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*Review*

# Insulin in Frail, Older People with Type 2 Diabetes—Low Threshold for Therapy

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**Abstract:** The global prevalence of comorbid diabetes and frailty is increasing due to increasing life expectancy. Frailty appears to be a metabolically heterogeneous condition that may affect the clinical decision making on the most appropriate glycaemic target and the choice of the most suitable hypoglycaemic agent for each individual. The metabolic profile of frailty appears to span across a spectrum that starts at an anorexic malnourished (AM) frail phenotype on one end and a sarcopenic obese (SO) phenotype on the other. The AM phenotype is characterised by significant weight loss and less insulin resistance compared with the SO phenotype, which is characterised by significant obesity and increased insulin resistance. Therefore, due to weight loss, insulin therapy may be considered as an early option in the AM frail phenotype. Insulin-related weight gain and the anabolic properties of insulin may be an advantage to this anorexic phenotype. There is emerging evidence to support the idea that insulin may improve the muscle function of older people with diabetes, although this evidence still needs further confirmation in future large-scale prospective studies. Long acting insulin analogues have a lower risk of hypoglycaemia, comapred to intermediate acting insulins. Additionally their simple once daily regimen makes it more appropriate in frail older patients. Future research on the availability of new once-weekly insulin analogues is appealing. The goals of therapy are to achieve relaxed targets, avoid hypoglycaemia and to focus on the maintenance of quality of life in these vulnerable patients.

**Keywords:** older people; diabetes mellitus; management; insulin therapy; frailty; sarcopenia



**Citation:** Abdelhafiz, A.; Bisht, S.; Kovacevic, I.; Pennells, D.; Sinclair, A. Insulin in Frail, Older People with Type 2 Diabetes—Low Threshold for Therapy. *Diabetology* **2022**, *3*, 369–383. https://doi.org/10.3390/diabetology3020028

Academic Editor: Giancarlo Tonolo

Received: 24 April 2022
Accepted: 17 June 2022
Published: 20 June 2022



## 1. Introduction

The global prevalence of diabetes is increasing, particularly, in the older age groups. For example, 44% of people with diabetes are above the age of 65 years [1]. Frailty is an emerging new complication of diabetes and increasingly recognised in clinical guidelines for diabetes management [2–6]. Frailty is not a homogeneous concept and appears to have a spectrum of different metabolic phenotypes, which may influence the choice of the most suitable hypoglycaemic agents for an individual [6]. The metabolic spectrum of frailty starts by the anorexic malnourished (AM) phenotype with significant weight loss and less insulin resistance on one end, and the sarcopenic obese (SO) phenotype with excess weight and increased insulin resistance on the other end [6]. Based on our experience in managing older people with diabetes, we hypothesise that insulin therapy, especially the long-acting insulin analogues, may be a good option to be introduced early in the AM phenotype due to its anabolic effects and the possible positive benefits on muscle function and body weight. This manuscript reviews the potential positive effects of insulin on muscle function in older people (≥60 years of age) with diabetes, explores the hypoglycaemic safety of insulin analogues in this population and presents a literature-based recommendation for an early introduction of insulin in the AM frail phenotype.

## 2. Methods

We undertook a literature search of the following databases: Google Scholar, PubMed and Embase. Medical Subject Heading (MeSH) terms used were: diabetes mellitus, older people, old age, elderly, frailty, sarcopenia, muscle function, muscle strength, muscle mass, muscle quality, insulin, therapy, management, anabolic effects, quality of life and hypoglycaemia, individually and in combination. Articles were reviewed for relevance by abstract. A manual search of citations in the retrieved articles was performed in addition to the electronic literature search. The search for articles on the effect of insulin on skeletal muscle was limited to studies published over the last 10 years and reported clear outcomes. The search for articles on the safety of long-acting insulin analogues in older people was limited to studies published over the last 5 years. The inclusion criteria were: 1. Studies that reported the impact of insulin therapy on muscle mass, strength, quality or function, and 2. Studies that investigated the safety of long-acting insulin analogues in older people aged $\geq$60 years with diabetes. The exclusion criteria were: 1. Non-English language or non-human studies, 2. Studies with no clear outcome, 3. Studies that compared first- with second-generation long-acting insulin analogues and 4. Case reports, review articles, editorials, abstracts, conference proceedings or expert opinions. All articles derived from the search enquiry were independently examined by the authors and data were extracted from each study in a predesigned standardised information table that included author, study design, year of publication, country of origin, participants studied, aim of the study and the main findings. Any disagreements between authors were resolved by consensus.

## 3. Effects of Insulin on Skeletal Muscles

Although insulin has physiologic anabolic properties, data on the effects of insulin on skeletal muscle mass, strength or function are limited. Insulin may have the potential to improve muscle mass and increase body weight in frail, older people with diabetes, especially in the AM phenotype where insulin-associated weight gain could be seen as an advantage. Previous studies have shown that insulin can stimulate muscle protein synthesis and anabolism in younger individuals, but this anabolic effect is blunted in older people, which suggests that higher doses of insulin may be required to achieve this anabolic effect in older age groups [7,8]. Through our literature search and after the application of exclusion criteria, five studies investigated the effect of insulin on muscle function and were included in this manuscript. Although the evidence is limited, these studies have shown some emerging evidence that insulin may be associated with some positive effects on skeletal muscles of older people with diabetes. (Table 1) Tanaka et al., in their cross-sectional study of 191 older Japanese men, with a mean (SD) age of 60.2 (12.5) years, with type 2 diabetes mellitus, found endogenous insulin to be significantly and positively correlated with skeletal muscles mass of the upper and lower limbs [9]. Insulin levels were also significantly lower in subjects with sarcopenia compared to those without ($p < 0.05$) [9]. This may suggest that the reduction in endogenous insulin plays an important role in the pathogenesis of sarcopenia in older people with diabetes mellitus, and maintaining endogenous insulin secretion may be important to prevent sarcopenia. Although this study included a reasonably large sample size, it included only men and excluded patients on insulin therapy; therefore, it was not able to draw similar conclusions for women or investigate the effect of exogenous therapeutic insulin on skeletal muscles. Bouchi et al., in their retrospective analysis of 312 Japanese older patients with type 2 diabetes, with a mean (SD) age of 64 (11) years, showed the positive effect of insulin therapy on the skeletal muscle index. They also demonstrated an improvement of the decline in muscle mass in the lower extremities after one year of insulin treatment compared to those not on insulin [10]. They concluded that insulin treatment could attenuate the progression of sarcopenia in older people with type 2 diabetes. Compared to patients not on insulin therapy, those who received insulin had a significantly longer duration of diabetes (10 vs. 6 years, $p < 0.001$). It is speculated that, compared to patients who have had diabetes for a short duration, those with a long duration of diabetes exhibit lower endogenous insulin levels, resulting

in impaired insulin signalling in skeletal muscles and lower muscle mass [11]. Therefore, the efficient supply of exogenous insulin could improve insulin signalling in the skeletal muscles, promote protein synthesis and protect against the loss of muscle mass among patients with a longer duration of diabetes [10]. Authors have also adjusted for change in muscle mass and HbA1c and found that the protective effects of insulin treatment on the decline in muscle mass may be independent of the improvement in glycaemic control. This is clinically relevant as muscle mass improvement may be achieved without tighter glycaemic control in older people with diabetes who are at an increased risk of hypoglycaemia. The cross-sectional analysis by Cui et al. found that insulin use was not significantly different among older people with combined diabetes and sarcopenia, and those with diabetes but no sarcopenia (68.4% vs. 74.5%, $p = 0.48$), respectively [12]. However, 36 out of 132 participants did not use exogenous insulin, and fasting insulin and HOMA-IR in the sarcopenia group were all significantly lower than those in the non-sarcopenia group ($p < 0.05$). In addition, the small sample size of this study (132 subjects) and the fact that the duration of diabetes in the sarcopenic and non-sarcopenic groups was similar, may have attenuated the significance effect between both groups. Recently, in the population-based KORA-Age study that included 118 older German people with type 2 diabetes, with a mean (SD) age of 74.6 (6.2) years, insulin therapy was associated with preserved muscle mass, but not muscle function parameters [13]. The strength of this study was the longitudinal design with a follow-up period of three years and the inclusion of relatively older participants with a longer duration of diabetes mellitus, with a mean (SD) duration of 10.1 (9.9) years, but it is limited by the small number of participants (only 20) treated with insulin. In addition, the discrepancy between the positive effects of insulin on muscle mass compared to its effects on muscle function needs future exploration. The most recent large prospective study conducted by Sugimoto et al., which included 588 Japanese older people with type 2 diabetes mellitus, with a mean age (SD) of 70.0 (8.0) years, found that insulin use significantly increased skeletal muscle mass index after one year of follow-up [14]. The strength of this study was the relatively large sample size, good number (25.9%) of participants on insulin treatment at baseline, its longitudinal design and the positive effect of insulin was independent of confounding factors. Although data from the above studies have their limitations, it appears that there is emerging evidence to suggest that insulin therapy may have some advantages on the skeletal muscle parameters of older people with diabetes.

**Table 1.** Recent studies exploring effects of insulin on skeletal muscle in older people with diabetes.

| Study | Patients | Aim to | Main Findings |
| --- | --- | --- | --- |
| Tanaka K et al., cross-sectional, Japan, 2015 [9]. | 191 men with type 2 DM, mean (SD) age 60.2 (12.5) Y. | Examine association of muscle mass with endogenous insulin secretion. | A. Endogenous insulin significantly and positively correlated with muscle mass of arms and legs as well as RSMI ($p < 0.05$).<br>B. Endogenous insulin significantly lower in subjects with compared to those without sarcopenia ($p < 0.05$). |
| Bouchi R et al., retrospective observational, Japan, 2017 [10]. | 312 patients with type 2 DM, mean (SD) age 64.0 (11.0) Y. | Examine impact of insulin treatment on muscle mass. | A. Insulin was protective against annual decline in SMI (standardized β 0.195; $p = 0.025$) adjusted for covariates.<br>B. In a cohort matched by propensity scores, insulin significantly increased the 1-year change in SMI compared with non-insulin-treated group; mean (SE) 2.40 (0.98%) vs. −0.43 (0.98%), $p = 0.050$). |
| Cui M et al., cross-sectional, China, 2020 [12]. | 132 patients with type 2 DM, aged ≥65 Y. | Explore factors associated with sarcopenia. | A. Insulin use was not significantly different between patients with sarcopenia and those with no sarcopenia (68.4% vs. 74.5%, $p = 0.48$).<br>B. Metformin was significantly less used in patients with compared to those with no sarcopenia (13.2% vs. 41.5%, $p = 0.002$). |

**Table 1.** *Cont.*

| Study | Patients | Aim to | Main Findings |
| --- | --- | --- | --- |
| Ferrari U et al., prospective, Germany, 2020 [13]. | 731 (118 type 2 DM) participants of KORA-Age study, mean (SD) age 74.6 (6.2) Y, F/UP 3 Y. | Investigate association of type 2 DM and insulin treatment with changes in muscle mass, muscle strength and physical performance. | A. DM associated with change in SMI (β −0.1 (95% CI −0.3 to −0.02) kg/m$^2$, $p$ = 0.02), but not with a change in GS (β −0.9, 95% CI −1.9 to 0.04 kg) or TUG (β −0.1, 95% CI −0.7 to 0.5 s).<br>B. Insulin therapy positively associated with change in SMI (β 0.6 (95% CI 0.3 to 0.9) kg/m$^2$, $p$ = 0.001), but not in GS (β −1.6, 95% CI −4.1 to 0.8 kg) or TUG (β 1.6, 95% CI −0.2 to 3.4 s). |
| Sugimoto K et al., observational longitudinal, Japan, 2021 [14]. | 588 patients with type 2 DM, mean (SD) age 70.0 (8.0) Y, F/U 1Y. | Examine relationship between glycaemic control and effect of antidiabetic agents on sarcopenia. | After 382 (53) days of F/U:<br>A. Frequency of sarcopenia non-significantly increased (7.8% vs. 6.3%, $p$ = 0.12).<br>B. Patients with ≥1% drop in HbA1c had significant increase in SMI (B = 0.113, $p$ = 0.027), gait speed (B = 0.145, $p$ = 0.002), but non-significant change in handgrip strength (B = −0.005, $p$ = 0.914).<br>C. Insulin use significantly increased SMI (B = 0.115, $p$ = 0.022).<br>D. Oral antidiabetic therapy has no effect on sarcopenia. |

DM = Diabetes mellitus, SD = Standard deviation, Y = Year, RSMI = Relative skeletal muscle index, SMI = Skeletal muscle index, SE = Standard error, F/U = Follow-up, CI = Confidence interval, GS = Grip strength, TUG = Timed up and go.

## 4. Insulin Analogues Safety

Insulin analogues, such as insulin glargine, detemir and degludec, are structurally altered human insulins that mimic the pharmacokinetic properties of endogenous insulin more closely than intermediate-acting insulins. Because of the long duration of action and the less pronounced insulin peak, long-acting insulin analogues have less risk of hypoglycaemia especially nocturnal hypoglycaemia. The evidence of this benefit was conflicting in earlier clinical trials [15–22]. However, most of these earlier studies predominantly included patients under the age of 60 years, which caused it to be less powered in detecting the efficacy and safety of long-acting insulin analogues in older age groups who are at increased risk of hypoglycaemia and its severe consequences than younger people. Through our literature search and following the application of the exclusion criteria, five studies investigated the safety of long-acting insulin analogues in older people with diabetes and were included in this manuscript. The recent studies that included older people with type 2 diabetes have shown some benefits of the new long-acting insulin analogues, compared to the older human insulins (Table 2). Fujimoto et al. showed that twice-daily insulin degludec/insulin aspart to improve daily glucose level variability, morning and evening glucose control and quality of life (QOL) in 22 Japanese men, with a mean (SD) age of 68.0 (9.9) years, previously treated with premixed insulin [23]. However, there was no significant difference in the incidence of hypoglycaemia before and after insulin switching. The total and therapy-related QOL feeling scores favoured insulin degludec/insulin aspart; whereas social, physical and daily activities scores were not significantly different. The flexibility of injection timing and glycaemic control may explain the improvement in the total and therapy-related feeling subscores in the QOL questionnaire. However, this study was limited by the small sample size and the short duration of follow-up, which may suggest that the switch in the insulin regimen might not explain all the changes in the endpoints, and other factors, such as lifestyle changes and physicians' motivations, might have contributed to the results. Another limitation was that the incidence in hypoglycaemia may have not been accurate, because the frequency of this event was calculated based on self-measured blood glucose levels or patients' symptoms. Lipska et al., in their large retrospective observational study of 22,489 patients with type 2 diabetes, found that the initiation of a basal insulin analogue (glargine or detemir) was not associated with

a reduced risk of hypoglycaemia-related emergency department (ED) visits or hospital admissions compared with NPH insulin. Glycaemic control was similar in both groups after one year of follow-up [24]. However, the population included in this study were relatively young, with a mean (SD) age of 60.2 (11.8) years. Previous studies using the national registries in Finland that included participants of similar ages to those presented in Lipska et al.'s study showed a significantly increased risk of hospitalisation related to severe hypoglycaemia with the use of NPH insulin compared with insulin detemir or glargine [25,26]. In addition, although Lipska et al.'s was a large study, only 1928 participants of the total 25,489 used insulin analogues, and despite matching on the propensity score quintiles, some differences between the two groups remained, suggesting that the study did not fully adjust for the confounding factors. Recently, Bradley et al. showed that the initiation of long-acting insulin analogues was associated with a lower risk of ED visits or hospitalisations for hypoglycaemia compared with NPH insulin in older patients ($\geq$65 years) with type 2 diabetes in Medicare beneficiaries [27]. The strength of this study was the large sample size of 575,008 patients with type 2 diabetes, of an older age, with a mean (SD) of 74.9 (6.7) years, and the fact that a large proportion of patients were treated with insulin glargine (407,018 patients) or insulin detemir (141,588 patients). The hazard ratio (HR) for hypoglycaemia was 0.71, 95% confidence interval (CI) 0.63 to 0.80 for glargine vs. NPH insulin, and 0.72, 0.63 to 0.82 for detemir vs. NPH insulin. The older ages of the participants in this study compared to the study conducted by Lipska et al., suggest that age may have contributed to the disparity between the two studies [24]. In the post hoc analysis, Bradley et al. observed that in participants aged 65–68 years; the use of glargine or detemir was not associated with ED visits or hospitalisations for hypoglycaemia compared with NPH insulin [27]. However, in older participants (69–87 years of age), the use of long-acting analogues was associated with a reduced risk of hypoglycaemia compared with NPH insulin. Betônico et al. demonstrated better glycaemic control and fewer nocturnal hypoglycaemia in 34 patients, mean (SD) age 63.0 (7.0) years, using insulin glargine compared with 16 patients, with a mean (SD) age of 60.0 (8.7) years, using NPH insulin [28]. The importance of this study was that it included patients with chronic kidney disease (CKD) stages 3 and 4, which is more common in older people. CKD is associated with a slower insulin degradation, increasing its duration of action that might increase the risk of hypoglycaemia [29]. However, because the insulin analogue has no peak action, it showed less risk of hypoglycaemia in this population. This is clinically relevant as, with the progression of CKD, most hypoglycaemic medications need dose reductions, and the adjustment of these medications, in the face of renal impairment, may not be enough to keep diabetes under control, and therefore insulin is the most effective therapy in this situation [30]. Özçelik et al. showed that the switch from premixed and intensive insulin to twice daily degludec/aspart insulin was associated with a significant reduction in the daily insulin dose requirement and the incidence of hypoglycaemia [31]. The use of premixed and intensive insulin is a complex regimen and may not be an easy option for daily life in older people with diabetes; therefore, the switch to degludec/aspart insulin may be a less complex regimen, as demonstrated in this study and previous studies [32]. Figure 1 illustrates the advantage of the physiological, clinical and therapeutic properties of insulin in the AM frail phenotype.

**Table 2.** Recent studies exploring efficacy and safety of insulin analogues compared with human insulin.

| Study | Patients | Aim to | Main Findings |
| --- | --- | --- | --- |
| Fujimoto K. et al., prospective, observational, Japan, 2018 [23]. | 22 patients with type 2 DM, mean (SD) age 68.0 (9.9) Y, treated with premixed insulin for 2 M, then IDegAsp for next 2 M. | Investigate changes in glucose variability and QOL during switch from premixed insulin to IDegAsp twice daily. | Switching to IDegAsp from premixed insulin:<br>A. Improved daily glucose level variability, morning and evening glucose control and QOL.<br>B. No change in day-to-day variability of morning fasting glucose levels. |
| Lipska KJ et al., retrospective observational, US, 2018 [24]. | 25,489 patients with type 2 DM initiated basal or NPH insulin, mean (SD) age 60.2 (11.8) Y. F/Up 1.7Y. | Compare rates of hypoglycaemia-related ED visits or hospitalisation associated with initiation of long-acting insulin analogues vs. NPH insulin. | A. In 1928 patients initiated on insulin analogue, there were 39 hypoglycaemia-related ED visits or hospital admissions (11.9 events, 95% CI 8.1 to 15.6/1000 person–years) compared with 354 events among 23,561 patients on NPH (8.8 events, 7.9 to 9.8/1000 person–years, $p = 0.07$).<br>B. Adjusted HR 1.16, 95% CI, 0.71 to 1.78 for hypoglycaemia-related events with insulin analogue use.<br>C. After one year, there was no significant difference in glycaemic control between both groups. |
| Bradley MC et al., retrospective, US, 2021 [27]. | Medicare 575, 008 patients, mean (SD) age 74.9 (6.7) Y with type 2 DM, 407,018 initiated insulin glargine, 141,588 detemir, 26,402 NPH. | Examine risk of ED visits or hospitalisations due to hypoglycaemia in older community patients with type 2 DM who initiated long acting or NPH insulin. | A. Incidence rates for ED visits or hospitalisations for hypoglycaemia per 1000 person–years were 17.37 (95% CI 16.89 to17.84) for glargine and 26.64 (95% CI 26.01–27.3) for NPH.<br>B. For detemir and NPH, incidence rates were 16.69 (15.92 to 17.51) and 25.04 (24.01 to 26.11), respectively.<br>C. Glargine or detemir use associated with reduced risk of hypoglycaemia compared with NPH (HR for glargine vs. NPH 0.71, 95% CI 0.63 to 0.80, and detemir vs. NPH insulin 0.72, 0.63 to 0.82). |
| Betônico CC et al., prospective, randomized, 2-way, crossover, open-label, Brazil, 2019 [28]. | 34 patients with type 2 DM randomly assigned to glargine U100 {16 patients, mean (SD) age 63.0 (7.0) Y} or NPH {18 patients, mean (SD) age 60.0 (8.7) Y}. | Compare glycaemic response to glargine U100 or NPH in patients with type 2 DM and CKD stages 3 and 4. | A. After 24 weeks, mean HbA1c declined from 8.86% (72.7 mmol/mol) to 7.95% (62.8 mmol/mol) in glargine group, but increased from 8.21% (66.2 mmol/mol) to 8.44% (69.4 mmol/mol) in INPH group, $p = 0.029$.<br>B. Incidence of nocturnal hypoglycaemia was 3 times lower with glargine (0.5 events/patient) than with INPH (1.5 events/patient; $p = 0.047$). |
| Ozcelik et al., prospective observational, Turkey, 2021 [30]. | 115 patients with type 2 DM, group 1, 55 on premixed insulin switched to IDegAsp; group 2, 60 on intensive insulin switched to bd IDegAsp, median (IQR) age 67.0 (62.0–69.0). Y. | Evaluate efficacy and safety of transition from premixed and intensive insulin to twice-daily insulin IDegAsp. | A. Mean (SD) rate hypoglycaemia 1.5 (0.85)/week before treatment switch in group 1 decreased to 0.03 (0.11)/week after IdegAsp ($p < 0.0001$).<br>B. In group 2, episodes of hypoglycaemia were 0.93 (1.17)/week before treatment transition, decreased to 0.07 (0.25)/week after IDegAsp ($p < 0.0001$). |

DM = Diabetes mellitus, SD = Standard deviation, Y = Year, M = Month, IDegAsp = Insulin degludec/aspart, QOL = Quality of life, NPH = Neutral protamine Hagedorn, F/U = Follow-up, ED = Emergency department, CI = Confidence interval, HR = Hazard ratio, CKD = Chronic kidney disease, IQR = Inter quartile range.

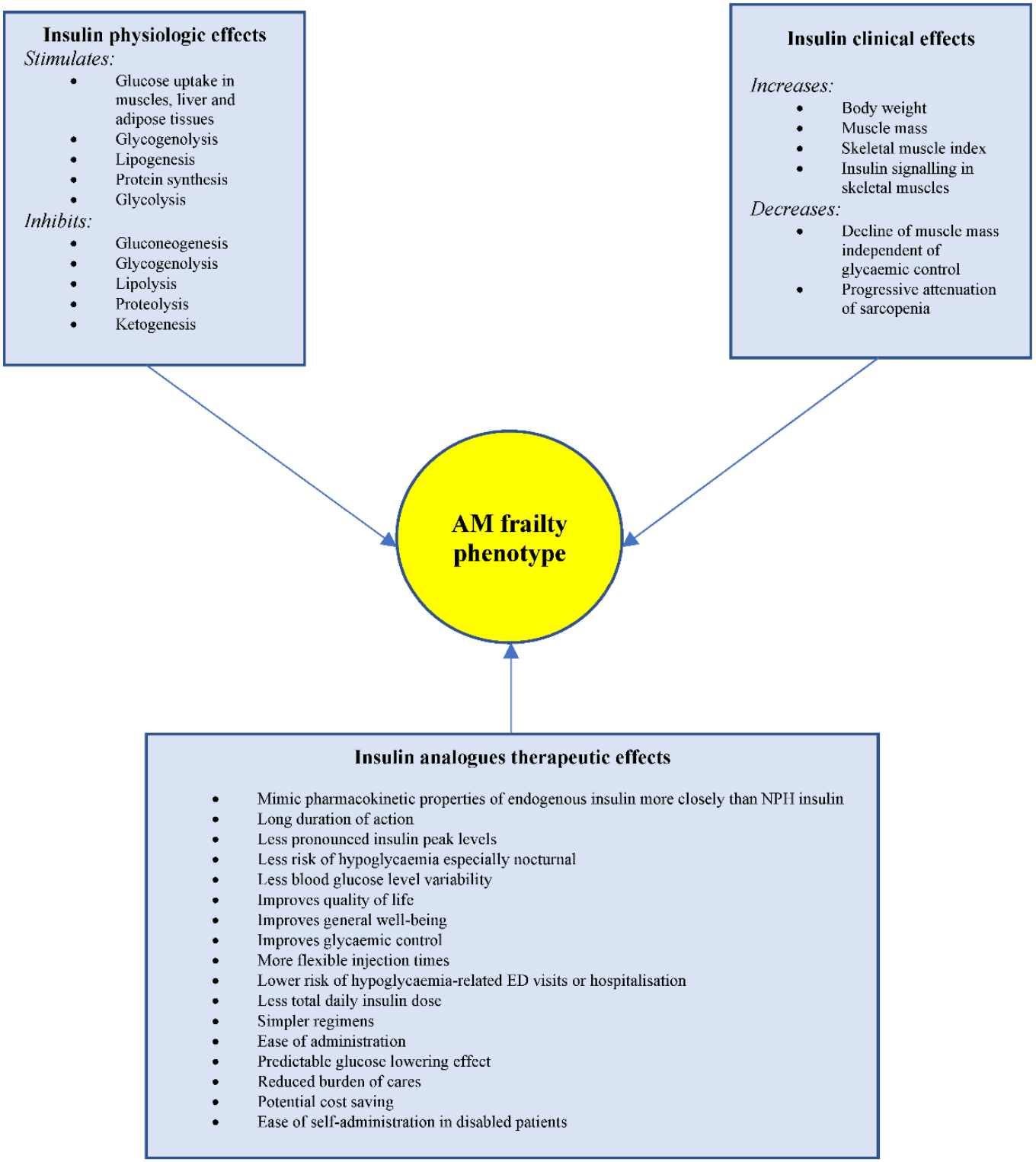


**Figure 1.** Advantage of the physiologic, clinical and therapeutic effects of insulin in the AM frailty phenotype. AM = Anorexic malnourished, ED = Emergency department.

## 5. Insulin—Low Threshold of Therapy

The potential effect on body weight should be considered when prescribing hypoglycaemic agents in frail older people with type 2 diabetes. For example, the use of weight limiting agents, such GLP-1RA and SGLT-2 inhibitors in the AM phenotype, are inappropriate due to the increased risk of further weight loss, dehydration, hypotension and increased risk of falls. Acarabose is associated with weight loss, significant gastrointestinal side effects and is less tolerated. Insulin secretagogues, such as sulfonylureas or glinides, although they have the advantage of desirable weight gain in the malnourished frail phenotype, are unsafe due to their high risk of hypoglycaemia. This population is also likely to have a high prevalence of dementia, which may be associated with erratic eating patterns, and the use of insulin secretagogues may significantly increase their risk of hypoglycaemia. Metformin may not be a suitable choice for many patients who have renal impairments. Additionally, pioglitazone is associated with the increased risk of lower-limb oedema, volume overload and exacerbation of congestive cardiac failure. Insulin has always been perceived as a last resort hypoglycaemic therapy after oral agents due to the associated side effects, such as the increased risk of hypoglycaemia, undesirable weight gain, inconvenience of frequent injections and the burden of blood glucose monitoring. However, in the AM phenotype of frailty, insulin may be a preferred early stage therapy. This phenotype is characterised by anorexia and significant weight loss. As a result, this phenotype has less insulin resistance and is likely to be more responsive to insulin therapy, in comparison to the SO phenotype that is characterised by increased insulin resistance [6]. Insulin-related weight gain is an advantage in this frailty phenotype. It may also have the potential to improve muscle mass and muscle function independent of glycaemic control. Therefore, in the milder form of the AM phenotype, such as people who are still compliant with oral therapy and nutrition, metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors or glitazones can be used as first-line therapy, mainly due to their lower risk of hypoglycaemia. However, in patients with severe malnutrition and those less compliant with oral medications, insulin could be the first line of therapy. Insulin therapy has been shown to produce a sustained improvement in the well-being of older people [33]. Insulin-associated side effects, such as the inconvenience of frequent injections, blood glucose monitoring and the increased risk of hypoglycaemia, should be considered. The new insulin analogues appear as potentially favourable therapy in the AM frail phenotype due to the low risk of hypoglycaemia and the convenience of a once daily injection. In the SO phenotype, insulin therapy remains a last resort choice due to the significantly increased insulin resistance and undesirable weight gain in this phenotype. Metformin is the preferred first-line agent due to its cardiovascular benefits, weight-neutral effects and a potential positive effect on frailty [34,35]. GLP-1RA and SGLT-2 should be considered as a second-line, or first choice in patients not tolerant to metformin, due to their advantage of inducing significant weight loss and their cardio-renal protective effects [36]. Dipeptidyl peptidase-4 (DPP-4) is well tolerated with a low risk of hypoglycaemia or weight gain. Acarabose can be considered as an add-on therapy, if well tolerated. Although it can cause diarrhoea, it may have some cardiovascular benefits, low risk of hypoglycaemia and it promotes weight loss [37]. Insulin secretagogues and glitazones should be avoided in this frailty phenotype due to their increased risk of further weight gain (Figure 2).

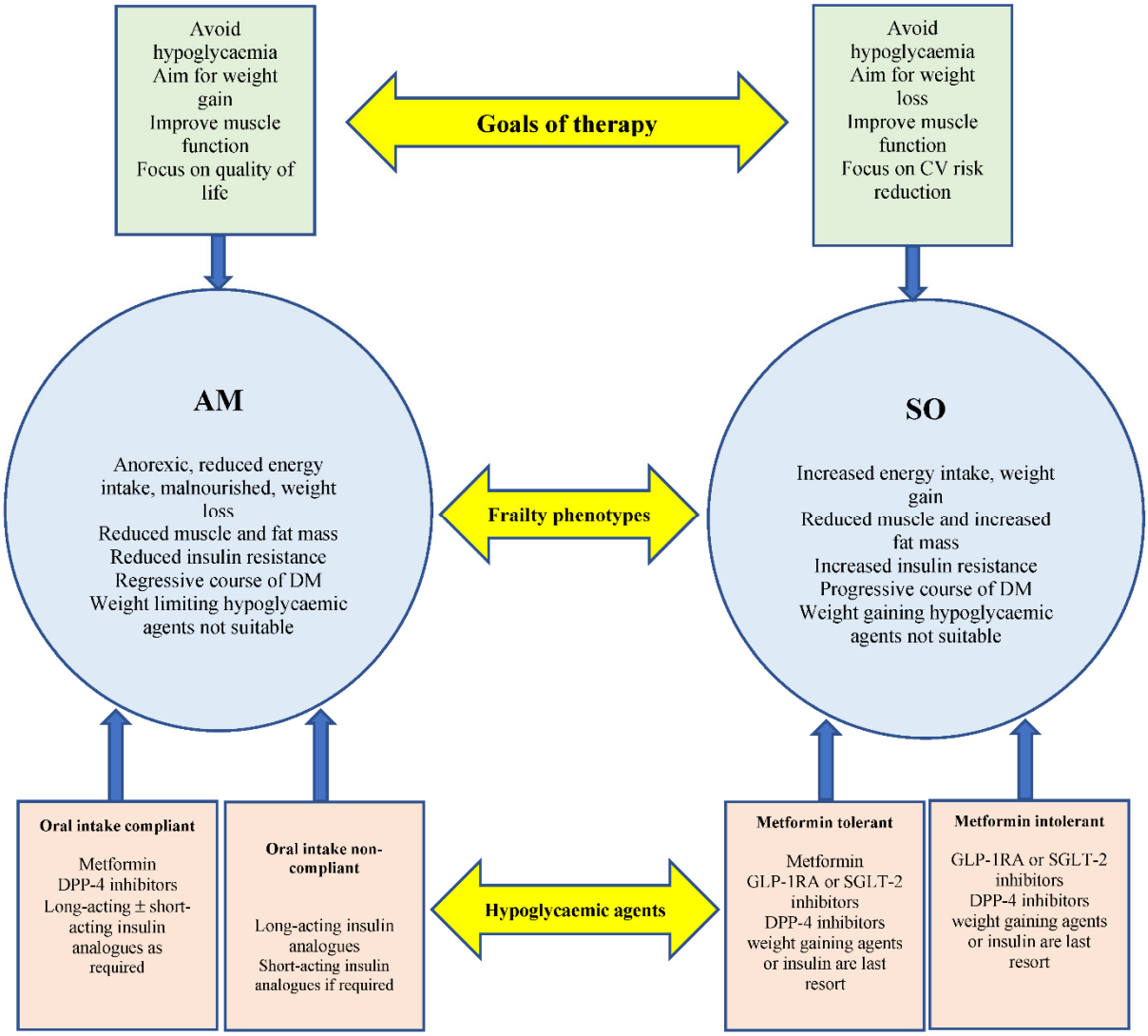


**Figure 2.** Two main metabolic frailty phenotypes' characteristics, hypoglycaemic agents and goals of therapy. Long-acting insulin analogues should be considered as an early option in AM frail patients with reduced and non-compliant oral intake. Weigh limiting agents should be considered as an early choice in the SO frailty phenotype. AM = Anorexic malnourished, SO = Sarcopenic obese.

## 6. Insulin Use in Frail, Older People with Diabetes

The decision to choose the type of insulin does not depend on the efficacy, but is largely based on other considerations, such as the risk of hypoglycaemia, impact on body weight, frequency of administration, cost and accessibility [38]. Barriers to the use of insulin, when clinically indicated, still exist at the physician, patient and healthcare system levels. These barriers include the complexity of an insulin regimen, lack of time and knowledge to appropriately prescribe insulin, anxiety about injections and monitoring, fear of hypoglycaemia and the lack of support [39,40]. These barriers may result in a significant delay in starting insulin in eligible patients [40,41]. The simplicity of the basal insulin analogues regimen may help to improve this clinical inertia. When choosing an insulin regimen for frail, older people with diabetes, the predictability of the glucose lowering effect, risk of hypoglycaemia, ease of administration and simplicity, as well as the flexibility of injection times, are important factors. Therefore, a single-dose regimen of a basal insulin analogue can play an important role in controlling hyperglycaemia in the AM frail, older patients. Multiple daily injections are too complex and not suitable or frail, older people, especially those with cognitive and physical dysfunctions. Long-acting,

peakless insulin analogues have prolonged duration of action, present less blood glucose variability and should be administered only once daily to avoid the risk of hypoglycaemia. Although long-acting insulin analogues may have a higher acquisition cost than basal human insulins, their longer duration of action, predictability, less monitoring required and once-daily injection translate into a reduced burden of care and potential cost savings. The once-daily injection with the prolonged half-life of insulin analogues enables a flexible dosing regimen without compromising its efficacy and safety, and provides a breathing space and convenience for the administering healthcare workers and carers. With the single daily dose, self-administration may still be possible in patients who develop certain clinical conditions, such as arthritis, tremors or visual impairments. In addition, the reduced risk of nocturnal hypoglycaemia of the long-acting insulin analogues is an important value, as nocturnal hypoglycaemia is associated with the greatest reduction in quality of life and is a major barrier for hypoglycaemic therapy titration [42]. In older people with diabetes, hypoglycaemia may present less specific symptoms due to reduced autonomic responses in old age [43,44]. Therefore, educational diabetes programmes are important for patients and their carers. For example, in a study that delivered a diabetes educational programme to staff in care homes, staff knowledge improved and was retained after one year, and led to the improved quality of care for residents with diabetes [45]. It is also important to recognise that relaxed glycaemic targets are not an assurance of a lower risk of hypoglycaemia, as continuous glucose monitoring has unmasked frequent episodes of hypoglycaemia in older people with diabetes and high HbA1c levels [46].

## 7. Goals of Therapy

In the advanced AM frailty phenotypes who have limited life expectancy, glycaemic control with tight HbA1c should not be the focus of treatment. The goals of therapy should be aimed at achieving the best suitable blood glucose levels that control symptomatic hyperglycaemia and avoid side effects, especially hypoglycaemia, and focus on quality of life, rather than long-term HbA1c objectives. Hyperglycaemia increases the risk of frailty, probably through inducing mitochondrial dysfunction, microvascular damage, increased inflammation and oxidative stress [47]. On the other hand, hypoglycaemia increases the risk of frailty by inducing repeated minor subclinical cerebral injuries or recurrent falls and fractures that may, over time, lead to functional impairment [48]. Therefore, in frail patients with a reasonable life expectancy, the ideal short-term glycaemic control is to avoid the wide glycaemic excursions to prolong time spent in the normal glycaemic range. Zaslavsky et al. found a U-shaped relationship between blood glucose levels and the risk of incident frailty with blood glucose levels <8.9 mmol/L (<160 mg/dL) and >10.0 mmol/L (>180 mg/dL) to be associated with an increased risk of frailty ($p = 0.001$) [49]. The ideal HbA1c that reduces the risk of frailty/physical dysfunction or mortality in older people remains less clear. The U-shaped relationship reported by Zaslavsky et al. found the HbA1c of 7.6% (59.6 mmol/mol) to be associated with the least risk of frailty [49]. Other studies found HbA1c ≥8.0 (>63.9 mmol/mol) to be associated with a slow walking speed, and HbA1c >7.0% (53.0 mmol/mol) with functional disability [50,51]. Similarly, in a UK population-based cohort study of >25,000 older people (aged 80–89 years) with type 2 diabetes followed-up for a median of 2 years, a U-shaped relationship between HbA1c and mortality was observed [52]. The lowest mortality was found in older people with HbA1c of 7–7.4% (53–57 mmol/mol), compared with HbA1c of <6.0% (<42 mmol/mol) or ≥8.5% (≥69 mmol/mol). The results from the National Health and Nutrition Examination Surveys (NHANES) showed that, following a follow-up period of 8.9 years, HbA1c >8.0% (>63.9 mmol/mol) was associated with an increased risk of all-cause and cause-specific mortality in older people with diabetes [53]. Not only glycaemic targets, but also the choice of hypoglycaemic agent and the physical function of the individual, appear to have had an impact on the outcome. It was shown that a lower HbA1c (<7.0%) was associated with an increased mortality risk, compared with moderate levels (≥7.0% <8.5%) in patients using regimens that were associated with hypoglycaemia [54]. High levels of HbA1c were consis-

tently associated with an elevated mortality risk in those regimens that had a lower risk of hypoglycaemia. These data suggest that the individualisation of glycaemic targets should consider the classes of glucose-lowering therapy, with less aggressive targets in patients treated with agents associated with a high risk of hypoglycaemia [54]. Similarly, a recent systematic review reported that better glycaemic control, HbA1c <7.0% (53.0 mmol/mol), and low glycaemic variability were associated with better maintenance of physical function. Higher HbA1c 8.0–8.9% (63.9–73.8 mmol/mol) was associated with a reduction in the composite outcome of death or functional decline in frail community-dwelling older people with diabetes who were in need for skilled assistance or classified as nursing-home-eligible [55]. These finding suggest that the greater the decline in function and the increase in frailty, the higher the targets should be.

## 8. Future Perspectives

Clinical guidelines still consider frail, older people with diabetes as one category, and therefore clinical practice does not characterise the metabolic profile of frailty and its impact on glycaemic control and choice of hypoglycaemic agents [56,57]. Recently, five different subtypes of patients with type 2 diabetes with different characteristics, insulin resistance, disease progression and risk of diabetes-related complications were identified [58]. Future clinical trials should consider the clear characterisation of older participants, rather than characterisation by age alone. Although we suggested that frail, older people with diabetes may have a wide spectrum of the metabolic profile, there is currently no research or evidence to support this view. Another limitation of this review was that the participants recruited to the studies included in this manuscript were of a relatively younger age, again, due to paucity of research in older age groups. Therefore, the metabolic spectrum of frailty and its effect on the choice of hypoglycaemic agents is another potential direction for future research. Little is known about the effects of hypoglycaemic agents on frailty, and future research is needed [59–64]. The anabolic properties of insulin and its effect on body muscle needs further exploration. The current scarce evidence suggests that insulin may have a positive effect on muscle function and attenuate the progression of sarcopenia in older people with diabetes, but this evidence is not yet substantial or evident in older age groups. In addition, frailty was not assessed in these studies. Therefore, future confirmation in large prospective studies is still required. The positive effect of insulin on muscle parameters appears to be independent of glycaemic control, which is an advantage in old age to achieve this beneficial outcome without inducing hypoglycaemia. Prospective studies that include muscle biopsies are also required to assess the effect of insulin therapy on muscle quality. The new insulin analogues appear as a potentially favourable therapy in the AM frail phenotype, as long as hypoglycaemia is avoided, but evidence is still required to explore its effect on muscle function and whether it can delay the progression of frailty to disability. The current research on the use of once-weekly insulin injections is an appealing convenience choice for frail, older people with diabetes, and may further encourage the early introduction of insulin in this vulnerable group of patients [65].

## 9. Conclusions

Frail, older people with diabetes appear to have a heterogeneous metabolic spectrum that clusters at an anorexic malnourished (AM) phenotype at one end and a sarcopenic obese (SO) phenotype at the other end. The use of oral hypoglycaemic medications in the AM phenotype may be limited by organ dysfunction and polypharmacy. In addition, the new agents of GLP-1RA and SGLT-2 inhibitors may not be suitable in this frailty phenotype due to their side effects of further weight loss, dehydration, hypotension and increased risk of falls. Therefore, insulin use may be considered as an early option in this group of vulnerable frail patients. The long-acting insulin analogues appear as safer options due to their low risk of hypoglycaemia and the convenience of single daily administration. The side effects of insulin-induced weight gain may be an advantage in this frailty phenotype. Insulin-related anabolic properties and its potential positive effect on muscle function is

another advantage, although this important effect still needs further exploration in future large prospective studies. The goals of therapy in this frailty phenotype should maintain a relaxed glycaemic control, avoid hypoglycaemia as much as possible and focus on the maintenance of good quality of life.

## 10. Key Points

- Frailty and sarcopenia are newly emerged diabetes-related complications in older people with diabetes.
- Frailty appears to be metabolically heterogeneous with anorexic malnourished (AM) phenotypes at one end, and sarcopenic obese (SO) phenotypes at the other end of the spectrum.
- The AM phenotype is likely to be less tolerant to oral hypoglycaemic therapy due to multiple comorbidities and organ dysfunction.
- Insulin therapy, especially long-acting insulin analogues, are an early option in the AM phenotype.
- Insulin may have positive effects on muscle function in this frail phenotype, although future confirmation studies are required.

**Author Contributions:** Authors contributed equally to the writing of this manuscript. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

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