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Article:
Clegg, A orcid.org/0000-0001-5972-1097 and Hassan-Smith, Z (2018) Frailty and the endocrine system. The Lancet Diabetes and Endocrinology, 6 (9). pp. 743-752. ISSN 2213-8587

https://doi.org/10.1016/S2213-8587(18)30110-4

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Title

Frailty and the endocrine system

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Abstract

Frailty is a condition characterised by loss of biological reserves, failure of homeostatic mechanisms and vulnerability to adverse outcomes. The endocrine system is considered of particular importance in frailty, including through complex inter-relationships with the brain, immune system and skeletal muscle. This review summarises evidence indicating a key role for the hypothalamo-pituitary (HP) axis in the pathogenesis of frailty through aberrant regulation of glucocorticoid secretion, insulin-like growth factor signalling and androgen production. Alongside the HP axis, available evidence indicates a potential role for vitamin D and insulin resistance. Key convergent pathological effects include loss of muscle mass and strength, with consequent impact on mobility and activities of daily living. Future translational research should focus on better understanding of endocrine mechanisms to identify potential biomarkers of the condition, modifiable targets for treatment, and novel pharmacological agents targeted at the endocrine components of frailty.

Background

Frailty is a condition characterised by loss of biological reserves across multiple organ systems, failure of homeostatic mechanisms, and vulnerability to physiological decompensation after minor stressor events (1). Older people living with frailty are at increased risk of a range of adverse outcomes which have considerable importance from an individual, health service and wider societal perspective (1).

Frailty is closely linked to the ageing process, which is considered to result from the accumulation of damage caused by multiple mechanisms at a molecular and cellular level, leading to gradual physiological decline. However, in frailty, the decline appears to be accelerated, and accumulates across multiple inter-related physiological systems (2, 3). The endocrine system is considered one of the key systems in frailty, including through complex inter-relationships with the brain, immune system and skeletal muscle. Alongside these key physiological systems, the cardiovascular, respiratory, renal and haematological systems are also considered of key importance in frailty. Evidence indicates that the absolute number of impaired physiological systems is more predictive of frailty than impairments in any particular system (4). This supports the concept that frailty becomes evident when physiological decline reaches a cumulative, critical level.

Epidemiology of frailty

Evidence indicates that frailty affects around 10% of people aged 65 and over, and between a quarter and a half of people aged over 85 (5). Frailty is

characterised by sudden, disproportionate changes in health following seemingly minor stressor events, such as an infection, new medication or minor surgical procedure, followed by an extended period of recovery and frequent failure to return to previous level of function (figure 1). Consistent associations between frailty and important adverse outcomes have been reported in a number of large epidemiological studies, including falls (adjusted 3 year hazard ratio, HR, 1.23, 95% confidence interval, CI, 1.00 to 1.68); disability (adjusted 3 year HR 1.70, 95% CI 1.47 to 2.17); delirium (adjusted odds ratio, OR, 8.5, 95% CI 4.8 to 14.8); nursing home admission (OR 2.60, 95% CI 1.36 to 4.96); hospitalisation (3 year HR 1.27, 95% CI 1.11 to 1.46) and mortality (OR 3.69, 95% CI 2.26 to 6.02) (6-8).

These frailty prevalence estimates and independent association with adverse outcomes have profound implications for the planning and delivery of health and social care systems internationally. However, the prevalence estimates also identify that many older people do not have frailty, indicating that frailty is not an inevitable consequence of ageing. Indeed, there is evidence that frailty may be modifiable and it is considered to have greater potential for reversibility than disability (9, 10). Better understanding of the pathophysiology of frailty is likely to help in the development and targeting of novel approaches to prevention and treatment. Greater insight into the role of the endocrine system in the pathophysiology of frailty is likely to be especially important because of the possibility of identifying potentially modifiable targets.

Frailty models

The phenotype model and the cumulative deficit model are the two best-established international frailty models (7, 11). Both have been extensively validated in large epidemiological studies, and demonstrate robust associations with a range of adverse outcomes.

The phenotype model identifies frailty on the basis of five physical characteristics: weight loss; exhaustion; low energy expenditure; slow gait speed; and reduced grip strength (7). People with no characteristics are identified as fit; those with one or two characteristics as pre-frail; people with three or more characteristics are identified as frail.

The cumulative deficit model identifies frailty on the basis of a range of 'deficit' variables, which can be clinical signs, symptoms, diseases, disabilities and abnormal laboratory test values (11). The model enables calculation of a frailty index (FI) score as an equally weighted proportion of the number of deficits present in an individual to the total possible in the model (e.g. if 9/36 deficits are present, the FI score = 0.25). The model is useful as it is very flexible - it has been established that a minimum of 30 deficits are required for a model to be valid (12).

There is an established association between frailty and cognitive impairment. Although measures of cognition are not explicitly included in the phenotype model, the individual components are risk factors for cognitive decline and dementia (13). The cumulative deficit model incorporates measures of

cognition as key variables, and a prospective independent association between frailty and future dementia has been reported using this approach (14).

Sarcopenia and frailty

Most older people with frailty also have sarcopenia, which is a syndrome characterised by the progressive and generalised loss of skeletal muscle mass and strength with age (15, 16). Sarcopenia is an especially important component of frailty because loss of muscle mass and strength can lead to loss of physical function and independence as key adverse outcomes (16).

Muscle power, the product of muscle torque and movement, appears to be more closely associated with functional physical performance than static muscle strength and declines more rapidly with age (17). Muscle power may therefore have greater utility as a measure of physiological impairment and functional deficit. As muscle strength and power do not depend entirely on muscle mass, and the relationship is non-linear, recent consensus criteria recommend using the presence of low muscle mass and either low muscle strength or low physical performance to diagnose sarcopenia (16). Observational studies have reported losses of muscle strength and power of between 1-3% per annum in older people, with even greater losses observed in the oldest old (18).

Identifying frailty in clinical practice

A range of simple frailty tools and questionnaires are available and validated

for use in clinical practice. The 2016 UK National Institute for Health and Care Excellence (NICE) guideline on the clinical assessment and management of multimorbidity recommends using one of: gait speed <0.8 m/s; timed up and go test score <12 seconds; self-reported health status score <6; PRISMA-7 questionnaire > 3; self-reported physical activity scale in the elderly (PASE) score <56 for men or < 59 for women to identify the possible presence of frailty (box 1) (19). The FRAIL questionnaire is an additional simple validated measure composed of five items, with a score of >3 indicating frailty (20).

The NICE guideline cautions against using a performance-based tool in people who are acutely unwell because frailty and acute illness can be conflated using, for example, gait speed. However, the Clinical Frailty Scale (CFS) and Reported Edmonton Frail Scale (REFS) have been validated in acute hospital settings, so are appropriate tools for the assessment of frailty in the context of acute illness (21, 22). More recently, an electronic frailty index (eFI) has been developed and validated using routinely available primary care electronic health record data, is supported in NICE guidance, and has been widely implemented across the UK to identify frailty in primary care settings (23).

The endocrine system and frailty

The brain and endocrine system are intrinsically linked through the hypothalamo-pituitary (HP) axis, which controls metabolism and energy use via the signalling action of a series of homeostatic hormones (24). There is accumulating evidence that the HP axis has a crucial role in the regulation of

organismal ageing and frailty. Regulation of glucocorticoid (GC) secretion, insulin-like growth factor (IGF) signalling and androgen production are considered to be of key importance, as deficits in these hormonal systems have been associated with adverse ageing profiles and frailty. Alongside the HP axis, Vitamin D and insulin resistance have been identified as having a potential role in the pathogenesis of frailty. A schematic representation of the potential endocrine mechanisms involved in the development of frailty is provided (figure 2)

A 2009 cross-sectional study investigated the relationship between multiple anabolic hormones and frailty using data from 494 older females. The reported evidence indicated that the absolute number of hormone deficiencies was more predictive of frailty than the type of deficiency, suggesting that frailty may arise as the result of a more generalised endocrine dysfunction, rather than through any particular hormonal deficiency (25).

Glucocorticoids

The hypothalamus receives and integrates multiple afferent inputs from diverse regions of the brain to coordinate the organismal response to stress and inflammation, partly through the control of GC secretion (26). Basal GC secretion is necessary for the normal function of many cells, and levels are increased in response to virtually any stress, including physical and psychological stress, or the presence of inflammation, to provide the altered physiological requirements that promote survival (27). Previous studies have investigated age-related changes in the hypothalamo-pituitary-adrenal (HPA)

axis and, although there is uncertainty whether overall GC secretion increases with age, there is overall evidence of blunting of the circadian rhythm (28), reduced suppression of cortisol secretion (29), and impaired recovery from stress (30).

GCs have effects on the range of metabolically active tissues that are important in development of the frailty phenotype, including skeletal muscle, bone and the cardiovascular system (31). Researchers have investigated changes to the HPA-axis and GC secretion in frailty. A cross-sectional study involving 214 female participants reported that frailty, measured using the phenotype model, was independently associated with chronically elevated diurnal cortisol levels, even after adjustment for depressive symptoms, which are themselves associated with increased cortisol (32). Persistently high levels of cortisol have been associated with increased catabolism of skeletal muscle (33), so a link between chronically elevated cortisol and frailty is biologically plausible through the development of sarcopenia as a core component of the condition. Other aspects of HPA-axis function have also been recently assessed in the context of frailty with evidence for reduced cortisol suppression in older people with frailty, compared to controls. One study reported significant correlation between post-dexamethasone suppression serum cortisol levels and a range of frailty markers, suggesting dysregulation of HPA-axis feedback (34).

A study involving 60 participants reported that frail individuals had a blunted response to a low dose synacthen (1mcg ACTH stimulation) test compared to

controls (35). Blunted diurnal cortisol rhythms were associated with poorer health outcomes in later life in a large community dwelling cohort (36). Taken together, the findings indicate chronically elevated diurnal levels of cortisol in the context of frailty are likely to result from failure of homeostatic control through impaired suppression, rather than as a result of an overactive ACTH stimulation response.

There has been additional interest in whether local tissue activation of cortisone to cortisol via 11beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) impacts on features of the ageing phenotype (37). Further studies in cohorts with well-defined frailty are required to establish the clinical impact of this activity, and whether 11β-HSD1 may be a potentially modifiable target for treatment.

Glucocorticoids and inflammation

Inflammation is a protective immune response that is triggered by conditions such as infection and tissue injury, including ischaemia, hypoxia, trauma and physical/chemical injury (38-40). Inflammation is designed to rid the organism of noxious stimuli and pathogens and hence restore physiological homeostasis; the absence of an adequate inflammatory response would lead to multiple detrimental outcomes, including unchecked infections and absence of wound healing (39). However, if the inflammatory response is not tightly regulated, chronic molecular and cellular damage may occur, accelerating biological mechanisms that drive the development of frailty (1). Supported by

a large meta-analysis, there is a growing consensus that reactivity of the HPA axis to inflammatory stimuli is significantly increased with age (41).

Detection of inflammation by the nervous system leads to activation of the HPA-axis and stimulation of cortisol release (27, 42). GC receptors in the brain are typically only occupied at levels of GC observed in stress and inflammation (43) so, at these times, circulating GC are sensed by the hippocampus, which suppresses hypothalamic stimulation of GC production in a negative feedback loop. Additional downstream effects include increased metabolism and altered brain function, characterised by increased hippocampal activity (44).

Uncontrolled inflammation has the potential to cause cellular damage, and a functional GC system is an important component of the homeostatic regulation of local and systemic inflammation. The loss of hippocampal neurons that is observed in both normal ageing and age-related conditions such as Alzheimer's dementia (AD) may impair the homeostatic control of the GC system, with the potential consequence of uncontrolled inflammation and increased cellular damage, promoting organismal ageing and frailty. Loss of homeostatic control of the GC system may itself promote further neurodegeneration, as chronically elevated levels of GC have been postulated to increase hippocampal neuronal damage (45). A schematic representation of the potential role of GC in the development of frailty, including impaired homeostatic regulation, is provided (figure 2).

Glucocorticoids and sarcopenia Under normal circumstances, muscle homeostasis is maintained in a delicate balance between new muscle cell formation, muscle cell hypertrophy and muscle cell protein loss. This delicate balance is coordinated by the neuroendocrine system and immune system and is influenced by nutritional factors and senescent physical activity.

GCs stimulate muscle atrophy by promoting myofibrillar degradation and inhibiting protein synthesis. GCs also regulate muscle wasting medicated by starvation, metabolic acidosis and sepsis, so are likely to play a key role in the characteristic loss of muscle mass and strength observed when older people with frailty are hospitalised for acute illness (46).

Muscle strength and power are required for the critical basic mobility skills of getting out of bed, standing up from a chair, walking a short distance and getting off the toilet (47). When the ability to perform these critical skills is impaired, as is frequently observed when an older person with frailty experiences an acute stressor event, there is risk of immobility, causing further loss of muscle mass, risk of falls and activity limitation (48). Indeed, sarcopenia has been independently associated with increased falls risk, functional decline and mortality (49).

Insulin-like growth factors and growth hormone

Insulin-like growth factors (IGFs) are a family of small peptides that increase anabolic activity in many cells. Promotion of neuronal plasticity and increased skeletal muscle strength are considered to be particularly important effects

(50). The principal IGFs are IGF-1, IGF-2 and insulin. IGF-1 is synthesised in the liver in response to circulating Growth Hormone (GH) in a process regulated by the HP axis.

GH secretion declines at a rate of 14% per decade from middle age onwards in a process termed the ‘somatopause’ (51). GH deficiency results in an adverse body composition profile, with increased fat mass and reduced lean mass. Historical studies have assessed the benefits of recombinant GH in older people, and evidence exists for improvements in body composition parameters but there is limited evidence for muscle strength changes (52). Data on GH-IGF dynamics are limited in cohorts with well-defined frailty.

A range of growth factors and hormones also stimulate local synthesis of IGF-1 by neurons, muscle cells and white blood cells (WBCs). The local autocrine and paracrine actions of IGF-1 are considered important for the promotion of neuronal plasticity and increased skeletal muscle strength (50, 53). Age-related impairments in autocrine, paracrine and endocrine activity of IGF-1 are considered to be important in the development of neuronal senescence and sarcopenia as a core component of frailty (50, 53).

IGF-1 regulates the production of a number of transcription factors that influence the expression of multiple genes that are implicated in inflammatory regulation and cellular autophagy as key potential mechanisms associated with frailty (54). One important downstream transcription factor is DAF-16 and preliminary evidence suggests that this may play a key role in influencing

organismal lifespan (55). Indeed, genetic variations in the IGF signalling pathway have been associated with increased life expectancy in humans (56). However, the relationships are complex, with both GH-IGF1 excess and deficiency in pituitary disease being associated with increased mortality and no evidence of a survival advantage in GH resistance.

IGFs and frailty

Available evidence supports the hypothesis that IGFs are likely to play an important role in frailty. A 2009 cross-sectional study involving 494 older women reported that participants with IGF-1 deficiency, in combination with either DHEAS or testosterone deficiency, were more likely to have frailty (OR 2.79, 95% CI 1.06 to 7.32) (25). A 2004 cross-sectional study including 51 older participants reported significantly lower levels of IGF-1 in those who were identified with frailty using the phenotype model, compared to age-matched controls (57). An inverse correlation between IGF-1 and IL-6 levels was observed, identifying a potential relationship between IGF-1 and inflammation that may be important in frailty.

A 2009 cross-sectional study involving 696 older women from the US Women's Health and Aging Study identified a significant correlation between white blood cell counts and IGF-1. A complex U-shaped association between IGF-1, WBC count and frailty was also reported. Compared to a reference of high IGF-1 and low WBC counts, when IGF-1 levels were low, both low and high WBC counts were associated with increased risk of frailty. Conversely,

when WBC counts were high, both low and high levels of IGF-1 were associated with frailty (58).

IGFs and sarcopenia

IGF-1 is considered to play a key role in the maintenance of muscle strength. Although systemic GH-dependent IGF synthesis by the liver may have a role, the autocrine and paracrine effects of GH-independent local IGF-1 production by muscle cells in response to changes in the microenvironment are believed to be of particular importance (53).

IGF-1 acts to increase muscle strength by promoting increased myocyte number, activating muscle cell hypertrophy and inhibiting muscle protein breakdown. Increased myocyte number is considered to be through promotion of muscle stem cell proliferation and differentiation (59). Activation of muscle cell hypertrophy is through an IGF-mediated direct and indirect cascade of kinase enzymes and the nutrient sensing mammalian target of rapamycin (mTOR) signalling pathway (60). Inhibition of muscle protein breakdown is facilitated through downregulation of components of the ubiquitin-proteasome (UP) pathway (61). IGF1 secretion is modulated by nutrient intake, with fasting and low energy diets resulting in reduced circulating concentrations. Conversely, IGF1 concentrations are also lower with increasing BMI.

A prospective cohort study involving 558 participants reported a multivariable analysis that identified a statistically significant association between IGF-1 levels and sarcopenia as a key component of frailty (62). Analysis of data

from 1833 community-dwelling older people participating in the I-Lan Longitudinal Aging Study identified a positive association between IGF-1 and improved muscle mass, grip strength and bone mineral density (63). An additional observational study in 3447 community-dwelling men aged between 70 to 89 years, reported that lower IGF1 and higher IGFBP1 concentrations were associated with increased incident frailty, defined using the FRAIL score (64).

Androgen deficiency

The hypothalamic-pituitary-gonadal (HPG) axis regulates testicular secretion of testosterone as the main human androgen through pulsatile hypothalamic secretion of gonadotropin releasing hormone (GnRH). This stimulates pituitary secretion of luteinizing hormone (LH), which binds to target cells to increase expression of steroidogenic acute regulatory protein (StAR). The adrenal is also a source of androgens including dehydroepiandrosterone sulphate (DHEAS) and androstenedione in women and men.

Androgens have effects on a range of target organs, including skeletal muscle, so are of potential interest in frailty because they may be a modifiable determinant of the condition. Testosterone increases muscle protein synthesis through both direct stimulation of muscle androgen receptors and through actions on the intramuscular IGF-1 system (65, 66). It is well-established that testosterone levels decrease with advancing age, with levels of bioavailable testosterone characteristically falling by around 2% per year (67). Although these reductions in testosterone can be considered as part of normal ageing,

a number of large epidemiological studies have reported consistent cross-sectional associations between low testosterone levels and frailty (68-70). However, although there appears to be a consistent cross-sectional association, studies reporting prospective associations have been equivocal, and it is possible that testosterone represents a surrogate marker for frailty, rather than a causal factor (65).

Testosterone supplementation can increase skeletal muscle mass in both young and older males, principally through promotion of myofibre hypertrophy and increased stem cell number (71). One randomised controlled trial (RCT) assigned 790 males aged 65 years and over with low serum testosterone levels to receive either testosterone gel or control gel (72). Although improvements in sexual function and mood were reported, there were no benefits identified regarding vitality or mobility, measured using the six-minute walking distance. One RCT of testosterone supplementation involving 209 older participants with limitations in mobility and low serum testosterone was terminated early due to safety concerns (73). Although the intervention group demonstrated significant improvements in arm and leg strength compared to the placebo group, a higher rate of adverse cardiovascular and respiratory events in the intervention group led to a recommendation from the data and safety monitoring board that the trial be discontinued.

Subsequent RCTs of testosterone treatment have reported outcomes relevant for older people with frailty, with evidence for improvements in bone density and anaemia, but no improvements in cognition and increased size of

coronary atheroma (74-77). As in clinical practice for confirmed male hypogonadism, future trials in this area would need to incorporate long-term safety monitoring for prostate cancer, polycythaemia, respiratory and cardiovascular events.

There has been preliminary exploration of the association between DHEAS and frailty. One cross-sectional study reported an association between DHEAS and frailty but the influence of comorbid conditions could not be confidently excluded (78). The importance of DHEAS in the pathogenesis of frailty may be most relevant as part of a generalised endocrine dysfunction (79).

Vitamin D deficiency

Vitamin D deficiency is highly prevalent globally, with prevalence estimates varying within individual populations based on ethnic diversity (80, 81). It is central to the development and maintenance of bone health and calcium metabolism, with severe deficiency resulting in the syndromes of rickets and osteomalacia (82). Based on trial evidence, current guidelines recommend vitamin D supplementation to prevent osteoporotic fractures (83-85). However, a 2017 meta-analysis of calcium and vitamin D supplementation, separately or in combination, pooled data from 33 randomized trials involving 51 145 participants and reported no overall reduction in total fracture risk (86).

Cross-sectional studies provide evidence for associations between vitamin D status and frailty. A study of participants (n=1659) in the Concord Health and

Ageing in Men Project found that low vitamin D status was associated with frailty and independently with four out of five frailty components (87). An analysis of the Toledo Study for Healthy Aging (n=592) reported that low serum 25OHD was associated with frailty (OR 1.65 95% CI 1.02-2.67, p=0.04), defined using the phenotype model (19). These findings were supported by an analysis of the European Male Ageing Study (n=1504) (88), a Mexican study of over 70s (n=331) (89), and a large Austrian study (n=940) (90), which also observed significant associations between low serum 25OHD and individual components of frailty including physical exhaustion, inactivity and reduced gait speed. A smaller Taiwanese study (n=215), reported a strong association between vitamin D status and frailty (odds ratio, OR, 10.7 (CI 2.6 to 44.3) (91).

Longitudinal studies have been established to investigate whether vitamin D status can predict subsequent development of frailty. The prospective association between vitamin D and frailty has been examined in one longitudinal US study involving 369 females, which reported an association between low vitamin levels and incident frailty (HR 2.77, 95% CI 1.14 to 6.71) that was attenuated following adjustment for cardiometabolic diseases (92). An Australian study of 4203 men aged between 70-88 years found that low vitamin D status was associated with increased risk of incident frailty and all-cause mortality, independent of baseline frailty (93). An analysis of the KORA-Age study cohort followed participants up over a mean of 2.9 years and found that low vitamin D status was associated with pre-frailty (OR 2.4, 95% CI 1.2-

5.0), combined pre-frailty/frailty (OR 2.53, 95% CI 1.2-5.2) and all-cause mortality (OR 3.4, 95% 1.1-10.7) (94).

Longitudinal data from the Third National Health and Nutrition Survey (NHANES III) (n=4731), and the Invecchiare in Chianti (InCHIANTI) study (n=1155) indicate that low vitamin D status is associated with increased odds of incident frailty (95, 96). However, conflicting results were reported in one additional US study involving 1,606 men aged over 65, which did not observe a prospective association, despite reporting a relationship between frailty and vitamin D status at baseline (97). The same group reported a U-shaped association between frailty status and vitamin D at baseline in 6307 women aged over 69 years (98). They also observed a trend towards a negative association between serum 25OHD and incident frailty.

The impact of vitamin D supplementation has been assessed in meta-analyses of clinical trials. One meta-analysis pooled data from 13 trials and concluded that there were consistent positive effects of 800-1000 IU doses of vitamin D on strength and balance (99). A 2014 meta-analysis reported a small positive effect of vitamin D supplementation on global muscle strength, but not on mass or power, using data from 30 RCTs involving 5,615 participants (100). A further meta-analysis reported that supplementation did not reduce falls risk by a threshold of 15%, using data from 20 RCTs with 29,535 participants (101).

Insulin resistance

Diabetes has been recognised as a risk factor for frailty. In recent years there has been interest in the role of insulin resistance (IR) in development of frailty and as a target for prevention. IR and associated components of the metabolic syndrome (MetS) are increasing in prevalence globally with industrialisation, and associated lifestyle changes (102, 103). A relatively small number of human studies have investigated these relationships.

A prospective cohort study has reported associations between IR and frailty, defined using the phenotype model, in 1499 individuals aged over 60 with 3.5 year follow up (104). MetS was associated with frailty risk, and this was largely due to central obesity. MetS also had an independent association with reduced grip strength. A further prospective study involving 3141 community dwelling older people reported a positive association between IR and frailty (HR 1.15, 95% CI, 1.02-1.31) (105).

A recent analysis of data from participants (n=1247) in the Longitudinal Aging Study Amsterdam found that although frailty appeared to make a contribution to the association between MetS and mortality, co-morbidities such as diabetes and cardiovascular disease played a larger part (106). A secondary analysis of data from the Beijing Longitudinal Study of Ageing also demonstrated clustering of MetS, frailty and mortality, but it was not possible to confirm directionality or causality (107). Frailty index scores, calculated using the cumulative deficit model, increased with each cardio-metabolic co-morbidity and those with the highest scores had greatest mortality.

Preliminary evidence indicates that MetS may strengthen the association between frailty and impairment of executive function (108).

Basic science research has identified putative mechanisms to account for the above associations, with common pathways for dysregulated skeletal muscle metabolic and contractile function. Central to this is the interplay between metabolically active tissues important in the pathway to frailty including adipose, muscle and bone. The concept of sarcopenic obesity may be important, with visceral adiposity and increased intramuscular lipid driving a pro-inflammatory, insulin resistant, catabolic state (109). Clinical trial evaluations of interventions targeted at components of MetS, including IR, for the prevention or treatment of frailty would be required to confirm clinical utility.

Thyroid and frailty

Changes in thyroid hormone status with normal ageing are well characterised with increases in TSH, decreases in FT3 and stable FT4 concentrations. Data in defined frail cohorts are scarce. Thyroid dysfunction however, has a myriad of effects with impacts on body composition, muscle strength, cognition, bone and cardiovascular health that are pertinent to the ageing phenotype.

Subclinical hyperthyroidism was associated with increased frailty prevalence (OR 2.48, 95% CI 1.15-5.34) but not subsequent frailty development over 5-year follow up in the Osteoporotic Fractures in Men Study (110). No associations were observed with the subclinical hypothyroidism group. The

study included 1455 men aged over 65 and defined frailty using a modified phenotype model. One additional study involving 641 older women reported reduced odds of frailty, defined using the phenotype model, for those with positive thyroglobulin and TPO antibodies, independent of thyroid hormone status (OR 0.30, 95% CI 0.10 to 0.85) (111). Conversely, higher serum FT4 concentrations were associated with increased risk of frailty in men aged between 70-89 years (n=3943) in a cross-sectional Australian study (OR 1.36 95% CI 1.04 to 1.79) (112). The study used the Fatigue, Resistance, Ambulation, Illnesses and Loss (FRAIL) scale. The association held even with FT4 concentrations within the normal reference range.

A 2017 study reported a significant inverse correlation between FT3 and frailty score in elderly subjects (n=112, 62 inpatients with hip fracture and 50 outpatient controls) (113). The study used the 'Survey of Health, Ageing and Retirement in Europe Frailty Instrument (SHARE-FI) to generate the frailty score with an r of -0.436 and $P<0.001$ when correlated with FT3. Furthermore, correlations with measures of nutritional status, disability, co-morbidities and grip-strength were also observed. These relationships were not observed with TSH or FT4. The central limitation of the study is that FT3 can be reduced by a number of factors that predispose to non-thyroidal illness and there is no evidence for supplementation with FT3 in such cases. Nevertheless, the authors proposed that FT3 may be used as a biomarker of frailty status. Reproducibility of findings in well-defined frail cohorts needs to be demonstrated.

Conclusion

Frailty involves complex systems with changes in multiple hormone axes moderated by factors such as nutrition, exercise, and inflammation. Available epidemiological evidence indicates that components of the HPA axis, IGFs and androgens may be of particular importance, with emerging data identifying potential links between single candidate hormones and frailty. However, preliminary evidence indicates that, in frailty, the cumulative burden of hormone deficiencies may be more important than the type of hormonal deficiency, as part of a generalised endocrine dysfunction.

Although there is evidence for vitamin D supplementation for people who are deficient, previous trials of supplementation to improve body composition and subsequent musculoskeletal and metabolic health with age have demonstrated limited efficacy.

Greater understanding of the role of the endocrine system in the development of frailty could lead to the identification of novel pharmacological treatments. Future translational research should focus on better understanding of the endocrine mechanisms of frailty to identify potential biomarkers of the condition, modifiable targets for treatment, and novel pharmacological agents targeted at the endocrine components of frailty. Well designed, appropriately powered consortia based studies will be required to establish the efficacy and long-term safety of potential therapeutic interventions, with a focus on clinically relevant outcomes of high priority for older people living with frailty.

Acknowledgements

None.

Declarations of interest

None.

Author contributions

AC led the development of the search strategy for this commissioned review. Both authors reviewed search results and retrieved relevant papers. Both authors contributed to the writing of the final manuscript, including development of figures.

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Search strategy and selection criteria

We developed a structured search strategy with the assistance of a research librarian at the University of Leeds, UK. We searched Medline, Embase, CINAHL, Web of Science and the Cochrane library; all searches were from January 2001 to May 2017. We combined the search terms frailty, pre frailty, sarcopenia and frail elderly with a wide range of endocrine search terms, including DHEAS, testosterone, IGF-1, cortisol and insulin. Additional papers were identified from the reference lists of retrieved articles and personal libraries.

- **Gait speed <0.8 m/s**
- **Timed up and go test score <12 seconds**
- **Self-reported health status score <6**
- **PRISMA-7 questionnaire > 3**
- **Self-reported physical activity scale in the elderly (PASE) score <56 (men) or < 59 (women)**

Box 1. Simple instruments for identifying frailty recommended by the National Institute for Health and Care Excellence (NICE)

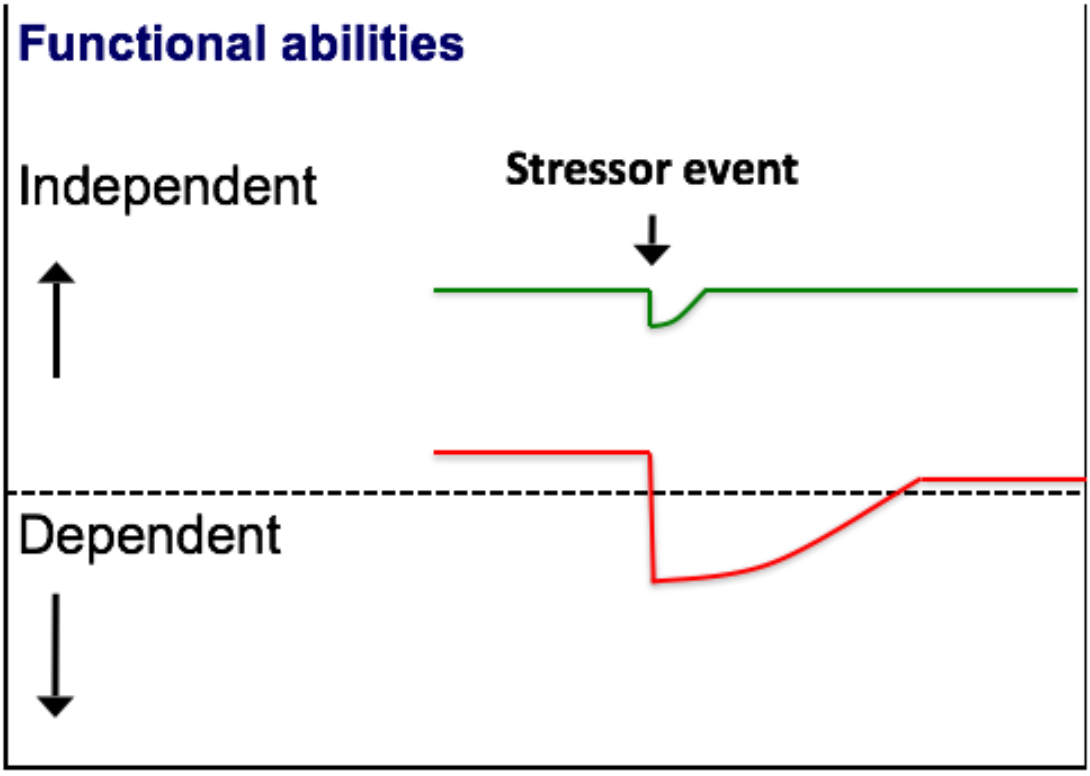

Figure 1.Vulnerability of older people with frailty to a sudden change in health status after a minor stressor event

The green line represents a fit older person who, after a minor stressor event such as an infection, has a small deterioration in function and then returns to baseline. The red line represents an older person with frailty who, after a similar stressor event, undergoes a larger deterioration, which may manifest as functional dependency, and who does not return to baseline. The horizontal dashed line represents the cutoff between dependent and independent.

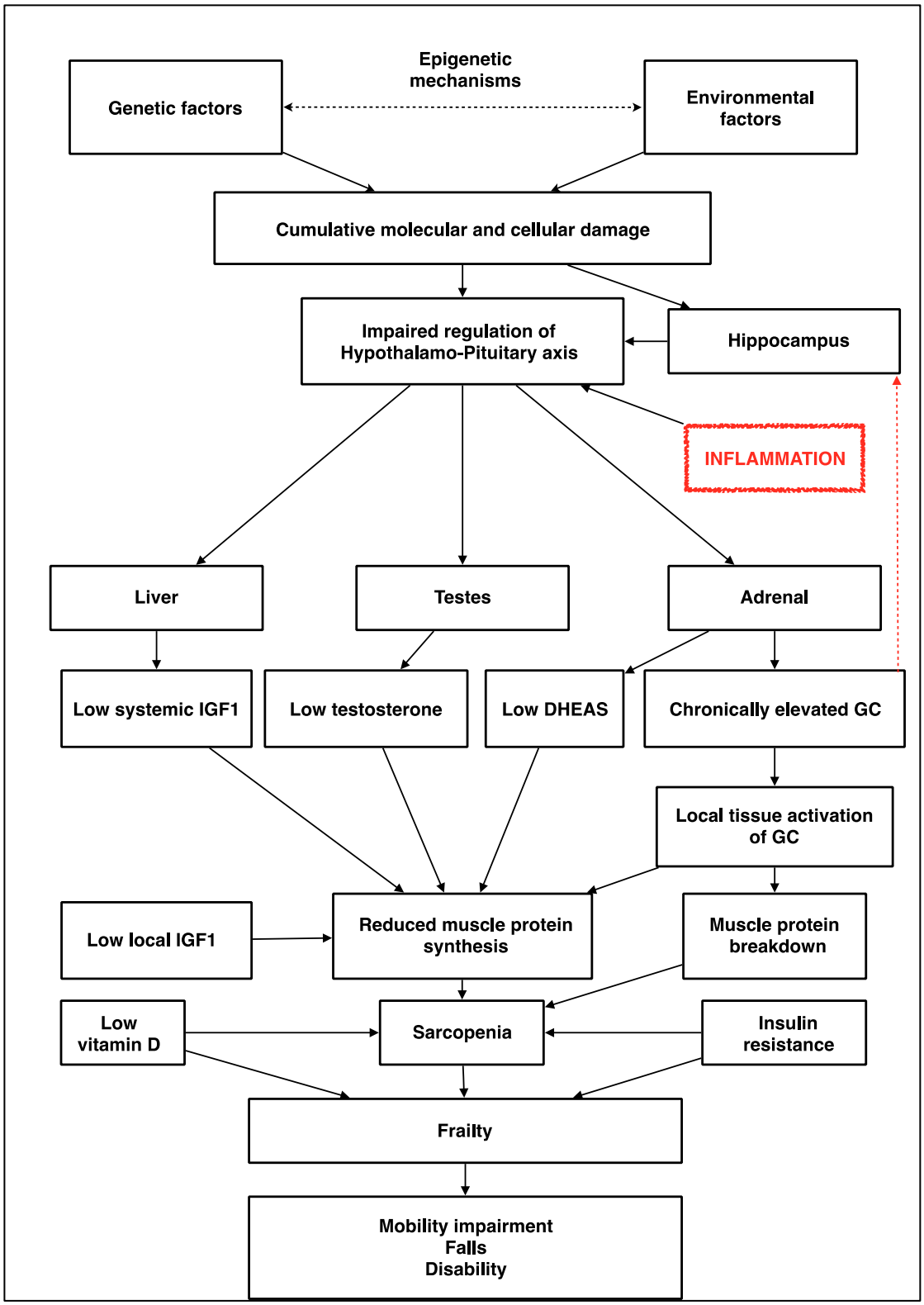

Figure 2. A schematic representation of the potential endocrine mechanisms involved in the development of frailty.