The effects of GLP-1 RAs compared to DPP4is or SGLT2is on appendicular lean mass index (ALMI): an interim analysis.

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Abstract

Newer antihyperglycemic medications, including glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sodium-glucose cotransporter 2 inhibitors (SGLT2is), and Dipeptidyl peptidase-4 inhibitors (DPP4is), have grown in popularity for their blood glucose-lowering effects and cardiorenal benefits, as well as their support for weight loss efforts. However, the relationships between these medications and changes in lean and muscle mass, specifically appendicular lean mass index (ALMI) are not fully explored. This retrospective cohort study using population-based data identified 82 individuals who initiated one or more of these medications between two dual-energy x-ray absorptiometry (DXA) assessments. A previously described model was applied to regional spine and hip data from DXA assessments to estimate ALMI (eALMI). In the cohort, 54 (66%) initiated a DPP4i, 38 (46%) initiated an SGLT2i, and 6 (7%) initiated a GLP-1 RA. Mean change in eALMI between one and five years across all medications was -0.13 kg/m^2 (SD 0.47). SGLT2is were associated with declining muscle mass, ranging from -0.31 kg/m^2 (95% CI: -0.59, -0.04) to -0.82 kg/m^2 (95% CI: -1.57, -0.07) after adjustments. There was no association with any medication class with a previously defined threshold for a large decline in eALMI of ≤ -0.45 kg/m^2, or any adverse clinical outcomes, including death, long-term care admission, or new home-care use. While SGLT2is were associated with a decline in eALMI, more research should be conducted to better understand this relationship, as well as ascertain if a relationship exists for DPP4i and GLP-1 RA medications.

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Introduction

Type 2 Diabetes Mellitus (T2DM) is a major global public health issue. This trend exists within Canada, where in 2019, 12.4% of the population aged 20-79 years old was determined to have prediabetes, with 7.5% having diagnosed or undiagnosed T2DM [1]. This issue is even more alarming in the Province of Manitoba, where the prevalence is estimated to be 8.4% in 2020 [2]. In addition to public health measures such as the promotion of affordable and accessible exercise and nutrition, medications exist to treat the many individuals living with T2DM. Over the past 20 years, three new drug classes have entered the market for patients living with T2DM; dipeptidyl-peptidase 4 inhibitors (DPP4is), sodium-glucose transport protein 2 inhibitors (SGLT2is), and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) [3,4]. These newer medications have been studied extensively for their ability to impact cardiovascular, renal, and metabolic health in T2DM patients [5–8]; however, there is a need for more research on their relationship with elements of frailty, including sarcopenia and low lean mass.

Sarcopenia, generally defined as the loss of muscle mass, strength, and function, is a lesser-known yet growing public health concern due to its associations with adverse clinical outcomes such as all-cause mortality [9,10]. It is difficult to assess the prevalence of sarcopenia due to the lack of consensus on diagnostic criteria and accessibility of testing [11,12]. Sarcopenia has classically been diagnosed through a combination of lean/muscle mass measures, muscle strength, and performance measures [11,13–23]. Appendicular lean mass, indexed to height (ALMI), is frequently used as the measure of lean or muscle mass for the diagnosis of sarcopenia [13–19]. ALMI can be ascertained through the use of dual-energy x-ray absorptiometry (DXA) scan, which is typically used for assessing osteoporosis [24,25].

Sarcopenia is associated with a higher prevalence in patients with T2DM due to the close association between muscle work and serum glucose uptake, chronic subclinical inflammation, and vascular damage [26,27]. Evidence exists regarding the associations between DPP4is and SGLT2is and the association of these drugs with sarcopenia and low and declining lean or muscle mass. Pharmacovigilance evidence regarding SGLT2i suggests a strong association with sarcopenia [28]; and associations between this medication and skeletal muscle mass measures have been mostly in favour of SGLT2is having a net neutral or negative effect on muscle mass measures [26,27]. Pharmacovigilance also suggests a weaker association with sarcopenia in comparison to SGLT2is [28], however other studies have reported improvements in muscle mass measures with some suggesting DPP4is could be an effective medication for individuals with diabetes who have sarcopenic features [26,27,29,30]. For these studies, it is critical to note that sample sizes are frequently fewer than 100 individuals, with the largest at 451.

Evidence regarding the association between sarcopenia measures, specifically muscle mass measures, with GLP-1 RAs is limited and mixed. GLP-1 RAs have recently gained popularity due to their weight-loss properties, including delayed gastric emptying, altered satiety perceptions, and increased insulin secretion [27,31,32]. Early studies on the effects of GLP-1 RAs are highly heterogeneous, which may be due to the strength of the weight-loss inducing effects between older classes of GLP-1 RAs (exenatide, liraglutide, dulaglutide), versus the newer and stronger semaglutide and tirzepatide [26,28,33,34]. Studies using exenatide, liraglutide, and dulaglutide have shown that weight loss primarily results from fat mass loss,

while preserving or even improving muscle mass [26,27]. However, studies involving semaglutide have suggested muscle mass losses in addition to fat mass losses [27,33–36].

There is significant heterogeneity in the data surrounding the effects of GLP-1 RAs on sarcopenia measures, particularly muscle or lean mass measures. Thus, the purpose of the current study is to contribute to the literature regarding GLP-1 RA medications on ALMI in comparison to SGLT2is and DPP4is using a large, population-based, retrospective cohort from the province of Manitoba in Canada.

Methods

This study used a retrospective cohort design with linked administrative data from the Manitoba Centre for Health Policy (MCHP) repository. MCHP houses population-level databases representing healthcare interactions for the entire province of Manitoba, and contains data from all individuals who have been covered by the Manitoba Health Services Insurance Plan at any point since 1970; these data are included in the Manitoba Health Insurance Registry and associated provincial and national healthcare databases. Individuals are linked to each database via a unique, scrambled personal health identification number (PHIN). The Manitoba Bone Mineral Density (BMD) Program registry, which contains all DXA data for the province of Manitoba, [24,25] was the main database used for these analyses. Individuals within the BMD Program registry reflect Manitoba provincial guidelines for osteoporosis screening, which include individuals with fragility fractures or high-risk medications (e.g., prolonged glucocorticoid use), all women aged 65 years and older, and younger women or men with additional risk factors for osteoporosis [25]. All DXA scans included in the study cohort were

performed with fan-beam scanners (Prodigy, GE Lunar, Madison, WI before 2012, iDXA, GE Lunar, Madison, WI after 2012). Crosscalibration between DXA scanners previously performed on this data demonstrated equivalence in BMD and non-BMD measures [25,37]. This study was approved by Research Improvements Through Harmonization In Manitoba (RITHIM) on behalf of the Research Ethics Board at the University of Manitoba, with Shared Health Manitoba Research and Innovation, and with the Provincial Health Research Privacy Committee (Project ID: 106). The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for observational studies.

All adults (age ≥ 18 years) in the province of Manitoba with two baseline hip and lumbar spine DXA assessments occurring between January 1st, 2007, and June 12th, 2020, were included. Eligible individuals were required to have initiated a new antihyperglycemic medication, specifically a GLP-1 RAs, DPP4is, or SGLT2is, after their index scan and prior to a follow-up scan. GLP-1 RAs were also flagged if they were semaglutide or tirzepatide. Individuals who had started a GLP-1 RA within 365 days before the index DXA assessment were excluded from analyses. Hospitalizations, physician visits, and other filled prescriptions were extracted and linked from the data repository to assess comorbidities.

Covariates for modelling include age, sex, estimated central mass index (eCMI; BMI – eALMI), comorbidities, and pharmaceutical prescription fills. eCMI was employed instead of BMI to reduce collinearity with eALMI in analyses. Comorbidities assessed include diabetes, hypertension, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), congestive heart failure (CHF), arthritis, and osteoporosis and

related fractures (Appendix C). Medications assessed besides the foci anti-hyperglycemic medications include statins, tricyclic antidepressants, prescription-strength calcium, prescription -strength vitamin D, and bisphosphonates (Appendix D).

For each DXA assessment, ALMI was estimated (eALMI) from hip and lumbar spine DXA as previously described (Rossum). An R^2 of 0.864 for measured versus predicted ALMI, and area under the receiver operator characteristic of 0.88 for ALMI consistent with sarcopenia as defined by the European Working Group on Sarcopenia in Older People version 2 (EWGSOP2) were reported [15]. High test-retest reproducibility for ALMI was seen in 297 individuals with paired measurements (median interval 8 days), with an intra-class correlation coefficient of 0.993 and coefficient of variation of 1.2%. A previously reported change in eALMI (first minus second) of $\leq$ -0.45 kg/m^2, which represents approximately one standard deviation in eALMI change, was employed to indicate a significant decline in eALMI [37,38].

Adverse clinical outcomes were included if they occurred between January 1, 2004, and December 31, 2024, and included 1) time to all-cause mortality, 2) time to long-term care admission, and 3) time to home care use. Adverse clinical outcomes were included for analyses if they occurred following the date of the second DXA assessment. Individuals who were previously admitted to long-term care or using home care services in the year before baseline DXA assessment were removed from the Cox proportional hazards analyses.

All analyses were conducted using SAS 9.4. For continuous variables, normality was assessed, and non-normal variables were converted to categorical variables. Cox proportional hazards

regression models were built to estimate the association between declining eALMI and time to adverse clinical outcomes. These models were adjusted with age and sex, and an interaction term between DPP4i and SGLT2i use. Subgroup analyses were conducted for each medication. Tables displaying the results of these analyses are presented in the Appendix.

Results

Descriptive Characteristics of the Study Cohort

The cohort included 82 individuals, 54 (66%) of whom started a DPP4i, 38 (46%) who started an SGLT2i, and 6 (7%) who started a GLP-1 RA between the first and second DXA assessments. Thirteen individuals were started on both an SGLT2i and a DPP4i. There were no individuals who were flagged as taking semaglutide or tirzepatide. Mean age was 64.4 (SD 8.7) and 79 (96%) individuals are identified as female. Mean eALMI at baseline was 7.4 kg/m^2 (SD 1.2), and at follow-up was 7.3 kg/m^2 (SD 1.3), with an average change in eALMI of -0.13 kg/m^2 (SD 0.47). Twenty individuals (24%) exhibited a significant decline in eALMI ($\leq$ 0.45 kg/m^2) between the first and second DXA assessments. The mean number of years between first and second DXA assessments was 3.5 (SD 0.8).

Power Considerations

Power was assessed via Cohen's D values for each medication. Mean difference between index and follow-up eALMI values in individuals who started on a DPP4i versus those who were not was 0 kg/m^2, resulting in a Cohen's D of 0, representing no effect on changes in eALMI. For SGLT2is, the mean difference between the index and follow-up eALMI measures was -0.16 kg/m^2, with a Cohen's D of -0.344, indicating a moderate effect on changes in eALMI. Finally,

the mean difference between index and follow-up eALMI in individuals started on a GLP-1 RA was -0.02 kg/m^2, with a Cohen's d of -0.04, indicating a very small effect on eALMI. These values highlight a caveat: while some results of the current study may not be significant due to limited power, future studies with more individuals may yield statistically significant results.

Relationship between Change in eALMI and Medication Use

Four unique linear models were developed to understand the association between changes in eALMI and medication usage. Across all four models, SGLT2is were consistently associated with decreased eALMI between index and follow-up assessments (Table 3). Without an interaction term, SGLT2is were associated with a -0.31 kg/m^2 (95% CI: -0.59, -0.04) to -0.32 kg/m^2 (95% CI: -0.60, -0.04) change in eALMI over time (Table 3). When the interaction term between SGLT2is and DPP4is was included in modelling, SGLT2is were associated with a -0.82 kg/m^2 (95% CIs: -1.57, -0.07; -1.59, -0.06) change in eALMI (Table 3). DPP4is and GLP-1 RAs were not significantly associated with changes in eALMI (Table 3). Similarly to linear methods, four unique logistic models to a significant change in eALMI of ≤ -0.45 kg/m^2 were created (Table 4). Among these models, none of the medications were associated with increased risk of this decline in eALMI (Table 4).

Relationship between Adverse Clinical Outcomes and Medication Use

In the study population, 19 individuals died and 8 individuals were admitted to a long-term care facility or began receiving home care services (Table 5). Mean time to death was 9.8 years (SD 2.7), mean time to long-term care admission was 5.2 years (SD 1.7), and mean time to home care usage was 3.7 years (SD 1.6). Death was seen in individuals from all medication classes,

whereas long-term care admission and home care usage was only seen in individuals started on a DPP4i (Table 5). Given the occurrence of long-term care admission and home care usage only in individuals who are receiving DPP4is, models could not be executed. Cox regression models for time to death were executed with each medication individually and combined, and with age and eCMI as controls. Changes in eALMI was not included in regression modelling due to a non-sensical relation with time to death. In these regressions of time to death, only age was consistently associated with increasing risk of death (Table 6).

Subgroup Analyses

Linear and logistic subgroup models were executed respectively for each medication alone, and with controls of age and eCMI (Appendix A, B). In these models, there was no significance between medications and changes in eALMI, or a large decline of ≤ -0.45 kg/m^2 (Appendix A, B).

Discussion

In this study of 82 individuals who received two DXA assessments and began one novel anti-hyperglycemic medication, SGLT2is were found to contribute to changes in eALMI. Specifically, SGLT2is contribute to a -0.31 kg/m^2 to -0.82 kg/m^2 decline in eALMI when controlling for other medication use, age, and eCMI. While GLP-1 RAs and DPP4is were also estimated to decrease eALMI, these results were not significant and thus not interpretable. There was no association with any medication with a significant decline (≤ -0.45 kg/m^2) in eALMI. Finally, there were no associations between medications and all adverse clinical outcomes

including death, new long-term care admission, and new home-care usage. In fact, modelling for long-term care and home-care usage were non-executable given the lack of outcomes in the GLP-1 RA and SGLT2i medication classes.

It is important to note that comparisons of the findings of this study to those of other studies of sarcopenic thresholds defined by skeletal muscle mass differ from appendicular lean mass. EWGSOP2 defines a threshold ALMI or appendicular skeletal mass index (ASMI) indicating sarcopenia to be < 5.5 kg/m^2 in females and < 7.0kg/m^2 in males, compared to SMI measures of < 5.7 kg/m^2 in females and < 8.33 kg/m^2 in males [15]. While we cannot directly compare our results with those of others that use skeletal muscle mass and SMI, they serve as adequate proxies for comparison. Additionally, some previous studies have used bioelectrical impedance analysis (BIA) to obtain lean mass data as opposed to our study using DXA. Fortunately, there is good correlation between BIA and DXA models for ascertaining lean mass data [39,40]. Finally, it is also critical to note that many studies of comparison also report small sample sizes with most including 20 to 141 individuals, with the largest study including 432 individuals.

Our findings that SGLT2is are associated with declines in eALMI are consistent with other findings in the literature. A 24-week study of 20 individuals with T2DM started on ipragliflozin were found to have significant declines in ASMI at the 12- and 24-week benchmarks [41]. Baseline ASMI was reported as 7.8 kg/m^2 ± 1.2, with 12-week ASMI to be 7.5 kg/m^2 ± 1.1 ($p = 0.006$), and 7.6 kg/m^2 ± 1.3 at 24-weeks ($p = 0.023$) [41], representing a -0.2 to -0.3 kg/m^2 change in eALMI over time. ASMI was measured via DXA [41]. Another study of ipragliflozin containing 24 individuals with 16-weeks of data also found ipragliflozin reduced SMI measures

amongst participants [42]. Baseline SMI was reported as 7.5 $kg/m^2 \pm 1.1$, with 8-week and 16-week SMI measures of 7.3 $kg/m^2 \pm 1.2$ ($p < 0.001$, $p < 0.001$) [42], representing a -0.2 kg/m^2 change in eALMI over time. SMI was measured via bioelectrical impedance analysis (BIA) [42]. Finally, a 52-week study of 37 moderately obese patients with T2DM found a non-significant decline in SMI over 24 weeks of Luseogliflozin therapy [43]. However, after 52 weeks, a decline in SMI of -0.155 kg/m^2 (95% CI: -0.287, -0.024) was significant ($p < 0.05$) [43]. DXA was the modality used to assess SMI [43]. It is critical to note that other studies have reported no association between SGLT2is and changes in eALMI. In a 24-week observational study of 31 adult patients with T2DM, individuals started on empagliflozin did not show significant changes in appendicular SMI (ASMI) between baseline and 6-month follow-up [44]. Additionally, there was no significant difference in ASMI between individuals started on a SGLT2i versus those not [44]. ASMI was measured through BIA [44]. Another study of 28 individuals with T2DM started on dapagliflozin compared 22 individuals with T2DM, found non-significant changes in SMI over 6 months ($p = 1.00$) [45]. Further, individuals started on dapagliflozin noted no significant declines in SMI over 6 months ($p = 0.30$) [45]. SMI was assessed via BIA [45]. When comparing the effects of SGLT2is with DPP4is, a study comparing ipragliflozin and sitagliptin in 101 patients with T2DM over 12 weeks, SMI was noted in the ipragliflozin group [46]. Specifically, in the ipragliflozin group ($n = 52$), patients lost an average of -0.10 kg/m^2 (95% CI: -0.17, -0.02), versus individuals in the sitagliptin group ($n = 49$) who gained SMI of 0.01 kg/m^2 (95% CI: -0.07, 0.09) ($p < 0.05$) [46]. SMI was assessed via BIA [46].

Our findings suggesting non-significant changes in eALMI after starting DPP4is is somewhat congruent with the literature. A retrospective follow-up study of 90 older adults with diabetes

found non-significant changes in SMI when comparing individuals starting a DPP4i (n = 48) compared to individuals not (n = 42), and within both study arms over 6 months of follow-up [47]. Despite these results being non-significant, DPP4is were noted to increase skeletal muscle mass index over six months at an average of 0.07 kg/m^2 [47]. SMI data were obtained via BIA [47]. However, most studies report an association between increasing eALMI with starting a DPP4i. In a retrospective observational study of 105 patients with T2DM, those started on a DPP4i (n = 37) were found to have greater skeletal mass compared to those not started on a DPP4i [29]. Specifically, individuals started on a DPP4i had an increase of skeletal mass of 0.05 kg ± 0.06, whereas individuals not started on a DPP4i were noted to have decreased skeletal muscle of -0.10 kg ± 0.04 (p = 0.046) after one year of observation [29]. This study used DXA to assess skeletal muscle mass index, and findings were confirmed with propensity matching [29]. Propensity matching also found an increase in skeletal muscle when started on a DPP4i, and a decrease when not started (p = 0.033) [29]. A 24-month trial of 80 older adults with diabetes reported higher SMI values after starting a DPP4i compared to sulfonylureas [30]. Individuals on a DPP4i (n = 37) were found to have an average SMI of 9.0 kg/m^2 ± 1.6 compared to 7.6 kg/m^2 ± 1.5 from individuals (n = 43) on sulfonylureas (p = 0.001) [30]. SMI was assessed by BIA [30].

As previously mentioned, the literature on the effects of new GLP-1 RA use is heterogenous. Our findings of non-significant changes in eALMI after starting a GLP-1 RA align with one study of 25 patients with T2DM [48]. Over 24-weeks, oral semaglutide was assessed for changes in body composition, and no changes in ASMI were noted over 24 weeks [48]. ASMI, measured via BIA, remained at 8.1 kg/m^2 ± at baseline, 12 weeks, and 24 weeks [48]. A retrospective study of lixisenatide plus basal insulin versus basal insulin alone found ASMI improved in the

lixisenatide study arm [49]. This study included 20 individuals, with 10 in each study arm [49]. In the group with lixisenatide, the change in ASMI was 0.78 kg ± 0.7 kg, compared to those receiving only basal insulin with 0.09 kg ± 0.8 (p = 0.013) [49]. Appendicular skeletal muscle mass was determined via BIA [49]. However, other studies have noted worsening of lean mass measures on starting a GLP-1 RA. A crossover study of 20 individuals with obesity found that limb lean mass was reduced after liraglutide treatment in comparison with placebo after 35 days of treatment [50]. Specifically, limb lean mass after the liraglutide treatment was reported as 25.6 kg ± 4.1, compared to placebo of 26.3 kg ± 4.2 (p = 0.002) [50]. Lean mass data were collected via DXA [50]. Additionally, a large retrospective cohort study of 432 individuals with T2DM, 220 treated with semaglutide and 212 controls, found reduced ASMI in the semaglutide arm compared with controls in both males and females [51]. At the end of study, females on semaglutide were noted to have an ASMI of 6.0 kg/m^2 ± 0.8, versus control ASMI of 6.35 ± 0.74 (p = 0.003) [51]. Similarly, males on semaglutide were reported to have an ASMI of 7.0 kg/m^2 ± 0.9 compared to control males with ASMI of 7.4 kg/m^2 ± 0.7 (p = 0.001) [51]. At baseline, ASMI values for males and females in both arms of the study were not significantly different [51]. ASMI data was obtained through DXA [51].

The association between antihyperglycemic medications with changes in skeletal or lean mass has also been studied through comparisons of DPP4is with GLP-1 RAs. A study of 21 insulin-using patients with T2DM on hemodialysis found that those who started dulaglutide (n = 11) had decreased skeletal mass compared to those in the teneligliptin group (n = 10) over 6 months [52]. Individuals who started teneligliptin had a change in SMI of 0.06 kg/m2 (95% CI: -0.02, 0.39, *p = 0.12*) [52]. Conversely, individuals using dulaglutide had a change in SMI of -0.20 kg/m2

(95% CI: -0.37, -0.03; $p < 0.01$) [52]. The comparison of the changes in SMI between the teneligliptin and semaglutide groups was also significant ($p < 0.01$) [52]. BIA was used to ascertain SMI data [52]. A study of 141 older men compared the effects of semaglutide versus sitagliptin in 68 and 73 individuals respectively at 6-month and 1-year intervals [53]. At baseline, the semaglutide population had a ASMI of 7.3 kg/m2 ± 1.2, with a significant change in ASMI to 6.8 kg/m^2 ± 0.9 at 1-year follow up ($p < 0.05$) [53]. Change from baseline to the 6-month follow-up was not significant [53]. In comparison, the sitagliptin group had a baseline ASMI of 7.0 kg/m^2 ± 1.1, and a 1-year follow-up ASMI of 6.9 kg/m^2 ± 0.9 ($p > 0.05$) [53]. ASMI data were obtained through DXA [53]. To the best of our knowledge, there has been no comparison of SMI, ASMI, or ALMI measures between individuals starting a SGLT2i vs a GLP-1 RA. However, studies reporting lean mass changes vary, with proportionate changes in lean mass ranging between 20% to 50% of weight loss in both GLP-1 RA and SGLT2i groups [54].

The findings of the current study are mixed in its alignment with the literature on the impact of these medications to death [55]. In 98 studies of over 60,000 individuals, GLP-1 RAs reduced all-cause mortality by 12% (HR: 0.88; 95% CI: 0.82, 0.94) [56]. For SGLT2is, three trials of over 34,000 individuals found that SGLT2is reduced cardiovascular death 23% (HR: 0.77; 95% CI: 0.71, 0.84) [57]. However, our findings suggest no reduced risk associated with onset of GLP-1 RAs or SGLT2is. Conversely, our findings did align with previous research on the effects of DPP4is on risk of death. Of three trials and over 36,000 individuals, studies have shown that DPP4i use did not affect all-cause mortality (HR: 1.03; 95% CI: 0.95, 1.11) when compared with placebo [58]. To the best of our knowledge, no data are available regarding the association of GLP1-RAs, DPP4is, or SGLT2is with long-term care admissions and home care use.

This current study contributes to the literature with its novel findings and associated implications. This is the first known study to directly compare the change in appendicular mass between SGLT2is and GLP-1 RAs, thereby filling a gap in the literature. Many studies report significant declines in lean or muscle mass when starting SGLT2is and stronger GLP-1 RAs like semaglutide individually [26–28,33–36]. While our study did not capture any individuals who were started on higher-strength GLP-1 RAs like semaglutide or tirzepatide, our study does suggest that SGLT2is have a greater association with declining eALMI compared to GLP-1 RAs. This insight provides important clinical context that may inform prescribers' decision-making of new anti-glycemic medications for patients at risk of declining lean or muscle mass and sarcopenia in the context of the comorbid conditions of the patient. While semaglutide has proven to be extremely effective at weight loss [31], patients who are sarcopenic or at risk of lean or muscle loss may better benefit from using an older and weaker GLP-1 RA agent such as dulaglutide or liraglutide to support weight loss and reduce loss of muscle or lean mass.

There are strengths to this study. First, this project used a longitudinal population-based cohort that reflects individuals at the greatest risk of declining lean or muscle mass or developing sarcopenia. This cohort enables greater generalizability to populations that use DXA screening for frailty assessment and may be especially generalizable to populations with similar DXA screening guidelines. Second, this study compares the associations with changes in eALMI between three medications, which to the best of our knowledge, is the first study to do so. Including three new antihyperglycemic medications allows us to include more individuals in our study population, and facilitated understanding of the impacts of these medications when used in

combination (i.e., SGLT2i with DPP4i) on changes in eALMI over time. Finally, this study continues to validate the previously developed eALMI algorithm [37] and contributes to efforts to highlight the accuracy and utility of predictive models for estimating ALMI and associated measures from regional DXA assessments.

This study also has its limitations. First, this study did not include other measures to diagnose sarcopenia, including muscle strength (i.e., grip strength) and muscle function/performance (i.e., gait speed). Many definitions of sarcopenia require an ALMI measure in conjunction with either or both muscle strength and/or performance to make a diagnosis [13–19]. Inclusion of these measures would have allowed for a more comprehensive understanding of the changes in muscle due to anti-hyperglycemic medications and would have facilitated classifying individuals on whether they met the criteria for a sarcopenia diagnosis. Still, the ALMI data presented in this current study supports clinical decision making, such that if individuals show reduced ALMI in follow-up DXA scanning, they should be flagged for further sarcopenia diagnosis investigations.

Second, while this study is generalizable to populations that use DXA screening for frailty assessment, there is reduced generalizability to males as DXA screening programs often centre on osteoporosis [24,25]. As males are at a lower risk of osteoporosis, they are not included in DXA screening programs based on age and instead will receive DXA assessments should they have fragility fractures or long-term use of high-risk medications like glucocorticoids [24,25]. However, males are also at lower risk of developing sarcopenia and having low lean or muscle mass, and the results centring on females better consider those who are at greater risk of developing sarcopenia.

Finally, the main limitation of this study is the small study cohort. As the data from the BMD database extends only until June 2020, before the increased interest and use of GLP-1 RA agents, the ability to assess the effects of these medications relative to SLGT2is and DPP4is is extremely limited. Once additional data inclusive of 2024 becomes available, the ability to assess these relationships will be greatly improved.

Conclusion

SGLT2is contribute to progression of declines in eALMI. Further research should be conducted which investigates the relationship between GLP-1 RAs and changes in eALMI.

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Tables

Table 1. Descriptive characteristics of the study cohort.

Variable	Overall N = 82	DPP4is n = 54	SGLT2i n = 38	GLP-1 RA n = 6
Age (years)	64.4 ± 8.7	64.3 ± 9.7	64.6 ± 6.2	58.6 ± 12.7
Female Sex (%)	79 (96%)	51 (94%)	38 (100%)	Suppressed
eCMI (kg/m^2)	24.3 ± 5.4	23.8 ± 6.1	25.1 ± 4.5	26.3 ± 4.0
Baseline Comorbid Conditions (%)				
Diabetes	80 (98%)	54 (100%)	38 (100%)	Suppressed
CKD	24 (29%)	18 (33%)	10 (26%)	Suppressed
Hypertension	77 (94%)	51 (94%)	36 (95%)	6 (100%)
COPD	Suppressed	Suppressed	Suppressed	Suppressed
CAD	29 (35%)	20 (37%)	11 (29%)	Suppressed
Stroke	Suppressed	Suppressed	Suppressed	Suppressed
CHF	Suppressed	Suppressed	Suppressed	Suppressed
Osteoporosis and Fractures	47 (57%)	30 (56%)	22 (58%)	Suppressed
Arthritis	10 (12%)	7 (13%)	Suppressed	Suppressed
Baseline Pharmaceutical Use (%)				
Statins	46 (56%)	29 (54%)	22 (58%)	Suppressed
Tricyclic Antidepressants	Suppressed	Suppressed	Suppressed	Suppressed
Diuretics	21 (26%)	13 (24%)	10 (26%)	Suppressed
Calcium	Suppressed	Suppressed	Suppressed	Suppressed
Vitamin D	Suppressed	Suppressed	Suppressed	Suppressed
Bisphosphonates	8 (10%)	Suppressed	Suppressed	Suppressed
Smoking History	9 (11%)	7 (13%)	Suppressed	Suppressed
eALMI Measures				
Index eALMI (kg/m^2)	7.4 ± 1.2	7.3 ± 1.4	7.5 ± 1.0	8.2 ± 1.5
Outcome eALMI (kg/m^2)	7.3 ± 1.3	7.2 ± 1.4	7.3 ± 1.1	8.0 ± 1.5
-0.45 kg/m^2 Decline in eALMI (%)	20 (24%)	11 (20%)	13 (34%)	2 (33%)
Change in eALMI (kg/m^2)	-0.13 ± 0.47	-0.13 ± 0.41	-0.21 ± 0.53	-0.15 ± 0.45
Years Between eALMI Assessments	3.5 ± 0.8	3.4 ± 0.8	3.5 ± 0.8	4.1 ± 0.5

*****per EWGSOP2 ALMI thresholds for sarcopenia.
Cells are suppressed if < 6 observations are available.

Table 2. Power analyses of change in eALMI for the study cohort.

Drug	Mean Diff (yes-no)	SD pooled	Cohen's D	95% CI of Mean Diff	Interpretation
DPP4i	0.00	0.47	0	-0.24, 0.24	No effect
SGLT2i	-0.16	0.47	-0.34	-0.37, 0.05	Moderate
GLP-1 RA	-0.02	0.47	-0.04	-0.40, 0.36	Very Small

Table 3. Linear models of change in eALMI between DXA assessments.

Variable	**Model** Estimate (95% CI) *p value*			
	1	**2**	**3**	**4**
GLP-1 RA	-0.20 (-0.63, 0.23) *0.37*	-0.44 (-0.98, 0.11) *0.11*	-0.23 (-0.68, 0.22) *0.31*	-0.47 (-1.03, 0.09) *0.10*
SGLT2i	-0.31 (-0.59, -0.04) *0.03*	-0.82 (-1.57, -0.07) *0.03*	-0.32 (-0.60, -0.04) *0.03*	-0.82 (-1.59, -0.06) *0.03*
DPP4i	-0.24 (-0.54, 0.07) *0.12*	-0.74 (-1.51, 0.02) *0.06*	-0.25 (-0.55, 0.06) *0.12*	-0.75 (-1.52, 0.02) *0.06*
SGLT2i × DPP4i		0.58 (-0.22, 1.37) *0.16*		0.57 (-0.23, 1.38) *0.16*
Age			-0.01 (-0.02, 0.01) *0.50*	-0.01 (-0.02, 0.01) *0.52*
eCMI			0.01 (-0.02, 0.02) *0.88*	0.01 (-0.02, 0.01) *0.82*
Intercept	0.19 (-0.14, 0.52) *0.27*	0.68 (-0.08, 1.44) *0.08*	0.43 (-0.61, 1.47) *0.41*	0.89 (-0.33, 2.11) *0.15*
Model	*0.17*	*0.13*	*0.36*	*0.28*

Table 4. Logistic models of risk of large eALMI decline between DXA assessments.

Variable	Model Odds Ratio (95% CI) *p value*			
	1	**2**	**3**	**4**
GLP-1 RA	2.18 (0.29, 16.37) *0.44*	5.76 (0.46, 72.49) *0.18*	2.19 (0.28, 17.45) *0.46*	5.67 (0.41, 77.64) *0.19*
SGLT2i	3.22 (0.85, 12.25) *0.09*	2.30 (0.55, 9.73) *0.95*	3.13 (0.81, 12.00) *0.10*	2.26 (0.53, 9.62) *0.95*
DPP4i	1.23 (0.31, 4.83) *0.77*	0.91 (0.21, 3.93) *0.95*	1.27 (0.32, 5.04) *0.74*	0.95 (0.22, 4.12) *0.95*
SGLT2i × DPP4i		-- *0.95*		-- *0.95*
Age			1.01 (0.95, 1,08) *0.72*	1.01 (0.95, 1.08) *0.74*
eCMI			1.04 (0.94, 1.14) *0.45*	1.04 (0.94, 1.14) *0.49*
Intercept	*0.02*	*0.94*	*0.44*	*0.94*
AUC	0.63	0.64	0.64	0.66

Table 5. Frequency of adverse clinical outcomes.

Medication	Death n = 19	Long Term Care or Home Care n = 8
GLP-1 RA (n = 6)	1	0
SGLT2i (n = 38)	6	0
DPP4i (n = 54)	16	8

Table 6. Cox proportional hazards model of time to death.

Variable	**Model** Hazard Ratio (95% CI) *p value*			
	GLP-1 RA	**SGLT2i**	**DPP4i**	**All Medications**
GLP-1 RA	0.66 (0.09, 5.03) *0.69*			1.88 (0.17, 21.43) *0.61*
SGLT2i		0.82 (0.29, 2.31) *0.71*		1.68 (0.48, 5.89) *0.41*
DPP4i			2.37 (0.68, 8.24) *0.18*	3.87 (0.70, 21.41) *0.12*
Age	1.07 (1.00, 1.15) *0.04*	1.07 (1.00, 1.15) *0.04*	1.07 (1.01, 1.15) *0.03*	1.08 (1.01, 1.16) *0.03*
CMI	1.03 (0.95, 1.12) *0.42*	1.04 (0.96, 1.12) *0.40*	1.04 (0.96, 1.12) *0.32*	1.04 (0.96, 1.12) *0.37*
Fit	0.65	0.64	0.67	0.68

Appendices

Appendix A. Linear subgroup analyses by medication for change in eALMI.

Variable	Model Estimate (95% CI) *p value*					
	GLP-1 RA		**SGLT2i**		**DPP4i**	
GLP1-RA	-0.03 (-0.43, 0.37) *0.89*	-0.05 (-0.46, 0.36) *0.81*				
SGLT2i			-0.17 (-0.37, 0.04) *0.11*	-0.17 (-0.38, 0.04) *0.12*		
DPP4i					-0.01 (-0.22, 0.22) *0.99*	-0.01 (-0.23, 0.22) *0.98*
Age		-0.01 (-0.02, 0.01) *0.55*		-0.01 (-0.02, 0.01) *0.62*		-0.01 (-0.02, 0.01) *0.57*
eCMI		-0.01 (-0.02, 0.01) *0.96*		0.01 (-0.02, 0.02) *0.88*		-0.01 (-0.02, 0.02) *0.94*
Intercept	-0.13 (-0.23, -0.19) *0.02*	0.12 (-0.86, 1.12) *0.80*	0.05 (-0.19, 0.09) *0.46*	0.10 (-0.86, 1.07) *0.83*	-0.13 (-0.31, 0.05) *0.16*	0.12 (-0.89, 1.12) *0.82*
Model	*0.89*	*0.94*	*0.11*	*0.42*	*0.99*	*0.96*

Appendix B. Logistic subgroup analyses by medication for change in eALMI.

Variable	Model Odds Ratio (95% CI) *p value*					
	GLP-1 RA		**SGLT2i**		**DPP4i**	
GLP1-RA	1.61 (0.27, 9.54) *0.60*	1.59 (0.26, 9.90) *0.62*				
SGLT2i			2.75 (0.96, 7.85) *0.06*	2.62 (0.91, 7.54) *0.07*		
DPP4i					0.54 (0.19, 1.52) *0.24*	0.57 (0.20, 1.61) *0.29*
Age		1.01 (0.95, 1.08) *0.70*		1.01 (0.94, 1.08) *0.82*		1.01 (0.95, 1.07) *0.79*
eCMI		1.05 (0.95, 1.15) *0.33*		1.04 (0.95, 1.15) *0.42*		1.04 (0.95, 1.15) *0.37*
Intercept	-- *<0.001*	-- *0.21*	-- *<0.001*	-- *0.24*	-- *0.06*	-- *0.35*
AUC	0.52	0.59	0.62	0.66	0.57	0.62

Appendix C. MCHP Definitions and ICD-9-CM and ICD-10-CA Codes of Comorbidity Covariates

Covariate	Definition
Diabetes	one or more hospitalizations with a diagnosis of diabetes OR two or more physician visits with a diagnosis of diabetes OR one or more prescriptions for medications to treat diabetes ICD-9: 250.0-250.4, 250.6, 250.7 ICD-10: E10-E14
Chronic Kidney Disease (CKD)	one or more hospitalizations with a diagnosis of chronic kidney disease OR two or more physician visits with a diagnosis of chronic kidney disease OR one or more prescriptions for medications to treat chronic kidney disease ICD-9: 250.4, 403, 404, 580-583, 585-588, 591, 593.9, 753 ICD-10: E10.2, E11.2, I12, I13, N00-16, N18, N19, N25, N26, N28.82, N39.1, Q60-64
Hypertension	one or more hospitalizations with a diagnosis of hypertension OR two or more physician visits with a diagnosis of hypertension OR one or more prescriptions for medications to treat hypertension ICD-9: 401-405 ICD-10: I10-I13, I15
Chronic Obstructive Pulmonary Disease (COPD)	one or more hospitalizations with a diagnosis of chronic obstructive pulmonary disease OR one or more physician visits with a diagnosis of chronic obstructive pulmonary disease ICD-9: 490-493 496 ICD-10: J40-J45
Coronary Artery Disease (CAD)	one or more hospitalizations with a diagnosis of coronary artery disease/ischemic heart disease OR two or more physician visits with a diagnosis of coronary artery disease/ischemic heart disease OR one or more prescriptions for medications to treat coronary artery disease/ischemic heart disease ICD-9: 410-414 ICD-10: I20-I22, I24, I25
Stroke	one or more hospitalizations with a diagnosis of stroke/cerebrovascular disease OR two or more physician visits with a diagnosis of stroke/cerebrovascular disease ICD-9: 430-438 ICD-10: I60-I69

Congestive Heart Failure (CHF)	one or more hospitalizations with a diagnosis of congestive heart failure OR two or more physician visits with a diagnosis of congestive heart failure ICD-9: 428 ICD-10: I50
Osteoporosis and Osteoporotic Fractures	one or more hospitalizations with a diagnosis of osteoporosis/osteoporotic fracture OR one or more physician visits with a diagnosis of osteoporosis/osteoporotic fracture OR one or more prescriptions for medications to treat osteoporosis ICD-9: 733, 805, 812-814, 820, 821 ICD-10: M81, S12.0-S12.2, S12.7, S12.9, S22.0, S22.1, S32.0-S32.2, S42.2-S42.4, S52, S62.0. S62.1, S72, T08
Arthritis	one or more hospitalizations with a diagnosis of arthritis OR one or more physician visits with a diagnosis of arthritis ICD-9: 274, 446, 710-721, 725-729, 739 ICD-10: M01-M03, M05-M07, M10-M25, M30-M36, M65-M79

Appendix D. Anatomical Therapeutic Chemical **(**ATC Codes) for Covariates and Prescription Medication Use

Medications Included	**Drug Name**	**ATC Codes or Prefixes**
Glucagon-like peptide-1 receptor agonists (GLP-1 RAs)	Exenatide, Liraglutide, Lixisenatide, Albiglutide, Dulaglutide, Semaglutide, Beinaglutide, Tirzepatide	A10BJ A10BX16
Sodium-glucose co-transporter 2 inhibitors (SGLT2is)	Dapagliflozin, Canagliflozin, Empagliflozin, Ertugliflozin, Ipragliflozin, Sotagliflozin, Luseogliflozin	A10BK A10BD15 A10BD16 A10BD20
Dipeptidyl peptidase-4 inhibitors (DPP4is)	Sitagliptin, Vildagliptin, Saxagliptin, Alogliptin, Linagliptin, Gemigliptin, Evogliptin, Teneligliptin, Gliptin + Statin	A10BH
Statins	Simvastatin, Lovastatin, Pravastatin, Fluvastatin, Atorvastatin, Cerivastatin, Rosuvastatin, Pitavastatin, Statins + Others	C10AA C10B
Tricyclic Antidepressants	Desipramine, Imipramine, Imipramine Oxide, Clomipramine, Opipramol, Lofepramine, Dibenzepin, Amytriptyline, Nortriptyline, Protriptyline, Doxepin, Iprindole, Melitracen, Butriptyline, Dosulepin, Amoxapine, Dimetacrine, Amineptine, Maprotiline, Quinupramine	N06AA
Diuretics	Bendroflumethiazide, Hydroflumethiazide, Hydrochlorothiazide, Chlorothiazide, Polythiazide, Trichlormethiazide, Cyclopenthiazide, Methyclothiazide, Cyclothiazide, Metbutizide, Quinethazone, Clopamide, Chlortalidone, Mefruside, Clofenamide, Metolazone, Meticrane, Xipamide, Indapamide, Clorexolone, Fenquizone, Mersalyl, Theobromine, Cicletanine, Fursoemide, Bumetanide, Pretanide, Torasemide, Etacrynic Acid, Tienilic Acid, Muzolimine, Spironolactone, Potassium Canrenoate, Canrenone, Eplerenone, Finerenone, Amiloride, Triamterene, Tolvaptan, Conivaptan, Combinations	C03

Calcium	Calcium Phosphate, Calcium Glubionate, Calcium Gluconate, Calcium Carbonate, Calcium Lactate, Calcium Lactate Gluconate, Calcium Chloride, Calcium Glycerylphosphate, Calcium Citrate Lysine Complex, Calcium Pangamate, Calcium Citrate, Calcium Laevulate, Calcium + Others	A12AA
Vitamin D	Ergocalciferol, Dihydrotachysterol, Alfacalcidol, Calcitriol, Colecalciferol, Calcifediol, Colecalciferol + Others	A11CC
Bisphosphonates	Etidronic Acid, Clodronic Acid, Pamidronic Acid, Alendronic Acid, Tiludronic Acid, Ibandronic Acid, Risedronic Acid, Zoledronic Acid	M05BA