Frailty predicts adverse outcomes in older people with diabetes

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Impact of frailty on adverse diabetes outcomes

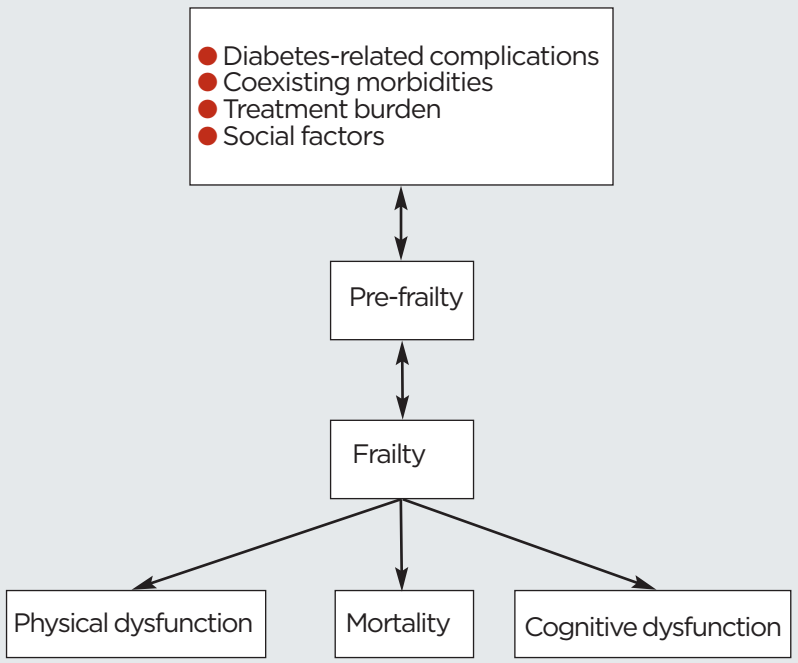

FIGURE 1
Impact of frailty on adverse diabetes outcomes. Multimodal intervention at the pre-frailty and frailty stages may help improve outcomes

What are the causes of frailty in older diabetes patients?

How should frailty be assessed?

How can the development of frailty be prevented?

DIABETES IS BECOMING AN INCREASINGLY GERIATRIC DISEASE WITH PREVALENCE LIKELY TO reach an epidemic level.[1] The greatest proportional increase in the number of people with diabetes by age group is predicted to occur in individuals between 60 and 79 years of age.[2]

In older people living with diabetes, geriatric syndromes, which indicate frailty, are emerging as a third category of complications in addition to the traditional microvascular and macrovascular sequelae. In turn, these syndromes lead to considerable disability and are associated with adverse outcomes, leading eventually to increased mortality.[3]

Understanding the pathway from diabetes to disability is essential for effective intervention and prevention. This article explores the key role of frailty in adverse outcomes of diabetes and suggests a management approach to delay the development of disability and thus improve outcomes.

FRAILTY

Frailty is a distinct health state that is characterised by a reduction in physiological reserve and the inability to resist minor physical or psychological stressors.[4]

Frailty is defined by the presence of three or more phenotypes (weight loss, muscle weakness, decreased physical activity, exhaustion and slow gait speed).[5] The presence of one or two phenotypes describes a pre-frail state, and the absence of phenotypes describes a non-frail person, see box 1, right.

It is important to note that frailty is not synonymous with either comorbidity or disability; rather that comorbidity is an aetiological risk factor for, and disability is an outcome of, frailty.

Sarcopenia, or loss of muscle mass, is the muscular manifestation of the frailty phenotype and is defined as a »

Box 1

Frailty phenotype and assessment scale [5,36]

1 Slow gait speed
2 Muscle weakness
3 Decreased physical activity
4 Exhaustion
5 Unintentional weight loss

- **Non-frail:** Absence of criteria
- **Pre-frail:** Presence of 1-2 criteria
- **Frail:** Presence of ≥ 3 criteria

FRAIL*
Fatigue: Self-reported
Resistance: Unable to climb a flight of stairs
Ambulation: Unable to walk a block
Illness: > 5 comorbidities
Lost weight: > 5 kg in past 6 months

*Three criteria are diagnostic of frailty

Box 2

Sarcopenia phenotype and assessment scale[6,37]

Sarcopenia
1 Low muscle mass
2 Low muscle strength
3 Low performance

- **Pre-sarcopenia:** Low muscle mass, normal strength and performance
- **Sarcopenia:** Low muscle mass, low strength or low performance
- **Severe sarcopenia:** Low muscle mass, strength and performance

SARC-F*
Strength (difficulty lifting 10 lb weight)
Assistance in walking (difficulty walking across a room)
Rise from a chair (difficulty transferring from chair to bed)
Climb stairs (difficulty climbing flight of stairs)
0 = No difficulty
1 = Some difficulty
2 = A lot of difficulty or unable to carry out the task

Falls (number of falls in previous year)
No falls = 0, 1-3 falls = 1, ≥ 4 falls = 2

*SARC-F score ≥ 4 indicates those at risk for adverse outcomes from sarcopenia

Box 3

Factors that reduce muscle function in older people with diabetes

- Malnutrition
- Anabolic resistance
- Decreased muscle protein synthesis
- Increased muscle protein breakdown
- Increased intramuscular lipid accumulation
- Decreased muscle mass
- Decreased muscle strength
- Decreased muscle quality (muscle strength per muscle area)

Box 4

Interventions to reduce frailty

- Regular screening
- Adequate protein intake
- Correction of vitamin D deficiency
- Resistance exercise training
- Glycaemic control
- Review of hypoglycaemic drugs

generalised loss of skeletal muscle mass and strength that leads to low physical performance, see box 2, left.[6]

PATHOGENESIS

The phenotype of frailty is thought to develop as a result of abnormalities at molecular, cellular and physiological levels. Accumulation of deficits across multiple physiological systems, such as cardiovascular, metabolic, inflammatory and neuroendocrine systems, increases the risk of frailty.[7]

With increasing age, body composition changes such that there is increased body fat and a reduction in muscle mass leading to increased insulin resistance which in turn leads to reduced protein synthesis and sarcopenia, see box 3, below left.[8]

Persistent hyperglycaemia associated with diabetes increases the production of advanced glycation end products that accumulate in muscle and cartilage causing muscular stiffness and reduced muscle function.[9,10]

Peripheral neuropathy and reduction in motor neurons is another cause of sarcopenia in diabetes. Patients with peripheral neuropathy have a greater calf intermuscular adipose tissue volume which has been shown to be associated with poor muscle strength and function.[11] Increased inflammatory cytokines associated with diabetes such as tumour necrosis factor and interleukin 6 also have negative effects on muscle mass, strength and physical performance.[12]

FRAILTY AND DIABETES

Ageing-related muscle loss, and the consequent development of sarcopenia and frailty, is accelerated when diabetes is present. Diabetes is associated with frailty and the risk increases further with co-existing hypertension, diabetes complications or renal disease.[13,14]

Diabetes is associated with a two- to four-fold higher risk of low muscle mass compared with control subjects which increases the risk of sarcopenia.[15] Persistent hyperglycaemia has been shown to be associated with poor muscle quality, performance and strength independent of age, race, sex, weight, height and physical activity.[16,17] The coexistence of dementia and diabetes also increases the risk of frailty.[18]

IMPACT OF FRAILTY ON OUTCOMES

Diabetes in older people is associated with an increased risk of adverse outcomes such as physical decline, cognitive dysfunction and mortality. Diabetes-related complications, associated comorbidities and treatment burden do not fully explain the risk of adverse outcomes.[19] Studies exploring the pathway from diabetes to adverse outcomes did not adjust for frailty.[20] This may suggest that another unmeasured factor such as frailty may be implicated in these adverse outcomes.

In one study, the presence of frailty or sarcopenia increased the risk of hospitalisation and activities of daily living (ADL) disability in older people with diabetes.[21] In another study, frailty indices, rather than the associated comorbidities, predicted the increased risk of incident disability.[22]

'Maintenance of adequate nutrition, physical exercise, and glycaemic control may help to delay or prevent the development of frailty and to improve outcomes'

Frailty is also associated with an increased risk of cognitive decline, thereby increasing the risk of disability when it comes to instrumental ADL (e.g. shopping, driving or managing personal finances). In a recent meta-analysis, frailty was a significant predictor of incident Alzheimer's disease, vascular dementia and all dementia.[23]

In a systematic review, there was evidence that midlife behaviours such as smoking, alcohol consumption, poor diet and low levels of physical activity are associated with frailty and dementia in later life. This may suggest that frailty and dementia share common risk factors and that the promotion of physical activity, healthy diet and smoking cessation in all mid-life populations may have a positive impact in promoting successful ageing and in reducing the incidence of frailty and dementia.[24]

In an Italian study a one point increase in the frailty index was associated with a 36% increase in long-term mortality in individuals without diabetes and a 93% increase in those with diabetes after 12 years of follow-up. Furthermore, increasing severity of frailty was predictive of mortality independent of diabetes-related complications, see figure 1, p17.[25] Frailty may therefore

key points

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The greatest proportional increase in the number of people with diabetes by age group is predicted to occur in those aged 60 to 79. In older people living with diabetes, geriatric syndromes, which indicate frailty, are emerging as a third category of complications in addition to the traditional microvascular and macrovascular sequelae.

Frailty is defined by the presence of three or more phenotypes (weight loss, weakness, decreased physical activity, exhaustion and slow gait speed). The presence of one or two phenotypes describes a pre-frail state, and the absence of phenotypes describes a non-frail person. Sarcopenia, or loss of muscle mass, is the muscular manifestation of frailty phenotype and is defined as a generalised loss of skeletal muscle mass and strength that leads to low physical performance.

Persistent hyperglycaemia associated with diabetes increases the production of advanced glycation end products that accumulate in the muscle and cartilage causing muscular stiffness and reduced muscle function. Peripheral neuropathy and reduction in motor neurons is another cause of sarcopenia in diabetes. Patients with peripheral neuropathy have a greater calf intermuscular adipose tissue volume which has been shown to be associated with poor muscle strength and function.

Persistent hyperglycaemia has been shown to be associated with poor muscle quality, performance and strength independent of age, race, sex, weight, height and physical activity. The coexistence of dementia and diabetes also increases the risk of frailty. There is evidence that midlife behaviours such as smoking, alcohol consumption, poor diet and low levels of physical activity are associated with frailty and dementia in later life.

Frailty is a dynamic condition which can worsen or improve over time. Patients may progress from a non-frail to pre-frail or frail state. There is evidence that, with timely intervention, there is a greater chance for an individual to recover from pre-frail to non-frail than to deteriorate into frailty. The progression of frailty is likely to be multifactorial, therefore multimodal intervention, including maintenance of adequate nutrition, physical exercise, and glycaemic control, may help to delay or prevent the development of frailty and to improve outcomes.

Adequate nutrition is essential for protection against the development of frailty. Muscular protein synthesis diminishes with increasing age, therefore older people will need more dietary protein to compensate for this anabolic resistance. Vitamin D levels < 15 ng/ml have been shown to be associated with pre-frailty and frailty. There is no specific medication at present for the prevention of frailty but it should be noted that hypoglycaemic medications have varying effect on muscle function and should be reviewed. Frailty and sarcopenia should be identified during the annual review of older people with diabetes.

be considered as a new prognostic factor to identify individuals with diabetes who are at high risk of mortality.

PREVENTION

Frailty is a dynamic condition which can worsen or improve over time. Patients may progress from a non-frail to pre-frail or frail state. There is evidence that, with timely intervention, there is a greater chance for an individual to recover from pre-frail to non-frail than to deteriorate into frailty.[26] The progression of frailty is likely to be multifactorial, therefore multimodal intervention, including maintenance of adequate nutrition, physical exercise, and glycaemic control, may help to delay or prevent the development of frailty and to improve outcomes, see box 4, opposite.

'With timely intervention, there is a greater chance for an individual to recover from pre-frail to non-frail than to deteriorate into frailty'

Assessment

Frailty and sarcopenia should be identified during the annual review of older people with diabetes. FRAIL and SARC-F scales have been developed and validated as sensitive and specific tools to assess patients for frailty and sarcopenia respectively, see box 1, p17 and box 2, opposite.

Intervention

Adequate nutrition is essential for protection against the development of frailty.[27] Muscular protein synthesis diminishes with increasing age, therefore older people will need more dietary protein to compensate for this anabolic resistance. A daily protein intake of 1.0-1.2 g/kg is recommended.[28] Proteins rich in the essential amino acid leucine may offset muscle loss, promote positive muscle protein balance and reduce sarcopenia.[29]

Vitamin D levels < 15 ng/ml have been shown to be associated with pre-frailty and frailty.[30] A diet rich in vitamin D and leucine enriched whey protein has also been shown to increase muscle mass and improve muscle function.[31]

In a secondary analysis of the longitudinal observational NuAge study, the combination of diet and physical activity was associated with better maintenance of muscle strength in older Australian men (aged 67 to 84 years) with diabetes than diet alone.[32] Adopting healthy behaviour such as a healthy diet and physical exercise has a more positive effect in frailty prevention than reducing cardiovascular risk factors.[33]

Good glycaemic control may also have a role in preventing frailty. In the Korean Longitudinal Study of Health »

Table 1

Effects of hypoglycaemic medications on sarcopenia and frailty[38-42]

Medication	Muscle effect
Metformin	Decreases odds of frailty Increases lean:fat ratio Reduces fat mass
Glitazones*, dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 agonists**	Increase lean muscle mass
Sulfonylureas and glinides***	Induce muscle atrophy
Insulin****	Neutral effect
Sodium-glucose cotransporter-2 inhibitors	Unknown effect

*Increases insulin sensitivity and muscle protein synthesis
**Increases muscular blood supply
***In rat experiments, glimepiride among sulfonylureas and repaglinide among glinides were the most potent atrophic agents
****Insulin increases protein synthesis in young adults but not in older people

and Aging, uncontrolled diabetes (HbA_{1c} > 8.5%), was associated with poor muscle quality in older people with diabetes (OR 4.51).[17] This has also been shown in the San Antonio Longitudinal Study of Aging where good glycaemic control (HbA_{1c} < 7%) had a positive impact on lower extremity performance compared with poor glycaemic control (HbA_{1c} > 7%).[34]

'Frailty and sarcopenia should be identified during the annual review of older people with diabetes'

However, hypoglycaemia should be avoided in this group of patients as it may be associated with increasing risk of falls and predisposition to frailty and disability.[35]

There is no specific medication at present for the prevention of frailty. However, it should be noted that hypoglycaemic medications vary in their effect on muscle function and should be reviewed, see table 1, p19.

CONCLUSION

Frailty is a significant complication of diabetes which has not been routinely measured in clinical studies examining the relationship between diabetes and adverse outcomes.

'Hypoglycaemic agents vary in their effect on muscle function and should be reviewed'

Diabetes is associated with a decline in muscle strength, mass and function which leads to sarcopenia, frailty and eventually disability. However, progression to frailty with its associated adverse outcomes may be slowed or even prevented with appropriate interventions such as review of adequate nutrition, exercise training, good glycaemic control and the use of appropriate hypoglycaemic medications. It is imperative therefore to identify the presence of frailty in the older person with diabetes if we are to avoid the associated adverse outcomes.

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