患有 2 型糖尿病的年老体弱者的胰岛素

——治疗的低门槛

艾哈迈德・阿卜杜勒哈菲兹[1*] 夏尔・比什特[1] 伊娃・科瓦切维奇[1] 丹尼尔・彭内尔斯[1] 艾伦・辛克莱尔[2,3]
1.S60 2UD 摩尔盖特路罗瑟勒姆综合医院老年医学科 罗瑟勒姆 英国
2.WC2R 2LS 国王学院 伦敦 英国
3.老年人糖尿病研究基金会（fDROP），Droitwich Spa WR9 0QH 英国

【摘　要】：由于预期寿命的延长，全球糖尿病和虚弱合并症的患病率正在增加。虚弱似乎是一种代谢异质性疾病，可能会影响关于最合适血糖目标的临床决策以及为每个个体选择最合适的降血糖药物。衰弱的代谢特征似乎跨越了一个谱系，一端是厌食性营养不良（AM）衰弱表型，另一端是肌肉减少性肥胖（SO）表型。与 SO 表型相比，AM 表型的特点是体重显著减轻和胰岛素抵抗较少，SO 表型的特点是显著肥胖和胰岛素抵抗增加。因此，由于体重减轻，胰岛素治疗可被视为 AM 虚弱表型的早期选择。胰岛素相关的体重增加和胰岛素的合成代谢特性可能是这种厌食表型的优势。有新的证据支持胰岛素可以改善老年糖尿病患者肌肉功能的观点，尽管这一证据仍需要在未来的大规模前瞻性研究中进一步证实。与中效胰岛素相比，长效胰岛素类似物发生低血糖的风险较低。此外，他们简单的每日一次方案使其更适合虚弱的老年患者。未来对新的每周一次的胰岛素类似物可用性的研究很有吸引力。治疗的目标是达到放松的目标，避免低血糖，并专注于维持这些易受伤害患者的生活质量。
【关键词】：老年人；糖尿病；管理；胰岛素治疗；虚弱；少肌症

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

Ahmed Abdelhafiz[1*] Shail Bisht[1] Iva Kovacevic[1] Daniel Pennells[1] Alan Sinclair[2,3]
1.Department of Geriatric Medicine, Rotherham General Hospital, Moorgate Road, Rotherham S60 2UD,UK
2.King’s College, London WC2R 2LS, UK
3.Foundation for Diabetes Research in Older People(fDROP), Droitwich Spa WR9 0QH,UK

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

1 简介

44% 65 [1]

AM

[2-6]

[6] [7,8]

AM

SO

[6]

1 Tanaka 191

SD 60.2 12.5 2

AM

≥ 60 [9]

AM p<0.05 [9]

2 方法

Google Scholar

PubMed Embase MeSH

Bouchi

312 SD 64 11

2

10 [10]

2

5 1.

10 vs.6 p<0.001

2. 60

1.

2. 3. [11]

4.

[10]

HbA1c

3 胰岛素对骨骼肌的影响 Cui

68.4%vs.74.5% p=0.48 [12] 132 36 HOMA-IR p<0.05 132

KORA-Age 118 2 SD 74.6 6.2 [13] 3 SD 10.1 9.9 20 Sugimoto 588 2 SD 70.0 8.0 [14] 25.9%

1

Study	Patients	Aim to	Main Findings
Tanaka K et al., cross-sectional, Japan, 2017 [9]	391 men with type 2 DM, mean (SD) age 69.2 (7.5) 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 ($p < 0.05$). B. Fasting serum C-peptide significantly lower in subjects with compared to those without sarcopenia ($p < 0.05$).
Bouchi R et al., retrospective observational, Japan, 2017 [10]	512 patients with type 2 DM, mean (SD) age 64.0 (12.0) Y.	Examine impact of insulin treatment on muscle mass.	A. Insulin was protective against annual decline in SMI (standardized β 0.199, $n = 0.024$) adjusted for covariates. B. In a cohort matched by propensity scores, insulin significantly increased the 3-year change in SMI compared with non-insulin-treated group, mean (SE) 2.40 (0.98%) vs. −0.43 (0.58%), $p = 0.036$).
Cui M et al., cross-sectional, China, 2020 [12]	132 patients with type 2 DM, aged ≥65 Y	Explore factors examined with sarcopenia	A. Insulin use showed significantly different proportions with sarcopenia and those with no sarcopenia (36.4% vs. 74.5%, $p = 0.48$). B. Metformin was significantly less used in patients with compared to those without sarcopenia (13.2% vs. 41.5%, $p = 0.003$).

1

Study	Patients	Aim to	Main Findings
Fercuri U et al., prospective, Germany, 2020 [13].	720 (138 type 2 DM) participants of KORA-Age study, mean (SD) age 74.6 (6.2) Y, F/U 7 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 −3.1 (95% CI −5.3 to −0.92) kg/m², $p = 0.02$), but not with a change in GS (β −0.9, 95% CI −1.8 to 0.24 kg) or TUG (β −0.2, 95% CI −0.7 to 0.5 s). B. Insulin therapy positively associated with change in SMI (β 0.6 (95% CI 0.3 to 0.9) kg/m², $p = 0.001$), but not in GS (β −1.5, 95% CI −4.1 to 1.1 kg) or TUG (β 1.6, 95% CI −0.2 to 3.3 s).
Sugimoto K et al., observational longitudinal, Japan, 2021 [14].	588 patients with type 2 DM, mean (SD) age 72.0 (8.0) Y, F/U 1 Y	Examine relationship between glycaemic control and effects of antidiabetic agents on sarcopenia.	After 382 (50) days of F/U: A. Frequency of sarcopenia non significantly increased (7.8% vs. 6.3%, $p = 0.17$). B. Patients with ≥1% drop in HbA1c had significant increase in SMI (B = 0.15, $p = 0.029$), gait speed (B = 0.03, $p = 0.036$), but non-significant change in handgrip strength (B = −0.005, $p = 0.914$). C. Insulin use significantly increased SMI (B = 0.11, $p = 0.022$). D. Oral antidiabetic therapy has no effect on sarcopenia.

DM= SD= Y= RSMI= SMI= SE= F/U= CI= GS= TUG=

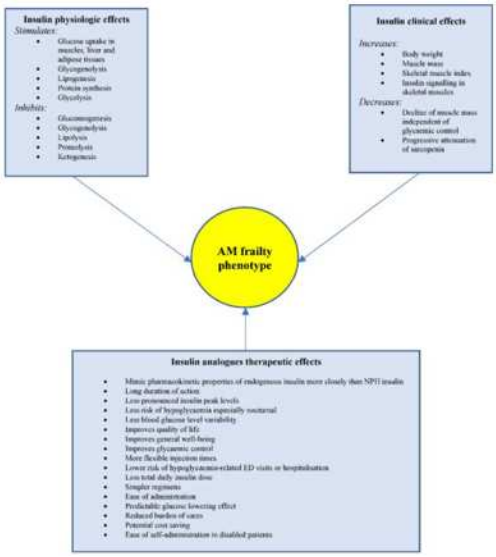
4 胰岛素类似物安全

[15-22] 60 2 / 22 QOL SD 68.0 9.9 [23] / QOL

Lipska 489 2 22 ED NPH [24] SD 60.2 11.8 Lipska NPH [25,26] Lipska 25,489 1928

NPH 2 ≥ 65 ED [27] 575,008 2

SD 74.9 6.7
407,018 141,588
NPH HR
0.71 95% CI 0.63 0.80
NPH 0.72 0.63 0.82 Lipska
[24]
65-68 NPH
ED
[27] 69-87
NPH
34
SD 63.0 7.0 NPH
16 SD 60.0 8.7
[28]
CKD 3 4
CKD
[29]
CKD
[30]
Özçelik
/
[31]
[32]
degludec/aspart 1
AM
2



1
AM
AM= ED=
5 胰岛素——治疗门槛低
2
AM
GLP-1RA SGLT-2

Study	Patients	Aim to	Main Findings
Fujimoto K. et al., prospective, observational, Japan, 2018 [23].	22 patients with type 2 DM, mean (SD) age 66.0 (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: A. Improved daily glucose level variability, morning and evening glucose control and QOL. 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 (11.6) 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 (1.9 events, 95% CI 0.2 to 15.6/1000 person-years) compared with 394 events among 23,561 patients on NPH (8.6 events, 7.9 to 9.8/1000 person-years, $p = 0.02$). B. Adjusted HR 1.16, 95% CI, 0.71 to 1.78 for hypoglycaemia-related events with insulin analogue use. 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 26.05–27.3) for NPH. B. For detemir and NPH, incidence rates were 16.69 (15.92 to 17.51) and 25.04 (24.01 to 26.11), respectively. C. Glargine or detemir use associated with reduced risk of hypoglycaemia compared with NPH (HR for glargine vs. NPH 0.71, 95% CI 0.65 to 0.80, and detemir vs. NPH insulin 0.72, 0.63 to 0.82).
Rotnitzki 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 8.06% (72.7 mmol/mol) to 7.95% (62.8 mmol/mol) in glargine group, but increased from 8.25% (66.2 mmol/mol) to 8.44% (69.4 mmol/mol) in INPH group, $p = 0.029$. B. Incidence of nocturnal hypoglycaemia was 3 times lower with glargine (0.5 events/patient) than with INPH (1.5 events/patient, $p = 0.047$).
Özçelik et al., prospective observational, Turkey, 2021 [31].	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 0.05 (0.11)/week after IdegAsp ($p < 0.0001$). 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 ($p < 0.0001$).

AM
SO
[6]
AM
-4(DPP-4)

[33]

AM

AM SO

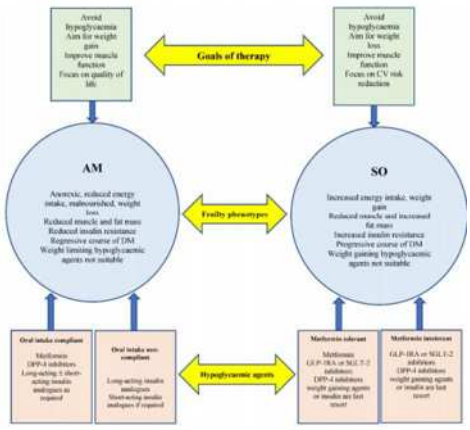
[34,35] GLP-1RA SGLT-2

[36]

4(DPP-4)

[37]

2



2

AM

SO

AM= SO=

6 体弱的老年糖尿病患者使用胰岛素

[38]

[39,40]

[40,41]

AM

[42]

[43,44]

[45]

HbA1c

[46]

7 治疗目标

AM HbA1c

HbA1c

[47]

[48]

U <8.9 mmol/L <160 mg/dL >10.0 mmol/L >180 mg/dL p=0.001 [49] /

HbA1c Zaslavsky

U 7.6% 59.6 mmol/mol

HbA1c [49] HbA1c ≥ 8.0 >63.9 mmol/mol HbA1c>7.0% 53.0 mmol/mol [50,51]

25,000 2 80-89 AM 2 HbA1c U [52] HbA1c<6.0% <42 mmol/mol ≥ 8.5% ≥ 69 mmol/mol HbA1c 7-7.4% 53-57 mmol/mol

NHANES 8.9 HbA1c>8.0% >63.9 mmol/mol [53]

HbA1c <7.0% ≥ 7.0%<8.5% [54] HbA1c

[54] HbA1c<7.0% 53.0 mmol/mol

HbA1c 8.0 – 8.9%(63.9 – 73.8 mmol/mol [55]

8 未来展望

[56,57]

2 [58]

[59-61]

9 结论

AM SO AM GLP-1RA SGLT-2

10 要点

-
-
- AM SO
- AM
- AM
-

参考文献：

[1] Sinclair,A.; Saeedi,P.;Kaundal, A.;Karuranga, S.;

Malanda,B.; Williams,R.Diabetes and global ageing among 65–99-year-old adults:Findings from the International Diabetes Federation Diabetes Atlas,9th edition.DiabetesRes.Clin.Pract.2020,162,108078.[CrossRef][PubMed]

[2] Sinclair,A.J.; Abdelhafiz,A.H.; Rodríguez-Mañas, L.Frailty and sarcopenia-newly emerging and high impact complications of diabetes.J.Diabetes Complicat.2017, 31,1465–1473.[CrossRef][PubMed]

[3] Hanlon,P.;Fauré,I.; Corcoran, N.; Butterly,E.; Lewsey,J.; McAllister, D.;Mair,F. S.Frailty measurement, prevalence, incidence,and clinical implications in people with diabetes:A systematic review and study-level meta-analysis.Lancet Health Longev.2020, 1,e106–e116. [CrossRef]

[4] Sinclair, A.J.; Abdelhafiz,A.; Dunning,T.; Izquierdo,M.;Manas,L.R.;Bourdel-Marchasson,I.;Morley,J.E. ;Munshi,M.; Woo,J.;Vellas,B.An International Position Statement on the Management of Frailty in Diabetes Mellitus:Summary of Recommendations 2017.J.Frailty Aging 2018,7,10–20.[CrossRef][PubMed]

[5] Leroith,D.; Biessels, G.J.; Braithwaite, S.S.; Casanueva,F.F.;Draznin,B.;Halter,J.B.;Hirsch,I.B.;McDonnel l,M.;Molitch,M.E.;Murad,M.H.E.;et al.TReatment of diabetes in older adults:An endocrine society clinical practiceguideline.J.Clin.Endocrinol.Metab.2019,104,1520–1 574.[CrossRef]

[6] Abdelhafiz, A.H.;Emmerton,D.;Sinclair,A.J.Impact of frailty metabolic phenotypes on the management of older people with type 2 diabetes mellitus.Geriatr. Gerontol. Int.2021,21, 614–622.[CrossRef]

[7] Abdulla,H.;Smith,K.;Atherton,P.J.;Idris,I.Role of insulin in the regulation of human skeletal muscle protein synthesis and breakdown:A systematic review and meta-analysis.Diabetologia 2016, 59,44–55.[CrossRef]

[8] Fujita,S.; Glynn,E.L.; Timmerman, K.L.; Rasmussen,B.B.;Volpi,E.Supraphysiologicalhyperinsulinaem ia is necessary to stimulate skeletal muscle protein anabolism in older adults:Evidence of a true age-related insulin resistance of muscle protein metabolism.Diabetologia 2009, 52, 1889–1898.[CrossRef]

[9] Tanaka,K.-I.;Kanazawa,I.;Sugimoto,T.Reduction in Endogenous Insulin Secretion is a Risk Factor of Sarcopenia in Men with Type 2 Diabetes Mellitus.Calcif.Tissue Res.2015,97, 385–390.[CrossRef]

[10] Bouchi,R.; Fukuda,T.; Takeuchi,T.; Nakano,Y.; Murakami, M.; Minami,I.;Izumiyama, H.; Hashimoto,K.; Yoshimoto,T.;Ogawa,Y.Insulin Treatment Attenuates Decline of Muscle Mass in Japanese Patients with Type 2 Diabetes.Calcif.Tissue Res.2017,101,1–8.[CrossRef]

[11]Kalyani,R.R.; Tra,Y.; Yeh,H.C.; Egan,J.M.;Ferrucci,L.;Brancati,F.L.Quadriceps strength, quadriceps power, and gait speed in older U.S.adults with diabetes mellitus: Results from the National Health and Nutrition Examination Survey,1999–2002.J. Am.Geriatr.Soc. 2013, 61,769–775.[CrossRef][PubMed]

[12] Cui,M.; Gang, X.;Wang,G.;Xiao, X.; Li, Z.;Jiang,Z.; Wang, G.Associations between sarcopenia and clinical characteristics of patients with type 2 diabetes. Medicine 2020, 99, e18708.[CrossRef][PubMed]

[13] Ferrari,U.; Then,C.; Rottenkolber,M.; Selte,C.; Seissler,J.; Conzade,R.;Linkohr, B.; Peters,A.;Drey, M.; Thorand, B. Longitudinal association of type 2 diabetes and insulin therapy with muscle parameters in the KORA-Age study.Acta Diabetol.2020,57,1057–1063.[CrossRef]

[14] Sugimoto,K.; Ikegami,H.;Takata,Y.; Katsuya,T.; Fukuda,M.; Akasaka,H.; Tabara,Y.; Osawa,H.;Hiromine,Y.; Rakugi,H. Glycemic Control and Insulin Improve Muscle Mass and Gait Speed in Type 2 Diabetes:The MUSCLES-DMStudy.J.Am.Med.Dir.Assoc.2021,22,834–83 8.e1.[CrossRef][PubMed]

[15] Rosenstock,J.; Schwartz,S.L.; Clark,C.M.,Jr.; Park,G.D.; Donley,D.W.;Edwards,M.B.Basal insulin therapy in type 2 diabetes:28-week comparison of insulin glargine(HOE 901)and NPH insulin.Diabetes Care 2001,24, 631–636. [CrossRef][PubMed]

[16] Riddle, M.C.; Rosenstock,J.; Gerich,J.Insulin Glargine 4002 Study Investigators.The treat-to-target trial: Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients.Diabetes Care 2003, 26,3080–3086.[CrossRef]

[17] Fritsche, A.; Schweitzer, M.A.; Häring,H.U.;4001 Study Group. Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin,or bedtime insulin glargine in patients with type 2 diabetes: A randomized, controlled trial.Ann.Intern.Med.2003, 138,952–959.[CrossRef]

[18] Haak,T.; Tiengo,A.;Draeger,E.; Suntum,M.;

Waldhausl, W.Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes.Diabetes Obes.Metab. 2005,7,56–64.[CrossRef]

[19] Hermansen,K.;Davies,M.;Derezinski,T.;Martinez Ravn,G.;Clauson,P.;Home,P.A 26-week, randomized, parallel, treatto-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naïve people with type 2 diabetes.Diabetes Care 2006,29,1269–1274.[CrossRef]

[20] Eliaschewitz, F.G.;Calvo,C.; Valbuena,H.; Ruiz,M.; Aschner,P.;Villena,J.;Ramirez,L.A.;Jimenez,J.Therapy in Type 2 Diabetes:Insulin Glargine vs.NPH Insulin Both in Combination with Glimepiride. Arch.Med. Res.2006,37, 495–501.[CrossRef]

[21] Horvath, K.;Jeitler, K.;Berghold, A.; Ebrahim, S.H.; Gratzer, T.W.; Plank,J.; Kaiser,T.;Pieber, T.R.; Siebenhofer, A.Long-acting insulin analogues versus NPH insulin(human isophane insulin)for type 2 diabetes mellitus.Cochrane Database Syst.Rev.2007, CD005613. [CrossRef][PubMed]

[22] Singh, S.R.;Ahmad,F.; Lal,A.; Yu,C.;Bai,Z.; Bennett,H.Efficacy and safety of insulin analogues for the management of diabetes mellitus:A meta-analysis.CMAJ 2009,180,385–397.[CrossRef][PubMed]

[23] Fujimoto,K.; Iwakura,T.; Aburaya,M.; Matsuoka,N. Twice-daily insulin degludec/insulin aspart effectively improved morning and evening glucose levels and quality of life in patients previously treated with premixed insulin:An observational study. Diabetol. Metab. Syndr.2018, 10,64.[CrossRef][PubMed]

[24] Lipska,K.J.; Parker,M.M.; Moffet,H.H.; Huang, E.S.; Karter,A. J.Association of Initiation of Basal Insulin Analogs vs Neutral Protamine Hagedorn Insulin with Hypoglycemia-Related Emergency Department Visits or Hospital Admissions and with Glycemic Control in Patients With Type 2 Diabetes.JAMA 2018, 320,53–62. [CrossRef] [PubMed]

[25] Haukka, J.; Hoti, F.; Erästö, P.; Saukkonen,T.; Mäkimattila,S.;Korhonen,P.Evaluation of the incidence and risk of hypoglycemic coma associated with selection of basal insulin in the treatment of diabetes:A Finnish register linkage study.Pharmacoepidemiol.DrugSaf.2013,22,1326–1335.[CrossRef]

[26] Strandberg, A.Y.; Khanfir, H.; Mäkimattila,S.; Saukkonen, T.; Strandberg,T.; Hoti,F.Insulins NPH, glargine,and detemir, and risk of severe hypoglycemia among working-age adults. Ann. Med. 2017,49, 357–364. [CrossRef]

[27] Bradley, M.C.; Chillarige, Y.; Lee,H.; Wu, X.; Parulekar, S.; Muthuri,S.; Wernecke, M.; MaCurdy,T.E.; Kelman,J. A.; Graham,D.J.Severe Hypoglycemia Risk with Long-Acting Insulin Analogs vs Neutral Protamine Hagedorn Insulin. JAMA Intern. Med.2021, 181, 598.[CrossRef]

[28] Betônico, C.C.;Titan,S.M.O.; Lira,A.; Pelaes, T.S.; Correa-Giannella,M.L.C.;Nery,M.; Queiroz, M.Insulin Glargine U100 Improved Glycemic Control and Reduced Nocturnal Hypoglycemia in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease Stages 3 and 4. Clin.Ther.2019,41,2008–2020.[CrossRef]

[29] Alsahli,M.;Gerich,J.E.Hypoglycemia in Patients with Diabetes and Renal Disease. J .Clin. Med.2015, 4,948–964.[CrossRef]

[30] Pecoits-Filho, R.;Abensur, H.; Betônico, C.C.R.; Machado, A.D.; Parente, E.B.; Queiroz, M.;Salles, J.E.N.; Titan,S.; Vencio,S. Interactions between kidney disease and diabetes: Dangerous liaisons. Diabetol. Metab. Syndr.2016,8, 50.[CrossRef]

[31] Özçelik,S.; Çelik,M.; Vural,A.;Aydın,B.; Özçelik, M.; Gozu, M. Outcomes of transition from premixed and intensive insulin therapies to insulin aspart/degludec co-formulation in type 2 diabetes mellitus: A real-world experience. Arch.Med.Sci.2021,17,1–8.[CrossRef][PubMed]

[32] Rodbard,H.W.; Cariou,B.; Pieber,T.R.; Endahl, L.A.;Zacho,J.;Cooper,J.G.Treatment intensification with an insulin degludec(IDeg)/ insulin aspart(IAsp)co-formulation twice daily compared with basal IDeg and prandial IAsp in type 2 diabetes: A randomized,controlled phase III trial.Diabetes Obes.Metab. 2016,18, 274–280. [CrossRef] [PubMed]

[33] Reza, M.; Taylor,C.; Towse,K.; Ward,J.; Hendra, T.Insulin improves well-being for selected elderly type 2 diabetic subjects.Diabetes Res.Clin.Pract.2002,55, 201–207. [CrossRef]

[34] Maruthur,N.M.; Tseng,E.;Hutfless, S.;Wilson,L.M.; Suarez-Cuervo,C.; Berger, Z.;Chu,Y.; Iyoha,E.;Segal,J.B.; Bolen,S.Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2

Diabetes.A Systematic Review and Meta-analysis. Ann. Intern.Med.2016,164,740–751.[CrossRef][PubMed]

[35] Crowley, M.J.; Diamantidis,C.J.; McDuffie,J.R.; Cameron,C.B.;Stanifer,J.W.; Mock, C.K.; Wang, X.;Tang,S.; Nagi,A.; Kosinski,A. S.; et al.Clinical Outcomes of Metformin Use in Populations with Chronic Kidney Disease, Congestive Heart Failure, or Chronic Liver Disease:A Systematic Review. Ann. Intern. Med.2017, 166, 191–200.[CrossRef][PubMed]

[36] Abdelhafiz, A.H.; Sinclair, A.J. Cardio-renal protection in older people with diabetes with frailty and medical comorbidities—A focus on the new hypoglycaemic therapy. J. Diabetes Complicat.2020,34,107639.[CrossRef]

[37] Chang,Y. C.; Chuang,L. M.;Lin, J.W.; Chen, S.T.; Lai,M.S.;Chang,C.H.Cardiovascular risks associated with second-line oral antidiabetic agents added to metformin in patients with Type 2 diabetes:A nationwide cohort study.Diabet.Med.2015,32,1460–1469.[CrossRef]

[38] Doyle-Delgado,K. ; Chamberlain, J.J.; Shubrook, J.H.;Skolnik,N.;Trujillo,K.Pharmacologic Approaches to glycemic treatment of type 2 diabetes:Synopsis of the 2020 American diabetes Association's standards of medical care in diabetes clinical guideline. Ann. Intern. Med. 2020, 173,813e21. [CrossRef]

[39] Blonde, L.; Aschner,P.; Bailey,C.;Ji,L.; Leiter,L.A.; Matthaei,S.; Global Partnership for Effective Diabetes Management. Matthaei S on behalf of the Global Partnership for Effective Diabetes Management.Gaps and barriers in the control of blood glucose in people with type 2 diabetes.Diabetes Vasc.Dis.Res.2017,14,172e83.[CrossRef]

[40] Reach,G.; Pechtner,V.; Gentilella,R.; Corcos,A.; Ceriello,A.Clinical inertia and its impact on treatment intensification in people with type 2 diabetes mellitus. Diabetes Metab.2017,43,501–511.[CrossRef]

[41] Khunti,K.; Gomes,M. B.; Pocock,S.; Shestakova, M.V.;Pintat,S.;Fenici,P.;Hammar,N.;Medina,J.Therapeutic inertia in the treatment of hyperglycaemia in patients with type 2 diabetes:A systematic Review.Diabetes Obes.Metabol. 2018,20,427e37.[CrossRef]

[42] Edelman,S.V.;Blose,J.S.The Impact of Nocturnal Hypoglycemia on Clinical and Cost-Related Issues in Patients with Type 1 and Type 2 Diabetes.Diabetes Educ.2014, 40,269–279.[CrossRef][PubMed]

[43] Jaap, A.;Jones, G.;McCrimmon,R.; Deary,I.J.; Frier,B.M.Perceived symptoms of hypoglycemia in elderly type 2 diabetic patients treated with insulin.Diabet Med. 1998, 15,398–401.[CrossRef]

[44] Goto, A.;Arah, O.;Goto,M.; Terauchi,Y.; Noda, M.Severe hypoglycaemia and cardiovascular disease: Systematic review and meta-analysis with bias analysis.BMJ 2013,347,f4533.[CrossRef][PubMed]

[45] Deakin, T.A.;Littley, M.D. Diabetes care in residential homes: Staff training makes a difference. J.Hum. Nutr. Dietet.2001,14,443–447.[CrossRef]

[46] Munshi, M.N.; Slyne,C.; Segal,A.R.; Saul,N.; Lyons,C.; Weinger,K.Liberating A1C goals in older adults may not protect against the risk of hypoglycemia.J.Diabetes Complicat.2017,31,1197–1199.[CrossRef]

[47] Stout, M.B.; Justice,J. N.; Nicklas,B.J.; Kirkland,J.L.Physiological Aging: Links Among Adipose Tissue Dysfunction, Diabetes, and Frailty.Physiology 2017, 32,9–19.[CrossRef]

[48] Abdelhafiz, A.H.; Rodríguez-Mãnas,L.; Morley, J.E.;Sinclair, A.J.Hypoglycemia in older people-a less well recognized risk factor for frailty.Aging Dis. 2015, 10, 156 –167.[CrossRef]

[49] Zaslavsky ,O.; Walker,R.L.; Crane, P.K.; Gray, S.L.; Larson,E.B.Glucose levels and risk of frailty.J.Gerontol.A Biol.Sci.Med.Sci.2016,71,1223–1229.[CrossRef]

[50] Yoon, J. W.;Ha ,Y.-C.; Kim,K.M.; Moon, J.H.; Choi,S.H.; Lim, S.; Park, Y.J.;Lim,J.-Y.;Kim, K.W.; Park, K.S.;et al. Hyperglycemia Is Associated with Impaired Muscle Quality in Older Men with Diabetes:The Korean Longitudinal Study on Health and Aging.Diabetes Metab.J.2016,40,140–146.[CrossRef]

[51] Godino,J.G.; Appel,L.J.; Gross,A.L.; Schrack,J.A.; Parrinello,C.M.; Kalyani,R.R.; Windham,B.G.; Pankow,J.S.; Kritchevsky,S.B.;Bandeen-Roche,K.;etal.Diabetes,hyperglycemia,and the burden of functional disability among older adults in a communitybased study. J.Diabetes 2017,9, 76–84. [CrossRef][PubMed]

[52] Hamada,S.;Gulliford,M.C.Mortality in individuals aged 80 and older with type 2 diabetes mellitus in relation to glycosylated hemoglobin,blood pressure, and total cholesterol.J.Am.Geriatr.Soc.2016,64,1425–1431.[CrossRef] [PubMed]

[53] Palta, P.;Huang, E.S.; Kalyani, R.R.; Golden,S.H.; Yeh,H.-C.Hemoglobin A1c and Mortality in Older Adults

With and Without Diabetes:Results From the National Health and Nutrition Examination Surveys(1988–2011). Diabetes Care 2017, 40, 453–460. [CrossRef] [PubMed]

[54] Currie, C.J.;Holden,S.E.;Jenkins-Jones,S.; Morgan, C.L.; Voss, B. ;Rajpathak,S.N.;Alemayehu,B.; Peters, J.R.; Engel, S.S.Impact of differing glucose-lowering regimens on the pattern of association between glucose control and survival.Diabetes Obes. Metab. 2018,20, 821–830. [CrossRef]

[55] Bollig,C.;Torbahn,G.;Bauer,J.;Brefka,S.; Dallmeier, D.;Denkinger,M.;Eidam,A.;Klöppel,S.;Zeyfang,A.;Voigtz-R adloff,S.; et al.Evidence gap on antihy perglycemic pharmacotherapy in frail older adults :A systematic review. Evidenzmangel für die antihy pergly kämische Pharmakotherapie gebrechlicherälterer Patienten:Ein systematisches Review.Z. Gerontol. Geriatr. 2021, 54, 278–284.[CrossRef]

[56] Ambrož,M.; de Vries,S.T.; Hoogenberg,K.; Denig,P.Trends in HbA1c thresholds for initiation of hypoglycemic agents:Impact of changed recommendations for older and frail patients.Pharmacoepidemiol.Drug Saf.2021, 30,37– 44.[CrossRef]

[57] Mangé, A.-S.; Pagès,A.; Sourdet,S.; Cestac,P.; McCambridge,C.Diabetes and Frail Older Patients:Glycemic Control and Prescription Profile in Real Life.Pharmacy 2021,9,115.[CrossRef]

[58] Ahlqvist,E.; Storm,P.; Käräjämäki,A.; Martinell,M.; Dorkhan,M.; Carlsson,A.; Vikman,P.; Prasad,R.; Aly,D.M.; Almgren,P.;et al.Novel subgroups of adult-onset diabetes and their association with outcomes:A data-driven cluster analysis of six variables.Lancet Diabetes Endocrinol. 2018,6, 361–369.[CrossRef]

[59] Shea,M.K.; Nicklas,B.J.; Marsh,A.P.; Houston,D.; Miller,G.D.;Isom,S.;Miller,M.E.;Carr,J.;Lyles,M.F.;Harris,T. B.;et al.The Effect of Pioglitazone and Resistance Training on Body Composition in Older Men and Women Undergoing Hypocaloric Weight Loss.Obesity 2011,19, 1636–1646. [CrossRef]

[60] Marsh,A.P.; Shea,M.K.; Locke,R.M.V.; Miller, M.E.;Isom,S.;Miller,G.D.;Nicklas,B.J.;Lyles,M.F.; Carr,J.J.; Kritchevsky, S.B.Resistance Training and Pioglitazone Lead to Improvements in Muscle Power During Voluntary Weight Loss in Older Adults.J.Gerontol.Ser.A 2013,68, 828–836. [CrossRef]

[61] Rajaobelina, K.; Helmer,C.; Vélayoudom -Céphise, F.-L.; Nov, S.; Farges,B.; Pupier,E.; Blanco,L.; Hugo,M.; Gin,H.; Rigalleau, V.Progression of skin autofluorescence of AGEs over 4 years in patients with type 1 diabetes. Diabetes Metab.Res. Rev.2017, 33,e2917. [CrossRef][PubMed]