated in development and DNA damage responses 1) and myostatin activation[158,179], as well as decreased plasma and muscle insulin-like growth factor I (IGF-I), which is known to activate the mTORC1 signalling pathway[175,180]. In summary, there is accumulating evidence that inhibiting mTORC1-related mechanisms with an increase in habitual alcohol intake
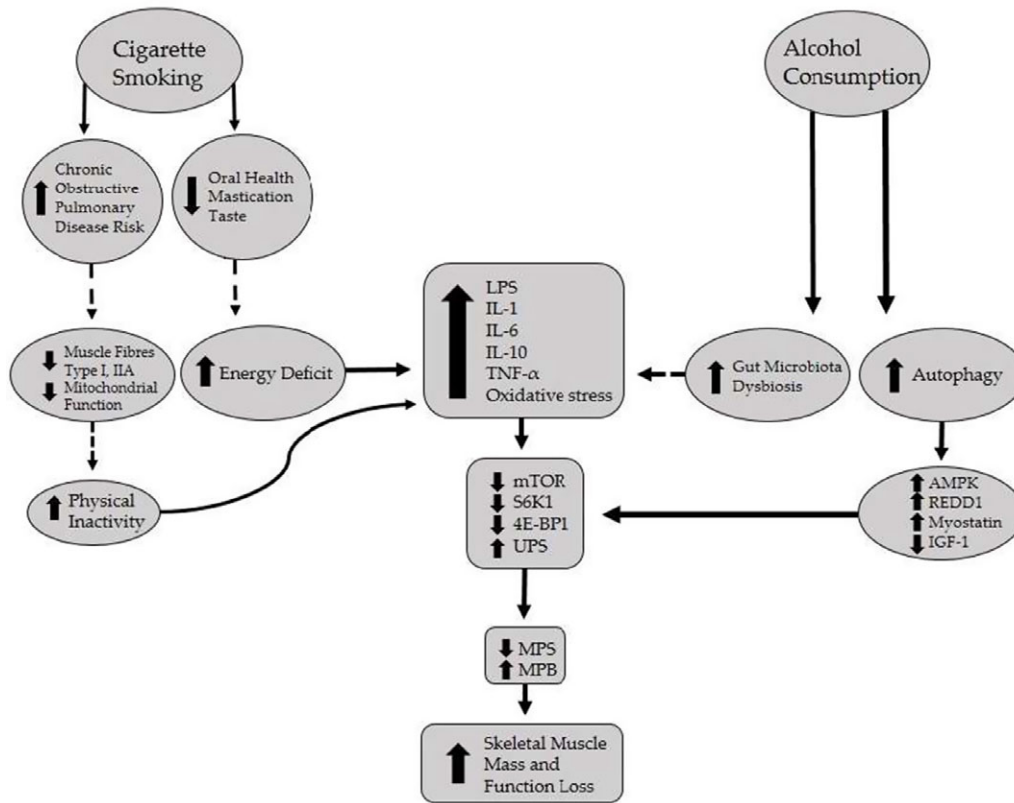
Fig. 2. Indirect and direct mechanisms that may underpin the decline in muscle mass and function with smoking and excessive alcohol consumption. 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; AMPK, AMP-activated protein kinase; IGF-1, insulin-like growth factor 1; IL-1, interleukin 1; IL-6, interleukin 6; IL-10, interleukin 10; MPB, muscle protein breakdown; MPS, muscle protein synthesis; mTOR, mammalian target of rapamycin; REDD1, regulated in development and DNA damage responses 1; S6K1, ribosomal protein S6 kinase 1; TNF-α, tumour necrosis factor-alpha; UPS, ubiquitin proteasome system. ↑ Solid arrows denote a direct impact; ⋮ broken arrows denote an indirect impact; ↑ indicates increase; ↓ indicates decrease.

attenuates MPS. However, follow-up pre-clinical human trials are warranted to definitively determine the impact of chronic excess alcohol consumption on skeletal muscle protein metabolism and subsequent onset of sarcopenia.

Conclusions

Accumulating evidence suggests that health implications of smoking and chronic excessive alcohol consumption extend to the musculoskeletal system, as mediated by the down-regulation of metabolic pathways that regulate muscle protein metabolism and subsequent increased risk of sarcopenia. Chronic use of tobacco products may contribute to undernutrition through oral health and dopamine receptor dysfunction and, combined with systemic inflammation, may impair basal rates of MPS. Similarly, excessive alcohol consumption is linked to the impaired stimulation of MPS, primarily due to contraindications that occur upstream in the mTORC1 signalling pathway that are driven by the expression of pro-inflammatory cytokines. Both smoking and chronic alcohol consumption also lead to metabolic damage through underlying conditions such as periodontitis, COPD and liver diseases, which may act synergistically to inhibit skeletal muscle function. Given that chronic smoking and alcohol consumption is common in Western society, these lifestyle habits have the potential to accelerate age-related muscle atrophy and sarcopenia.

Author contributions

K.P. conceived and wrote the initial draft of the manuscript; O.C.W. reviewed and revised the manuscript.

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