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Body composition changes in diabetes and aging

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ABSTRACT

Aging is associated with changes in body composition, including both fat gain and muscle loss beginning in middle age, and is associated with increased risk of type 2 diabetes. Moreover, changes in fat distribution take place in adults as they age and may contribute to the increased risk of type 2 diabetes. Recent literature has shown differences in the age-related changes in body composition by diabetes status suggesting that some of these changes might not only be a risk factor of the development of diabetes but could also be a consequence of the disease. In this article, we review the current evidence on body composition changes that take place in adults after the diagnosis of type 2 diabetes and compare them to those observed in adults without diabetes as they age. We also review the effect of various lifestyle, pharmacological, and surgical treatments that lower blood glucose on body composition in adults with type 2 diabetes.

1. Introduction

Progressive and metabolically unfavorable changes in body composition have long been observed with aging. Accumulation of fat (especially abdominal fat) and loss of lean mass (LM) are important changes that take place in adults as they age and have been linked to an increased risk of the development of type 2 diabetes in older adults. This is also of importance from a public health perspective where aging of the population is considered a factor contributing to the global burden of type 2 diabetes. The pattern and rate of age-related changes in body composition may vary by sex, ethnicity, physical activity level, and caloric intake. Interestingly, recent evidence from longitudinal studies has shown differences in the pattern of body composition changes in adults by diabetes status, suggesting that the metabolically unhealthy body composition (i.e. increased body fat) in individuals with diabetes may not only be a risk factor of the development of diabetes but might also be a consequence of the disease.[1,2] This has tremendous consequences on functional status and quality of life in adults with diabetes as they age.

Important Definitions:
Total Body Mass = Total Lean Mass (LM) + Total Fat Mass (FM) + Total Bone Mass

1) **Total LM** = Total Fat Free Mass (FFM)
= Trunk LM + Appendicular LM*

2) **Total FM** = Total Fat Mass (FM)
= Trunk + Appendicular FM*

* Arms and legs

2. Techniques for body composition measurement

Examples of anthropometric measurements include body mass index (BMI), abdominal waist circumference, and skinfold measurements (Table 1). The benefit of these measurements is that they are relatively quick and inexpensive. However, they have major limitations related to lack of consistency among protocols and potential for measurement errors when measuring waist circumference and skinfold. There is also a lack of universal cut off points for waist circumference due to heterogeneity across ethnicities. More importantly, BMI alone (i.e. weight and height) cannot differentiate between LM and FM, nor between subcutaneous and visceral fat.[3] BIA is another indirect method used to assess body composition. This modality has the benefit of being safe and noninvasive and the machinery is portable, making it apt for the ambulatory setting. BIA uses the resistance of the body as a conductor to an electrical current in order estimate the total body water, FM and FFM, where FFM is considered a conductor of charge and FM is a non-conductor.

Several measurement techniques are available to directly assess body composition. DXA is a technically simple and reproducible method to assess FM, LM, and bone mineral mass. Recently, DXA software has become available to measure both subcutaneous and visceral fat, as well. However, DXA is less valid in very lean or very obese adults and cannot account for ectopic fat deposition in muscle. CT and MRI use high-resolution cross sectional images to directly quantify body

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Table 1
Direct and indirect measurement techniques to assess body composition.

Methods of body composition assessment	
Direct measures	Indirect measures
Cadaveric	Body mass index
Computed Tomography (CT)	Biometric Impedance Analysis
Dual energy x-ray absorptiometry (DXA)	Waist circumference
Magnetic resonance imaging (MRI)	Waist to hip ratio
	Skin caliper

composition at the tissue level. CT uses the Hounsfield scale of tissue density to differentiate between tissue type and skeletal muscle is assessed as individual muscles or muscle groups. Whereas, MRI uses fat-water separated imaging techniques to obtain quantitative fat images and can also distinguish skeletal muscle. One major limitation of the use of CT may be the ionizing radiation dose particularly with repeated scans. MRI does not involve exposure to radiation and is becoming frequently used in body composition analysis. While both modalities are accurate and reproducible, one disadvantage may be the relatively higher cost. There is no gold standard for the measurement of body composition except cadaveric analysis, so multiple techniques are often combined to improve the accuracy of body composition assessment.

3. Age-related changes in body composition in the general population

The Health, Aging, and Body Composition (Health ABC) Study and the Fels Longitudinal study are among two of the largest studies that have described the pattern of age-related changes in body composition and functional status in the general population (Table 2).

3.1. Fat mass (FM)

The Health ABC study showed that aging is associated with a slow weight loss that becomes more rapid after the age of 75. However, as the participants in the Health ABC study were losing weight, they were still gaining FM up until age 75.[4] Loss of FM began around the age of 75 and resulted in a steeper weight loss than the one seen before the age of 75.[4,5] U.S. men and women between the ages of 45 to 65 years old in the Fels Longitudinal Study had an annual gain of FM of 0.37 kg (0.34%) and 0.52 kg (0.47%), respectively; and an annual increase in BMI of 0.12 kg/m^2 and 0.18 kg/m^2, respectively.[6] Moreover, aging is accompanied by metabolically unfavorable redistribution of body fat including ectopic fat deposition in the abdomen, liver, skeletal and cardiac muscles, and bone marrow.[5,7–10] These changes in body composition have been linked with an increased risk of insulin resistance, type 2 diabetes, and coronary artery disease.[11–16]

3.2. Lean mass (LM)

Aging is associated with a decline in LM that is commonly referred to as sarcopenia. Due to the lack of a standard definition of sarcopenia in the literature, there are no clear estimates of its incidence and prevalence rates. The pattern and magnitude of age-related decline in LM vary by sex and physical activity level. Studies in the general population including adults with and without diabetes have shown a more rapid age-related decline in LM in men compared to women; with a steeper loss of LM between the ages of 70 to 79 in both sexes.[4,17] Compared to women, men have a greater decline in appendicular skeletal muscle, especially leg muscle mass as they age.[17,18] While adults in the Health ABC study had a linear progressive decline in LM over the study period of 8 years across all fitness levels of the participants, a larger decline in LM was noted in those with the least fitness level at baseline compared to the very fit group.[4,19]

4. Age-related changes in body composition in adults with diabetes

There are very few longitudinal studies designed specifically to address differences in body composition by diabetes status. However, some of the largest longitudinal studies examining age-related changes in body composition in the general population have recruited a relatively sizeable number of adults with diabetes, as shown in Table 2, and compared them to participants without diabetes.

4.1. Fat mass (FM)

Park et al. examined changes in body composition by diabetes status in 2675 adults from the Health ABC study who had an average age of 73 years at baseline.[20] Participants were assigned to one of three categories based on their diabetes status: adults with diagnosed type 2 diabetes (defined as being on oral glucose-lowering agent or insulin with onset after age 25 years or reported to have type 2 diabetes by a physician), adults with previously undiagnosed diabetes (defined as fasting plasma glucose of ≥126 mg/dl or 2-h post-challenge glucose of ≥200 mg/dl), and adults without diabetes. Adults with diagnosed diabetes ($n = 402$) and previously undiagnosed diabetes ($n = 226$) had an annual decline rate of total FM of 0.066 kg and 0.094 kg, respectively, compared to an annual gain of FM of 0.025 kg in the group without diabetes ($n = 2047$). Only the decline rate in trunk FM was significantly higher in adults with diagnosed and undiagnosed diabetes compared to those without diabetes. No significant differences were noted in the decline rate of appendicular fat by diabetes status.[20] Interestingly, when adjusted for changes in total body weight, all three groups had increased trunk, appendicular, and total FM over time. Similar age-related changes in body weight and FM were observed in another cohort of Chinese adults ≥65 years old.[21]

4.2. Lean mass (LM)

Individuals with diabetes lose more LM as they age compared to those without diabetes. Participants with previously undiagnosed diabetes, diagnosed diabetes, and no diabetes in the Health ABC study had annual decline rates of total LM of 0.34, 0.22, and 0.198 kg respectively.[20] Most of the decline in total LM in individuals with diabetes was due to loss of appendicular LM.[20,21] More recent longitudinal studies, looking at three-year changes in LM by diabetes status, revealed a greater decline in LM in those with versus without diabetes in the legs (−0.29 vs. −0.23 kg over 3 years, $p = 0.035$; respectively) and the arms (−0.08 vs. −0.06 kg over 3 years, $p = 0.025$; respectively).[22] This decline in LM was accompanied by a significant decline in muscle strength in the legs, but not arms, in adults with diabetes. The relative preservation of arm muscle strength in individuals with diabetes was also noted in other studies; suggesting discordance between changes in the upper and lower extremity strength and between muscle mass and strength changes in individuals with diabetes as they age.[2,23] An interaction effect of sex and diabetes status on the age-related decline in muscle mass has been reported. While women in the general population have lower rates of decline in appendicular LM compared to men, this beneficial effect of female sex seems to disappear in the presence of diabetes, particularly in the thigh muscle area.[17,19,20] Women with diabetes, in the Health ABC study, had two- to threefold increase in rates of decline in thigh muscle mass compared to women without diabetes, however, no significant differences by diabetes status were noted in the rates of declines in thigh muscle mass in men.[20]

While more rapid declines in LM have been noted in persons with versus without diabetes, the contribution of hyperglycemia per se to the accelerated loss of muscle mass and strength has been further investigated by our group in the National Health Nutrition Examination Survey and Baltimore Longitudinal Study of Aging. Not only were higher levels of A1C related to relatively lower muscle mass and strength in cross-sectional studies but relatively greater levels of hyperglycemia

Table 2
Longitudinal studies reporting age-related changes in body weight, body composition, and muscle strength in the general population and among those with diabetes.

Study	Age and sample size	Follow up duration	Rate of change in mean body weight		Rate of change in lean mass		Rate of change in total fat mass		Techniques used to measure body composition
			Men	Women	Men	Women	Men	Women	
General population									
Hughes et al., 2002[19]	60.7 ± 7.8 y (n = 53 men and 78 women)	Changes per ~10 years of follow up	+0.1 kg/10 years	+1.2 kg/10 yr	−1.1 kg/10 yr (−2% /10 yr)	−0.1 kg/10 year	+1.2 kg/10 yr (+ ~7.5%/10 yr)	+1.3 kg/10 yr (+ ~7.5%/10 yr)	Hydrodensitometry system
Siervogel et al., 1998[6] (The Fels Longitudinal Study)	18–45 years (n = 149 men; 159 women)	Annual change is presented. Follow up durations varied between participants.	BMI: +0.2/yr	BMI: +0.16/yr	+0.08 kg/yr	+0.04 kg/yr	+0.57 kg/yr (0.55%/yr)	+0.44 kg/yr (0.41%/yr)	Hydrodensitometry system
	45–65 years (n = 53 men; 62 women)		BMI: +0.12	BMI: +0.18	−0.13 kg/yr	0.00 kg/yr	+0.37 kg/yr (+0.34%/yr)	+0.52 kg/yr (+0.47%/yr)	
Gallagher et al., 2000[78]	60–96 years old (n = 24 men; 54 women)	Annual change is presented. Study follow up duration: 4.7 years	−0.1 kg/yr	−0.2 kg/yr	−0.3 kg/year	0.0 kg/yr	+0.3 kg/year	−0.2 kg/yr	DXA
Zamboni et al., 2003[18]	68–78 years old	Changes per 2 years of follow up	+0.3 kg/2 yr	0	−0.32 kg/2 yr	−0.16 kg/2 yr	+0.27 kg/2 yr	+0.39 kg/2 yr	DXA
By diabetes and glycemic status									
Lee et al., 2010[21]	≥65 years old (n = 442 with diabetes; 2711 without diabetes)	Changes from baseline to year 4	**Without diabetes:** −0.576 kg/4 yrs **With diabetes:** −1.482 kg/4 years	**Without diabetes:** −0.67 kg/4 yrs **With diabetes:** −1.297 kg/4 years	**Without diabetes:** −0.709 kg/4 yrs **With diabetes:** −1.251 kg/4 yrs	**Without diabetes:** −0.606 kg/4 yrs **With diabetes:** −0.957 kg/4 yrs	**Without diabetes:** +0.107 kg/4 yrs **With diabetes:** −0.269 kg/4 yrs	**Without diabetes:** −0.07 kg/4 yrs **With diabetes:** −0.332 kg/4 yrs	DXA
Park et al., 2009[20] (Health ABC cohort)	73 ± 2.8 years old (n = 2675)	Duration of follow up: 6 years in men and women Annual changes are presented	**Without diabetes:** −0.193 kg/yr **Diagnosed diabetes:** −0.293 kg/yr **Undiagnosed diabetes:** −0.435 kg/yr		**Without diabetes:** −0.198 kg/yr **Diagnosed diabetes:** −0.222 kg/yr **Undiagnosed diabetes:** −0.340 kg/yr		**Without diabetes:** +0.025 kg/yr **Diagnosed diabetes:** −0.094 kg/yr **Undiagnosed diabetes:** −0.066 kg/yr		DXA
Kalyani et al., 2015[25] (Baltimore Longitudinal Study of Aging)	25–96 years old (n = 984)	Duration of follow up: up to 7.5 years	Not available		**A1C Quartiles for knee extensor strength**[a] <**5.5%:** Reference **5.5–5.79%:** −0.69 ± 2.05 **5.8–6.09%:** −0.004 ± 2.17 **≥6.1%:** −4.47 ± 2.32 p value for trend: 0.05		Not available		Isokinetic dynamometer

Abbreviations: DXA, Dual energy X-ray absorptiometry;
[a] B coefficient ± SE in the regression model adjusted for age at first visit, race, sex, time since first visit, weight, height, physical activity, and peroneal motor nerve conduction velocity (the group with A1C <5.5% is the reference group).

Table 3
Clinical trials reporting the effect of lifestyle interventions on body composition in adults with type 2 diabetes.

	Intervention and sample size	Follow up duration	Rate of change in mean body weight		Rate of change in lean mass		Rate of change in total fat mass		Techniques used to measure body composition
			Men	Women	Men	Women	Men	Women	
Gallagher et al., 2014[32] (Ancillary study of the Look AHEAD trial)	57.8 ± 6.7 years old (A subset of 54 females and 38 males in the Look AHEAD trial)	Changes from baseline to year 1	**DSE group:** −0.76 kg/yr **ILI group:** −9.83 kg/yr	**DSE group:** −0.3 kg/yr **ILI group:** −5.95 kg/yr	N/A	N/A	**DSE group:** +0.09 kg/yr **ILI group:** −8 kg/yr	**DSE group:** +0.22 kg/yr **ILI group:** −4.8 kg/yr	MRI
Pownall et al., 2015[31] (The Look AHEAD Trial)	58 ± 7 years old (598 females and 421 males in the Look AHEAD trial)	Changes from baseline to year 1	**DSE group:** 0 kg in the first year **ILI group:** −9.4 kg in the first year	**DSE group:** −0.5 kg in the first year **ILI group:** −7 kg in the first year	**DSE group:** 0 kg in the first year **ILI group:** −2.8 kg in the first year	**DSE group:** −0.5 kg in the first year **ILI group:** −2 kg in the first year	**DSE group:** −1 kg in the first year **ILI group:** −6.6 kg in the first year	**DSE group:** 0 kg in the first year **ILI group:** −5 kg in the first year	DXA
		Changes from baseline to year 8	**DSE group:** −1 kg/8 yrs **ILI group:** −3 kg/8 yrs	**DSE group:** −3 kg/8 yrs **ILI group:** −5 kg/8 yrs	**DSE group:** −2 kg/8 yrs **ILI group:** −2.5 kg/8 yrs	**DSE group:** −2.5 kg/8 yrs **ILI group:** −3 kg/8 yrs	**DSE group:** 0 kg/8 yrs **ILI group:** −1 kg/8 yrs	**DSE group:** 0 kg/8 yrs **ILI group:** −2 kg/8 yrs	
Yalamanchi et al., 2016[34]	40 to 65 years old (33 men and 17 women) Data from the SHAPE 2 trial	Changes from baseline to 6 months in men and women	**Resistance and aerobic exercise:** −2.1 kg/6 months		**Resistance and aerobic exercise:** +0.5 kg/6 months		**Resistance and aerobic exercise:** −2.1 kg/6 months		DXA
Cauza et al., 2009[37]	48–64 years old	Changes from baseline to 4 months in men and women	**Resistance training:** −1 kg/4 months		**Resistance training:** +3 kg/4 months		**Resistance training:** −3.8 kg/4 months		CT

Abbreviations: DSE, Diabetes Support and Education; ILI, Intensive Lifestyle Intervention; DXA, Dual energy X-ray absorptiometry; MRI, Magnetic resonance imaging; CT, Computed tomography.

also predicted persistently lower muscle strength up to 7.5 years later, in part related to the presence of peripheral neuropathy.[24–27] Together, these studies suggest a putative role for hyperglycemia in the accelerated decline of muscle mass and strength observed in persons with diabetes.

5. Effect of lifestyle interventions on body composition in T2DM

5.1. The Look AHEAD trial

The Look AHEAD trial was designed to test whether an Intensive Lifestyle Intervention (ILI) to reduce weight and increase physical activity would reduce cardiovascular morbidity and mortality in individuals, ages 45–76 years, with type 2 diabetes and BMI ≥25 kg/m^2 compared to the Diabetes Support and Education (DSE) intervention. Participants in the ILI group were assigned to caloric intake goal of 1200–1500 or 1500–1800 kcal/day depending on initial weight and advised to increase their physical activity to 175 min/week.[28] Participants in the DSE group received general information related to healthy eating and physical activity but did not receive specific strategies for weight loss nor comprehensive components of the intervention.[29] The trial was stopped after a median follow-up of 9.6 years due to lack of differences in CVD event rates between the two groups; however, the overall rate of CVD events was much lower than what was predicted at the beginning of the study. Yet, the ILI group had significantly more weight loss that was maintained throughout the 9.6 years of the trial, desirable changes in body compositions, improvements in glucose, lipid, and blood pressure control, less number of glucose lowering medications, and many other benefits.[30]

At the end of one year of ILI in men and women, there were significant declines in body weight (−9.4 kg and −7 kg, respectively), total FM (−6.6 kg and −5 kg, respectively), and LM (−2.8 kg and −2 kg, respectively) from baseline (Table 3). Because the FM lost during the one year of ILI exceeded the LM lost in men and women, the overall percent FM declined from baseline to 1 year whereas the percent LM increased during that year. Little to no changes in body weight, FM, and LM were noted in the DSE group during the first year.

Between years 1 and 8, men and women in the intervention group regained most of the FM that they had lost during the first year and continued to lose more LM, albeit at a slower rate. This has resulted in an overall increase in percent FM and decline in percent LM from baseline to year 8. The DSE group, on the other hand, lost a significant amount of LM (−2.2 kg) between baseline and year 8 which counted for nearly all the body weight loss they had as they did not lose any significant FM during those 8 years. Throughout the 8 years, the intervention group maintained a significantly lower FM and LM compared to the DSE group.[31]

In an ancillary study using MRI to characterize adipose tissue depots in the Look AHEAD trial, one year of ILI was associated with significant reductions in total FM in men and women (−8 versus −4.8 kg/year, respectively), subcutaneous FM (−5.57 versus −4.1 kg/year, respectively), and visceral FM (−2.15 versus −0.83 kg/year, respectively).[32] Interestingly, the ILI did not result in a significant change in the intermuscular FM but it may have prevented the gain of intermuscular FM that was noted in the DSE group (+0.46 kg/year in women and 0.47 kg/year in men). The rates of decline in leg, arm, and trunk LM among men in the Look AHEAD trial were comparable to those seen in women, supporting findings from other studies suggesting loss of the beneficial effect of female sex on preserving appendicular muscle mass with aging in the presence of diabetes.[20,33] Taken together, the ILI in overweight and obese individuals with type 2 diabetes in the Look AHEAD trial resulted in an initial loss of FM and prevention of age-related gain in intermuscular fat but failed to maintain that loss of FM beyond the first year of intervention and did not prevent the age-related loss of LM. However, structured exercise interventions in people with diabetes have been found to maintain or increase LM. Resistance training alone, or in combination with aerobic exercise has been shown to reduce FM and increase LM in adults with type 2 diabetes; with greater benefits seen in individuals who had higher fasting glucose at baseline in one study.[34–37]

Table 4
The effect of pharmacotherapy and metabolic (bariatric) surgeries on body composition in adults with type 2 diabetes.

	Total body weight	Total lean mass	Total fat mass	Techniques used in relevant studies	Studies evaluating body composition
Pharmacotherapy					
Insulin	↑	↑	↑	CT DXA	Elish et al. (2016); Hartemann-Heurtier et al. (2009); Shah et al. (2011)[41,42,79]
Metformin	↓	←→ or ↑	↓	BIA CT DXA Waist circumference	Rodriguez- Moctezuma et al. (2005); Wang et al. (2013)[45,46]
GLP-1 agonists	↓	↓ or ↑	↓	CT DXA	Jendle et al. (2009)[48]
Sulfonylureas	↑	←→ or ↑	↑	DXA CT	Basu et al. (2006); Jendle et al. (2009)[48,54]
TZDs	↑	←→	↑	CT DXA	Basu et al. (2006); Miyazaki et al. (2002); Shah et al. (2011); Smith et al. (2005); Wang et al. (2013)[46,54,58,79,80]
SGLT2 inhibitors	↓	←→ or ↓	↓	BIA BMI DXA Waist circumference	Blonde et al. (2016); Neeland et al. (2016); Tobita et al. (2017); Inoue et al. (2018), Bolinder et al. (2012); Sasaki et al. (2019)[60–63,65,66]
DPP-4 inhibitors	←→ or ↑	←→	←→ or ↑	BIA CT Waist circumference	Nahon et al. (2018); Takeshita et al. (2018)[67,68]
Metabolic (bariatric) surgery					
Roux en Y gastric bypass, LSG LGBP	↓	↓	↓	BIA BMI CT DXA MRI	Guida et al. (2005); Heath et al. (2009); Metcalf et al. (2005); Strain et al. (2009); Tamboli et al. (2010)[69–72,81]

Abbreviations: BIA, Bioimpedance Analysis; GLP-1, Glucagon-like peptide 1; TZD, Thiazolidinediones; SGLT, Sodium-glucose cotransporter; DPP-4, dipeptidyl peptidase 4; DXA, Dual energy X-ray absorptiometry; MRI, Magnetic resonance imaging; CT, Computed tomography; LSG, laparoscopic sleeve gastrectomy; LGBP, laparoscopic adjustable gastric band surgery.

6. Effect of glucose-lowering medications on body composition in type 2 diabetes

Antihyperglycemic agents for diabetes can have a wide range of effects on weight loss, lean mass, and fat mass (Table 4). These are detailed in the following sections.

6.1. Insulin

Insulin therapy is associated with overall weight gain relative to dose, but there are few studies evaluating the changes in body composition in patients who are treated with insulin. Jang Won Son et al., studied patients with newly diagnosed type 2 diabetes treated with glargine and lispro (0.4–0.5 units per kg) over a 12 week period and found that while there was not a significant change in total FM from baseline, intensive insulin therapy was associated with a significant increase in subcutaneous adipose tissue (135.2 ± 55.4 to 155.2 ± 65.1) and a significant decrease in visceral adipose tissue (108.7 ± 53.0 to 98 ± 44.9) from baseline as measured by CT scan.[38] In addition, appendicular skeletal muscle mass increased (18.7 ± 5.2 to 19.6 ± 5.2). Similarly, Juurinen et al., showed that while total body weight and total FFM increased in patients treated with 7 months of insulin therapy (75 ± 10 units per day), there was no significant change in FM and the liver fat content actually decreased by 20%(17 ± 3 to 14 ± 3%).[39] A recent meta-analysis assessed ten basal insulin analogues and high-to-moderate quality evidence suggested that detemir had a favorable weight profile including less weight gain versus the comparators including U-100 and U-300 degludec and glargine (and excluding NPH).[40] In a small prospective trial of insulin-naive patients with type 2 diabetes, glargine was associated with a greater overall weight gain (+4.2 ± 4.1 vs. +0.6 ± 2.5 kg), a greater gain in total FM (+0.9 ± 2.2 vs. +2.9 ± 2.4 kg), and a greater gain in truncal FM (+0.8 ± 1.5 vs. +2.1 ± 1.7 kg) compared to detemir in patients treated over six months with similar doses of insulin (0.5 units/kg ± 0.3 vs. 0.6 units/kg ± 0.5).[41] With regard to LM, detemir was associated with a reduction whereas glargine was associated with a gain in both total LM (−0.4 ± 1.1 vs. +1.3 ± 2.9 kg) and truncal LM (−0.8 ± 1.9 vs. +0.3 ± 1.7 kg) at similar doses. However, in a separate study, there was no change in FM, FFM, visceral fat or subcutaneous fat seen with addition of NPH (compared to add-on therapy with pioglitazone), in spite of a statistically significant weight gain.[42] Shah et al. found that combination therapy with insulin and pioglitazone also resulted in gains in both total FM and LM compared to insulin therapy alone.[42] Total body weight gain was greater with combination of insulin and pioglitazone (+4.9 ± 4.5 kg) versus insulin therapy alone (+1.7 ± 0.7 kg). Whereas, LM increased significantly (+1.92 ± 0.74 kg) with combination insulin and pioglitazone treatment.

6.2. Metformin

Metformin use is associated with mild weight loss, ranging from −2.0 to −3.8 kg in randomized controlled trials of up to twelve months duration comparing metformin to placebo or to comparators.[43] In the UK Prospective Diabetes Study, patients were able to maintain a steady weight on metformin up to a maximum dose of 2550 mg compared to the sulfonylurea and insulin groups who experienced weight gain over the same time period.[44] There has also been some data to suggest that use of metformin also results in improvement of several body composition parameters. In a study of twenty-one patients with risk factors for diabetes on metformin therapy compared to placebo, there was a reduction in FM (25.9 ± 9.4 to 20.8 ± 9.2 kg vs. 20.7 ± 11 to 19.1 ± 10) and an increase in LM (57.05 ± 13.6 to 61.9 ± 16.5 kg vs. 63.6 ± 12 to 63.5 ± 11) after two months of metformin use at a dose of 1700 mg/day.[45] Wang et al. showed that patients with newly diagnosed type 2 diabetes who were treated with metformin at a maximum dose of 1700 mg per day for six months experienced a decrease in absolute FM (20.79 ± 6.45 to 17.28 ± 6.12 kg).[46] However, there was no significant change in body weight, LM, subcutaneous adipose tissue, or visceral adipose. Notably, this study was a small study and it excluded patients with a BMI ≥35 kg/m^2.

6.3. GLP1 receptor agonists

The GLP-1 RA class of drugs is associated with weight loss ranging from −1.1 to −6.9 kg.[47] There have been several studies on GLP-1 RA and changes in body composition with the majority focused on liraglutide, and some using exenatide and dulaglutide. The Liraglutide Effect and Action in Diabetes (LEAD-2 and LEAD-3) trials demonstrated that monotherapy with liraglutide at all doses resulted in a mean weight loss of −2.3 to −2.5 kg. Substudy analysis showed that weight loss due to liraglutide monotherapy or liraglutide added to metformin was primarily due to a decrease in FM rather than loss of LM, and that abdominal visceral fat loss was greater than subcutaneous tissue fat loss.[48] In LEAD-2, mean dose-dependent reductions of FM from baseline were −0.7, −1.6 and −2.4 kg with liraglutide 0.6, 1.2 and 1.8 mg in combination with metformin over a duration of 26 weeks. In the LEAD-3, mean FM reductions were −2.0 and −1.0 kg with liraglutide 1.2 and 1.8 mg monotherapy, respectively, over 52 weeks. This was statistically significant compared to the mean increase from baseline of +2.4 kg seen with glimepiride monotherapy. In LEAD-2, mean reductions of absolute LM from baseline was −0.3, −0.8 and −1.5 kg with liraglutide 0.6, 1.2 and 1.8 mg (in combination with metformin) were not statistically different from the mean decrease from baseline of −1.3 kg observed with placebo (in combination with metformin). CT measurements were obtained in LEAD-2 and showed that visceral adipose tissue area was reduced by 13–17% in liraglutide at all doses (in combination with metformin) compared to a 5% reduction observed in the glimepiride group and −8% reduction in the placebo group. Interestingly, in small study of nine elderly patients (mean age 68.2 ± 3.86 years) treated with 3.0 mg of liraglutide over 24 weeks, there was an increase in appendicular skeletal mass (median skeletal muscle index +0.03 kg/m^2) as calculated by DXA in the setting of a median reduction of 2 kg of body weight and reduction of 1.4 kg FM.[49] A similar trend toward an increase in LM percentage (1.0% vs. 0.2%) was seen in a small study of patients treated with 0.6 mg liraglutide versus placebo after 8 weeks.[50] The effect of dulaglutide (added on to insulin) on body composition in patients with diabetes on hemodialysis showed that both FM (21.9 to 18.9 kg) and skeletal muscle mass (21.0 to 20.2 kg) were significantly reduced after six months of 0.75 mg of dulaglutide therapy compared to add on therapy with 20 mg/day of teneligliptin. Exenatide showed reductions in total FM, trunk fat, limb fat and limb lean tissue. However, there was a significantly increased percentage of total LM compared to glargine.[51] Exenatide also decreased visceral fat compared to glargine as well as improvement of hepatic steatosis.[52,53]

6.4. Sulfonylureas

Sulfonylureas are associated with mild weight gain (+2.0 to 2.3 kg), but there are few studies looking at changes in body composition.[47] A more comprehensive look at body composition changes was undertaken in substudy LEAD-2 and LEAD-3 trials, where the liraglutide comparison arms were glimepiride 4 mg plus metformin and glimepiride 8 mg alone.[48] In LEAD-2, treatment with glimepiride 4 mg plus metformin resulted in mean increase of 1.1 kg in FM and 1.3 kg in LM and total body weight gain of 2 kg from baseline. In LEAD-3, there was an increase of 2.4 kg from baseline in FM observed with glimepiride 8 mg. Furthermore, there was a mean increase of 2.6% percentage body fat from baseline in the glimepiride 8 mg group compared to liraglutide 1.2 mg and 1.8 mg monotherapy. In a small study of 10 patients comparing body composition changes with the use of glipizide 10 mg compared to pioglitazone 45 mg, there was no significant difference in the increment of body weight change between groups.[54] However, there was a

detectable significant increase in visceral fat (+38 vs. −32 cm^2) and total abdominal fat (+19 vs. −16 cm^2) in the glipizide group compared to the pioglitazone group.

6.5. Thiazolidinediones (TZDs)

There have been several studies showing weight gain (+2.3 to 4.5 kg) with use of the thiazolidinediones (TZD).[47] In a substudy of the DREAM trial,[55] compared with placebo, rosiglitazone 8 mg was associated with an increase in total body fat (+4.1 kg) and subcutaneous adipose tissue (+23 cm^2) over 3.5 years whereas total LM was not different between the groups. Treatment with 8 mg of rosiglitazone for 16 weeks, in another study, was associated with increases in total body weight (2.1 ± 2.0 kg) and FM (1.4 ± 1.6 kg) with 95% of the increase localized to the abdominal region.[56] There was an 8% increase in subcutaneous fat (+25 ± 28.7 cm^2), but no change in visceral FM. The increase in LM was not significant. Whereas, Nam et al. did show a statistically significant increase in mid-thigh low-density muscle area (23 ± 9.6 to 26 ± 8.2 cm^2 $p = 0.009$) and reduction in abdominal visceral adipose tissue area (145 ± 65.6 to 129 ± 73.1 cm^2) after twelve weeks of therapy with rosiglitazone, but there was no control group.[57] In a randomized, double-blind, placebo-controlled trial, body weight increased in the pioglitazone group (+3.88 ± 3.11 kg) compared to the placebo group which experienced weight loss (−0.79 ± 3.36 kg), with most of the weight gain attributable to FM.[58] LM did not change significantly. Subcutaneous fat in the trunk, arms, and legs were all increased in the pioglitazone-treated group. Visceral fat did not change significantly in either group. The lack of change in visceral fat was also seen with troglitazone use.[59]

6.6. SGLT2 inhibitors

SGLT2 inhibitors are associated with weight loss of around −0.9 to −2.5 kg, and studies analyzing changes in body composition suggest that this weight loss is primarily related to a reduction in FM.[47] In studies of canagliflozin (100 mg and 300 mg), patients achieved larger reductions in total fat (−1.6 and −2.1 kg, respectively) and LM (−0.6 and −0.9 kg, respectively) compared with placebo after 26 weeks. About two-thirds of the weight loss was due to loss of FM. Both canagliflozin doses also provided reductions in subcutaneous and visceral adipose tissue.[60] In studies of dapagliflozin as an add on therapy to metformin compared to metformin plus placebo, there were reductions in both FM (−2.22 vs. −0.74 kg) and LM (−1.1 vs. −0.6 kg), after 24 weeks of therapy.[61] Similarly, in a separate study dapagliflozin was studied in patients with type 2 diabetes and nonalcoholic steatohepatitis and showed a reduction in FM(28.3 to 22.2 kg) and percentage of body fat (42.4 to 38.2%), as well as an increase in percentage lean body mass (30.9 to 34.1%).[62] However, there was not a significant increase in absolute total LM. Appendicular muscle mass increased significantly from 23.3 to 25.5%. In the LIGHT trial conducted in Japanese participants with type 2 diabetes, luseogliflozin (approved for treatment of type 2 diabetes in Japan) resulted in reduction in lean mass by −0.798 kg and −0.992 kg at 24 and 52 weeks, respectively, and total fat mass by −1.97 kg and −1.96 kg at the same time points.[63] This was also consistent with another study that showed 12 weeks of tofogliflozin (still in development) resulted in significant weight loss (−2.87 ± 1.48 kg) and reduction of body FM (−1.33 ± 0.99 kg) and LM (−1.54 ± 0.77 kg).[64] Changes in body composition on empagliflozin were studied in the EMPA-REG H2H SU Trial.[65] In the cohort followed for 24 weeks, there was a greater reduction in estimated total body fat for empagliflozin versus placebo (−0.3%). Similarly in a recent study, ipragliflozin (an SGLT-2 inhibitor approved for clinical use in Japan) resulted in weight loss, mainly from fat mass without a significant change in lean mass, when used as an add-on therapy to insulin for 24 weeks in adults with type 2 diabetes.[66]

6.7. DPP-4 inhibitors

There are surprisingly few studies evaluating the effect of DPP-4 inhibitors on body composition. DPP-4 inhibitors are considered weight-neutral. A randomized controlled trial of patient with prediabetes treated with sitagliptin vs. placebo did not find a difference in weight loss or body composition though the primary endpoint was brown adipose tissue volume and activity.[67] In another study comparing alogliptin 25 mg daily versus metformin 1000 mg twice daily for 12 weeks, there was a statistically significant increase in body weight with alogliptin compared to metformin (+0.84 ± 1.57 vs. −0.35 ± 1.53; $p = 0.002$). FM was increased in the alogliptin group and reduced in the metformin group (+1.49 ± 5.06 vs. −0.04 ± 1.81; p 0.042) and LM was not significantly changed in either group.[68]

7. Effect of metabolic (bariatric) surgeries on body composition

Bariatric surgery is an effective treatment for obesity and diabetes. The goal of weight loss is primarily reduction of FM. Today, the most common performed bariatric procedures are Roux-en-Y gastric bypass (RYGB), laparoscopic sleeve gastrectomy (LSG), and laparoscopic adjustable gastric band surgery (LGBP).

Most studies demonstrate that these procedures cause a greater reduction of FM compared to FFM (Table 4). This trend holds true across all ranges of BMIs. The amount of physical exercise is an important factor in the loss of body weight and in gains in LM. Specifically, patients who undergo bariatric surgery and follow up with physical exercise see gains of 15% LM, while sedentary patients lose 11% LM by the end of the first year of observation.[69]

For RYGB, most studies demonstrated that the loss of FM was approximately 50% and loss of FFM was approximately 15% after 6 months. The loss of LM occurs mostly during the first six months after RYGB with LM accounting for up to 32.5 ± 10.6% of weight loss during this time in one study. The loss of LM during the second six months is more variable, ranging from 0 to 2.4 kg in the same study.[70]

A few studies have looked at the long-term changes in body composition with laparoscopic gastric banding. Guida et al. found that in patients maintained on a well-balanced hypocaloric diet, experienced overall loss of predominantly FM (28 kg FM and 2.9 kg FFM) in the first year post-surgery.[71] During the second year, there was a roughly equivalent loss of FM and FFM (1.9 kg of FM and 1.2 kg FFM).

Only one study directly compared different bariatric procedures,[72] and showed that the change in mean percentage of body fat after RYGB, LSG, and LVBG was 7, 7.9, and 6.8% respectively. Furthermore, there was a strong correlation among all the patients between BMI change and the change in body fat. The greatest correlation was within the RYGB group.

Most of the studies available are from small cohorts. There is a need for studies with larger sample size and longer follow up to more fully understand the changes in body composition after surgical weight loss procedures.

8. Clinical implications in adults with type 2 diabetes

Due to the lack of readily available tools to directly measure body composition in the clinical setting, many of the metabolically unfavorable changes in body composition in adults with type 2 diabetes are often overlooked. Total body weight and BMI, which are commonly used to assess anthropometry, have limitations and often remain relatively stable in adults with type 2 diabetes during middle-age, even though a relative decline in lean mass and increase in fat mass may be occurring (i.e. sarcopenic obesity). Lower lean body mass has been associated with worse glycemic control in people with diabetes, likely due to the fact that skeletal muscle is a main target of insulin action and accounts for most of the body's insulin-mediated glucose uptake. In fact,

the increase in lean mass in adults with type 2 diabetes after resistance training has been associated with improved glycemic control in several studies.[73–75] Therefore, the American Diabetes Association (ADA) and American College of Sports Medicine recommend that resistance training be part of a the routine physical activity in adults with type 2 diabetes.[76,77] Similar to resistance training, it may be hypothesized that pharmacological and surgical treatment strategies that specifically promote metabolically favorable body composition changes (i.e. maintain or increase lean body mass and/or reduce total fat mass) would be associated with an overall better glycemic control and cardiometabolic health in adults with type 2 diabetes. By considering the effects of antihyperglycemic therapies on body composition in routine clinical management, health outcomes for patients may be optimized, particularly for older adults with diabetes.

9. Conclusion

Type 2 diabetes is associated with metabolically unfavorable changes in body composition that are not necessarily apparent when surrogate measures such as BMI are used to track anthropometric changes. There is an overall greater gain of FM and a more rapid loss of LM in adults with versus without diabetes. Future studies are needed to better understand the best method to assess body composition changes in people with diabetes, particularly to better account for the presence of ectopic fat, and the relationship of hyperglycemia to these body composition changes in people with diabetes. There is also a strong need to identify effective strategies to prevent, or at least slow down, the unfavorable change in body composition seen in adults with type 2 diabetes as they age; specific glucose-lowering therapies may offer potentially favorable effects on body composition and further research is needed. When managing adults with type 2 diabetes, it is important to consider the effect of diabetes on body composition, particularly in older adults, and consider treatment strategies (lifestyle, pharmacological, and surgical) that have the potential to improve, or at least not worsen, body composition in these individuals as they age. For instance, by solely focusing on promoting total body weight loss in people with diabetes, the resultant decline in lean mass that often occurs together with the loss of fat mass may be potentially detrimental for the functionally limited older adult with diabetes. Whether adding the measurement of body composition to the current standard of care in diabetes and promoting treatment strategies that enhance metabolically favorable body composition would result in a clinically meaningful reduction in morbidity and/or mortality remains an open question and should be investigated in future studies.

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