The importance of identifying a frailty metabolic phenotype in managing frail older people with type 2 diabetes

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Diabetes mellitus affects around 589 million adults (20-79 years old) worldwide and this is expected to increase to 853 million by the year 2050, an increase of 46%. The peak prevalence (24.8%) is in the older age group, 75-79 years, because of increased life expectancy.[1] In old age, frailty is an emerging complication of diabetes, with a prevalence of up to 48%.[2-5] The development of frailty is associated with an increased risk of adverse events such as injurious falls, disability, poor quality of life and mortality. These adverse events lead to more emergency department visits, hospitalisation and institutionalisation, with greater overall costs.[6-8]

Diabetes-associated morbidities and diabetes-related complications increase the risk of frailty. While clinical manifestations of multimorbidity reflect the underlying clinical conditions, frailty is a syndrome of symptoms characterised by weakness, wasting and lack of endurance, which is not part of co-morbidity.[9] In older people with diabetes, morbidity mediates the progression to frailty, especially when diabetes-related conditions such as hypertension and renal impairment coexist.[10,11] Other factors common in older people with diabetes, such as inadequate nutrition, reduced physical exercise, decline in neuromuscular function, vitamin D deficiency and geriatric syndromes, contribute to the development of frailty.[12-14]

Both morbidity and frailty follow the pathway of a disablement process model (DPM), which leads to functional decline and eventually disability.[15] Therefore, screening for frailty should be an integrated part of diabetes care in older people, and should be considered in primary care predominantly but also opportunistically in hospitals in outpatient settings and during emergency admissions. The current screening tools are based on two conceptual frames, either recognition of a phenotype such as the criteria proposed by Fried or accumulation of deficits such as those proposed by Rockwood.[16,17] Comprehensive geriatric assessment (CGA), a multidimensional evaluation of physical, cognitive, psychological, functional and social aspects, is central in any tool to assess frailty and tailoring (individualising) the care needs of older people with diabetes.[18] Although no cost-effective strategies for frailty have yet been identified, there is ongoing interest in AI detection through medical electronic records, assessment of frailty via telephone calls, and use of frailty biomarkers.

In addition to the impact on adverse outcomes, frailty affects the metabolic profile of older people with diabetes. Frailty is associated with significant skeletal muscle loss or sarcopenia, which results in reduced glucose muscle uptake.[19] With the development of frailty, there is also a predominant loss of the insulin-resistant type II muscle fibres rather than the insulin-sensitive type I fibres.[20,21] Although weight loss is one of the frailty criteria, it is not a prerequisite for frailty diagnosis. Obesity can also be associated with frailty and a U-shaped relationship has been reported between body mass index (BMI) and frailty.[22] Therefore, frail older people with diabetes are likely to be on a metabolic spectrum, which starts from a sarcopenic obese (SO) phenotype at one end and has an anorexic malnourished (AM) phenotype at the other end. In the SO frailty phenotype, although the predominant loss of type II muscle fibres reduces insulin resistance, the presence of obesity attenuates this effect and shifts the balance into unfavourable metabolism, with an overall increased insulin resistance and a progressive course of diabetes trajectory. On the other hand, in the AM frailty phenotype, the predominant loss of the insulin-resistant muscle fibres type II associated with significant weight loss reduces insulin resistance, improves hyperglycaemia and leads to a regressive course in the diabetes trajectory.[23]

This commentary does not relate to type 1 diabetes (T1DM) although many of the features described would still be applicable. Earlier this year, NICE published NG 28 which was an update to their 2015 guidance on management of type 2 diabetes.[24] In this version, they have incorporated rather basic but practical advice on managing older adults with frailty but

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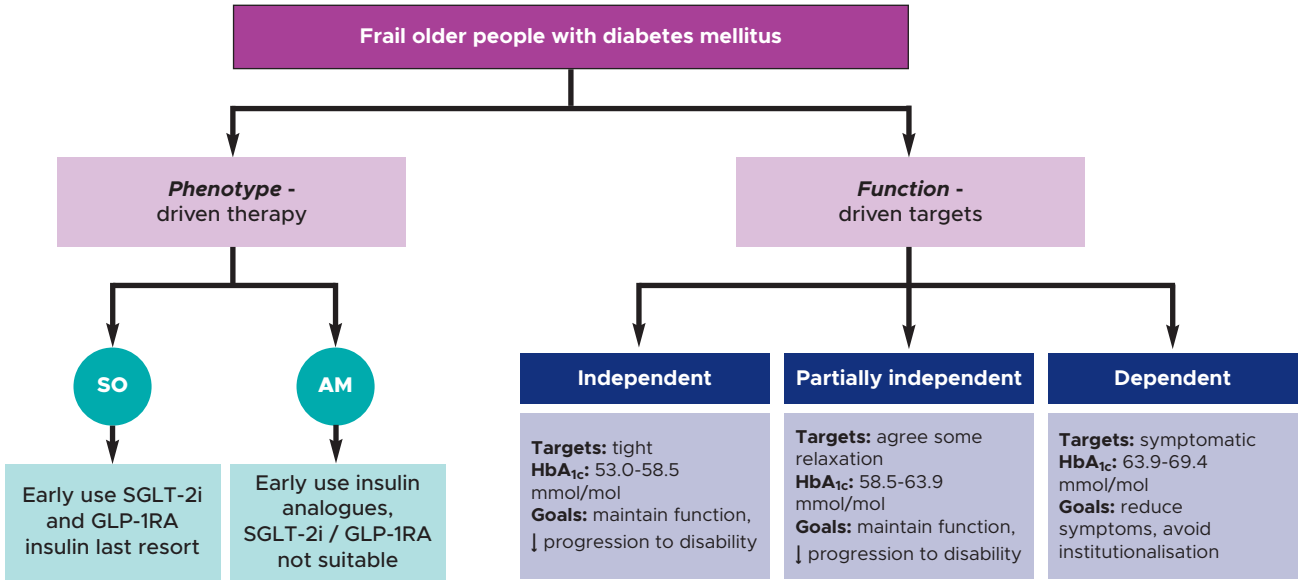
Figure 1. Metabolic phenotype-driven choice of hypoglycaemia therapy and function-driven targets. In the SO phenotype, the early use of SGLT-2i and GLP-1RA is appropriate due to the unfavourable metabolic profile in this phenotype and high cardiovascular risk. In the AM phenotype, the early use of long-acting insulin analogues is appropriate due to anabolic properties of insulin. Targets move from tight to symptomatic relief depending on function.



SO=Sarcopenic obese, AM=Anorexic malnourished.

have missed the opportunity to emphasise the complexity of varying degrees of frailty in considering the choice of hypoglycaemic therapy.

We believe the choice of glucose-lowering therapy in frailty should be determined by the metabolic frailty phenotype of the individual.[25] In the SO (sarcopaenic obese} phenotype, the early use of sodium glucose transporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RA) is required because of their weight-losing properties and their favourable effect on metabolism and cardiovascular outcomes.[26] This represents an intensification of therapy. Insulin is the last resort due to risk of further weight gain and the increased insulin resistance in this phenotype. In the AM (anorexic malnourished) phenotype, the early use of long-acting insulin analogues is appropriate due to a lower risk of hypoglycaemia and the advantage of weight gain in this anorexic group of patients. We consider that SGLT-2 inhibitors and GLP-1RA are not suitable in this frailty phenotype due to the effects of significant weight loss, risk of dehydration, hypotension, falls and fractures.[23] In the AM phenotype the aims are to de-intensify therapy and maintain quality of life. In summary, the spectrum of frailty phenotypes is associated with different metabolic changes which require customised management. See Figure 1 for glycaemic HbA_{1c} targets based on function and independence/dependence.

In conclusion, the development of frailty increases the risk of diabetes-related adverse outcomes and induces unfavourable metabolic changes, which lead to different metabolic phenotypes. Future outcome studies are required to investigate whether improved glycaemic control reduces the risk of frailty as the main outcome. In addition, investigations to explore the metabolic spectrum of frailty are still needed as they are not routine in clinical practice. This is a complex area associated with a growing interest in the metabolic contributors to frailty and the reverse scenario of frailty having metabolic consequences. This will require studies into the relationship between frailty and dietary factors, glucose-insulin dynamics, insulin resistance, and metabolomic studies in frailty.

Individual frailty phenotypes need to be characterised from the outset of clinical trials to specifically investigate outcomes relevant to the underlying metabolic profile. Novel hypoglycaemia agents with muscle-protective effects to reduce the risk of sarcopenia and frailty need future exploration. Finally, myostatin inhibitors are gaining promise in frailty and sarcopaenia management by increasing muscle mass and improving physical muscle function.

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