Myopathy Associated With Statins and SGLT2 – A Review of Literature

Rahul Gupta, MD, Ryan Alcantara, BS, Tarun Popli, MD, Sugandhi Mahajan, MD, Umair Tariq, MD, Raman S. Dusaj, MD FACC, and Aaqib H. Malik, MD

Abstract: Drug-induced myopathy is a well-described clinical entity characterized by muscle damage leading to symptoms ranging from myalgias to rhabdomyolysis and acute kidney injury. Many pharmacotherapies are known to precipitate myopathic symptoms. Recent case reports suggest a potential relationship between the use of sodium/glucose cotransport 2 (SGLT2) inhibitors and onset of myopathy. The pathogenesis of this has yet to be elucidated. The relevance of this association is augmented by the recent popularity of SGLT2 inhibitors as well as the tendency for them to be prescribed alongside statins. This study reviewed the literature on the incidence and mechanism of drug-induced myopathy in patients with type 2 diabetes mellitus who are taking SGLT2 inhibitors with and without the use of statins. (Curr Probl Cardiol 2021;46:100765.)

Drug Induced Myopathy

The spectrum of drug-induced myopathy can range from mild muscle pain without weakness to full-blown rhabdomyolysis leading to acute kidney injury.[1,2] Various mechanisms have been implicated in drug-induced myopathies.[3,4] The most common mechanism is direct muscle damage either by vacuolar or mitochondrial injury. Statins have extensive data to support this direct muscle damage leading

Disclosures: The authors have no conflicts of interest to disclose.
Curr Probl Cardiol 2021;46:100765
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2020.100765

to myopathy along with glucocorticoids, zidovudine, and colchicine just to name a few. Other mechanisms include immune-mediated inflammatory damage for which D-Penicillamine is a classic example. Lastly, indirect muscle damage caused by drugs due to secondary effects from their action can occur, such as for diuretics by causing electrolyte abnormalities and for phenothiazines leading to dystonic state, hyperthermia, and neuroleptic malignant syndrome.

Statin-Associated-Muscle-Symptoms and Muscle Injury

Statins, which are primarily used as lipid-lowering agents for coronary artery disease and hyperlipidemias, are generally considered safe. Clinicians and researchers need to understand the spectrum of Statin-Associated-Muscle-Symptoms (SAMS) and muscle injury as statins are extensively used in clinical practice (Table 1).[5] Common presentations include myalgias that can be multifactorial and are usually not associated with weakness or elevated creatine kinase (CK). The next in order of severity on the spectrum is myopathy, which causes muscle weakness that may or may not cause elevated CK, however, is associated with positive histopathological findings of inflammation and atrophy. Myositis is next, which on histopathology would reveal macrophages along with T and B cell infiltration into the affected muscle. Myonecrosis leads to CK elevations (3-fold for mild, 10-fold for moderate, and 50-fold for severe)

TABLE 1. Statin associated muscle symptoms

Spectrum	Clinical features	Histopathological findings
1) Myalgia	• Muscle discomfort with normal CK Levels. • Aches and soreness. • Tenderness and cramps.	None.
2) Myopathy	• Weakness in the affected muscle. • CK may or may not be elevated.	Inflammation and atrophy may be seen.
3) Myositis	• Pain and tenderness. • Redness and swelling. • Elevated temperature.	Macrophages and inflammatory T and B cells may be seen.
4) Myonecrosis	• Elevated CK levels. • Mild: >3 times of Upper limit of normal (ULN). • Moderate: >10 times ULN. • Severe >50 times ULN.	Inflammatory T and B cells along with macrophages usually seen.
5) Rhabdomyolysis	• Features of myonecrosis and elevation of serum creatinine ≥0.5 mg/dL from baseline.	Severe inflammation and dead tissue.

and histopathological findings similar to myositis, which is followed by the most severe injury of rhabdomyolysis (that includes myoglobinuria and serum creatinine increase >0.5 from baseline). Rhabdomyolysis and severe myonecrosis are rare in statin users, about 0.1%.[6]

The precise mechanism by which statin causes SAMS and muscle injury is poorly understood; however, much progress has been made to understand the pathogenesis, including genetic studies,[5,7] which are discussed below.

Various genes such as CYP2D6, CYP3A4, CYP3A5 causing variation of cytochrome P450 expression and vitamin D receptor, have been implicated in SAMS. The mechanism of action, transport, and metabolism of statins are impacted by these genes (Table 2). The SLCO1B1 rs4149056 gene variants affect the uptake of statins in the liver. Due to the loss of function variant rs4149056, some statins particularly simvastatin, more than atorvastatin achieve higher than usual levels in the plasma and at the level of muscle causing SAMS. Another mechanism of SAMS includes autoimmune myopathy caused by autoantibodies developed against hydroxymethylglutaryl-CoA reductase, leading to full spectrum of SAMS from myalgias to severe myonecrosis.

Another aspect of statins is their effect on synthesizing an important muscle cell energy production enzyme called Coenzyme Q10, also called ubiquinone or CoQ10. Prior studies have produced mixed results on whether statin reduced the levels of CoQ10 in plasma and at the level of

TABLE 2. Mechanism of statins inducing SAMS

Pathways	Actions
1) Gene studies: • Cytochrome P450 genes, CYP3A4, CYP3A5, CYP2D6 and vitamin D receptor Gene	• Affects statin transport, metabolism and its action
2) GENOME WIDE STUDIES: • SLCO1B1 • rs 4149056	• SLCO1B1 affects hepatic uptake of statins. • rs 4149056 associated with higher plasma levels of statins
3) Human leucocyte antigen pathway	• Autoimmune myopathy resulting from autoantibodies to HMG-CoA-reductase
4) Coenzyme Q10 (ubiquinone) pathway	• Reduction in ubiquinone(CoQ10) levels in skeletal muscle and possibly plasma
5) Fatty acid oxidation pathway	• Increase fatty acid oxidation by lovastatin • Statins causing increased expression of mitochondrial carnitine acylcarnitine translocase leading to altered FAO
6) Atrogin-1 (Ubiquitin protein ligase) pathway	• Statins causing increased expression of Atrogin-1 (needs further evidence)

skeletal muscles. Some studies suggested decreased levels of ubiquinone in plasma whereas one prior study suggested otherwise.[8-11] Coq10 (Ubiquinone) levels in skeletal muscles also have mixed results from various studies, while one study did indicated reduced levels in both plasma and the skeletal muscles.[12,13]

Other mechanisms include the implication of intrinsic fatty acid oxidation (FAO) abnormality suggested by increased FAO response to lovastatin demonstrated by some statin intolerant patients along with mitochondrial carnitine acylcarnitine translocase increased expression by statins contributing to altered FAO.[14,15] Another study found increased expression of muscle-specific enzyme atrogin-1 (ubiquitin-protein ligase) in several in vitro models of humans with statin myopathy and suggesting another pathway contributing to SAMS but needs further evidence for confirmation.[16]

Diabetes, SGLT2 Inhibitors, and Muscle Disease

Sodium/glucose co-transporter 2 (SGLT2) inhibitors are a class of oral agents used to treat diabetes mellitus. The mechanism of action involves the inhibition of glucose reabsorption in the proximal convoluted tubule of the kidneys, the site of approximately 90% of filtered glucose reabsorption.[17,18] The resulting glucosuria produces an insulin-independent reduction in serum glucose concentrations. Furthermore, their use in type 2 diabetes mellitus (T2DM) has been associated with favorable decreases in blood pressure and weight, and baseline HbA1c level.[19,20]

In recent years, their utility has extended beyond glycemic control in T2DM due to clinical trials elucidating their unforeseen benefits across various disciplines. Their use in patients with heart failure with reduced ejection fracture (HFrEF) with or without T2DM has been associated with a significant reduction in cardiovascular mortality, hospitalizations for worsening heart failure, and major adverse cardiovascular events.[21-25] Their use has also demonstrated protective effects in diabetic nephropathy, including delaying renal dysfunction, reducing the risk of end-stage renal disease, and reducing renal-associated mortality.[21,26] Based on these findings, SGLT2 inhibitors are emphasized as a second-line pharmacotherapy in patients with T2DM and established atherosclerotic heart disease, heart failure, or chronic kidney disease.[27] They are currently being studied for their observed efficacy in nondiabetic kidney disease, type 1 diabetes mellitus, nonalcoholic steatohepatitis, diseases associated with hyponatremia, obesity, and polycystic ovarian syndrome.[21,28-37]

While SGLT2 inhibitors have emerged as a therapeutic wonder in recent years, some severe adverse reactions have been documented with their use. Their glucosuric properties have consistently been associated with an increased risk of urogenital infections, volume-depletion, and acute kidney injury. The poorly elucidated systemic role of SGLT2 has also given rise to unforeseen adverse effects such as euglycemic diabetic ketoacidosis, skin and subcutaneous tissue infections including Fournier's gangrene, bone fractures, and lower limb amputations.[21,26,38-41]

Recently, limited data have emerged suggesting a potential association between chronic SGLT2 inhibitor usage and accelerated sarcopenia. Sarcopenia is the generalized loss of skeletal muscle mass and function that is commonly seen with advanced age. Its presence is associated with adverse health outcomes, including physical disability, poor quality of life, and mortality. While not directly measurable, assessments of muscle mass, grip strength, and gait speed are commonly used as surrogates to diagnose and quantify sarcopenia.[42] The pathophysiology of sarcopenia is believed to involve the molecular interplay mediating skeletal muscle catabolism and anabolism favoring that of protein degradation and skeletal muscle loss.[42,43] While it is commonly considered an age-associated condition, many factors have been identified to increase the risk of developing sarcopenia, including genetics, inflammation, nutritional deficiencies, low body mass index, insufficient physical activity, and chronic diseases.[42-44]

Sarcopenia is particularly prevalent in elderly patients with T2DM. Studies have reported a 3-fold higher risk of sarcopenia in patients with T2DM compared to those without T2DM.[42,45,46] Within the diabetic population, an independent association between poor glycemic control and sarcopenia has also been established.[47,48] The pathophysiology of this is multifactorial and involves impaired intramuscular glucose metabolism secondary to insulin-resistance. The inability to respond to insulin results in impaired muscle function due to decreased glucose uptake and utilization. On a molecular level, the lack of insulin and insulin-like growth factor 1 produces downregulation of the Akt-mTOR pathway largely responsible for protein synthesis and muscle anabolism. Furthermore, the accumulation of cytokines released by chronic inflammation and advanced glycation end-products enhance muscle catabolism, lipolysis, and nitrogen wasting.[49,50]

There is some evidence accumulating that SGLT2 inhibitors may induce or accelerate T2DM-associated sarcopenia, possibly due to their insulin-independent euglycemia effect. The resultant decrease in insulin-mediated utilization of glucose and amino acids in muscle and increased

glucagon-mediated proteolysis is thought to precipitate an overall catabolic effect.[51-54] However, other studies have found no association or a protective effect between SGLT2 inhibitor usage and T2DM-associated sarcopenia.[54-59] The results of these findings are summarized in Table 3. Presently, there is inconclusive evidence to determine the effects of SGLT2 inhibitor usage on sarcopenia, and further human studies are needed to explore this association.

A similar disease entity to sarcopenia is drug-induced myopathy, characterized by the acute or subacute onset of myopathic features including myalgias, fatigue, weakness, or myoglobinuria. The presentation may vary in severity, ranging from an asymptomatic CK elevation to rhabdomyolysis and chronic renal failure. Many pharmacotherapeutic agents are known to cause drug-induced myopathy through a variety of mechanisms including direct myotoxicity, the alteration of muscle antigens and subsequent generation of an autoimmune or autoinflammatory response, or by a disruption of the electrolyte or nutritional balance. Early recognition is crucial as the symptoms of drug-induced myopathy classically resolve following discontinuation of the offending agent. However, they may persist in a subset of cases.[60-62]

Until recently, the association between SGLT2 inhibitors and clinical myopathy had not been documented. A 2017 case report by Kabadi et al described weakness, proximal muscle wasting, fatigue, polyuria, nocturia, polydipsia, and an elevated CK that began within 2 weeks after initiation of empagliflozin. Most of the symptoms resolved within 2 weeks of discontinuing the drug, but the patient's strength and muscle mass persisted throughout the entire 12 months follow-up period.[63] The association was not described in the literature again until April 2020, when Gao et al documented a patient with fatigue, myalgias, weakness, muscle wasting, and an elevated CK shortly after beginning treatment with empagliflozin. The patient continued taking the medication for 1 year with the persistence of symptoms. A biochemical workup failed to reveal the etiology of the myopathy, and magnetic resonance imaging demonstrated findings consistent with myositis. Within weeks of discontinuing the drug, the symptoms resolved, and a repeat magnetic resonance imaging showed complete resolution of previous changes.[62]

Most recently, a third case report by Brailovski et al described a case of profound proximal muscle weakness, myalgias, and fatigue with laboratory evidence of rhabdomyolysis 3 days after beginning treatment with canagliflozin. As in previous cases, a biochemical workup failed to reveal an etiology of the myopathy. Of note, the patient had previously been taking rosuvastatin, a known culprit of causing myopathy, for over 5 years without complications. On admission, the patient's plasma levels of

TABLE 3. Summary of studies regarding SGLT2 inhibitor use and sarcopenia

Study	Study type	SGLT2 inhibitor	Findings
Bolinder et al (2013)	Randomized control trial (n = 182)	Dapagliflozin	The use of dapagliflozin over a 102-week period was associated with a reduction in body fat mass but no significant difference in lean tissue mass when compared to placebo.
Yabe et al (2015)	Meta-Analysis	N/A	The decrease in serum insulin and increased glucagon levels caused by SGLT2 inhibitor use may enhance proteinolysis and impair muscle utilization of glucose and amino acids, inducing or accelerating T2DM-associated sarcopenia.
Sano et al (2016)	Observational (n = 112)	Ipragliflozin Luseogliflozin Dapagliflozin	10 weeks of SGLT2 inhibitor treatment was associated with a statistically significant increase in hand grip strength compared to baseline.
Sugizaki et al (2017)	Randomized control trial (n = 100)	TA-1887	Lean body mass did not decrease in diabetic mice given the SGLT2 inhibitor TA-1887 and was protective against cachexia.
Tsurutani et al (2018)	Randomized control trial (n = 124)	Ipragliflozin	After 12 weeks of receiving ipragliflozin versus sitagliptin, ipragliflozin was associated with a statistically significant decrease in skeletal muscle mass index.
Sugiyama et al (2018)	Randomized control trial (n = 50)	Dapagliflozin	Six months of treatment with dapagliflozin significantly reduced body weight and fat mass but did not produce any change in skeletal muscle mass when compared to other antihyperglycemic medications.
Inoue et al (2018)	Randomized control trial (n = 49)	Ipragliflozin	After 24 weeks of receiving ipragliflozin, participants had a statistically significant decrease in muscle mass in the arms when compared to the control group (no treatment). There was no overall difference between total muscle mass.
Inoue et al (2018)	Observational (n = 20)	Canagliflozin	After 12 months of receiving canagliflozin, participants had a significant reduction in body and fat mass, with an insignificant reduction in lean muscle mass.
Yasuda et al (2019)	Case report (n = 1)	Dapagliflozin	An elderly diabetic patient was diagnosed with sarcopenia after 1 year of Dapagliflozin-use.
Schork et al (2019)	Observational (n = 27)	Empagliflozin Dapagliflozin	After 6 months of SGLT2 inhibitor use, participants had a significant reduction in adipose tissue mass without any changes in lean tissue parameters.

rosuvastatin were 176 ng/mL, a more than 15-fold increase in the mean concentration expected in patients taking the same dose.[64] Upon discontinuing both the rosuvastatin and the canagliflozin, the patient experienced a prompt improvement in her symptoms.[65]

While it is possible that the clinical myopathy described with SGLT2 inhibitor usage lies on a spectrum with that of sarcopenia or remains an idiosyncratic phenomenon, one possible mechanism involves the potentiation of statin-induced myotoxicity. Statin use is exceedingly common in the diabetic population, and, of note, the patients described by Kabadi and Gao et al had both been taking atorvastatin for several years without complication. The temporal relationship between the SGLT2 inhibitor usage and symptom onset led investigators to discount the statin use as the etiology, and statin drug levels were not measured in these cases. While neither empagliflozin nor canagliflozin are known to influence metabolism by the hepatic cytochrome P450 system appreciably, they are known substrates for drug transporters involved in statin absorption, distribution, and elimination.[65-67] While further studies are needed to determine the relationship between SGLT2 inhibitors and drug-induced myopathy, it is a crucial entity that everyday clinicians should remain mindful of with increased utilization of these agents.

Author Contributions

Every author listed contributed to our work in a substantial manner. Each author's contribution is as listed. (1) Conception and design: Rahul Gupta, Ryan Alcantara, Tarun Popli; (2) Drafting of the manuscript and revising it critically for important intellectual content: Rahul Gupta, Ryan Alcantara, Sugandhi Mahajan, Umair Tariq, Raman S. Dusaj, Aaqib H. Malik**;**(3) Final approval of the manuscript submitted: Raman S. Dusaj, Aaqib H. Malik.

REFERENCES

1. Prendergast BD, George CF. Drug-induced rhabdomyolysis—mechanisms and management. *Postgrad Med J* 1993;69:333–6.
2. Zuckner J. Drug-related myopathies. *Rheum Dis Clin North Am* 1994;20:1017–32.
3. Sieb JP, Gillessen T. Iatrogenic and toxic myopathies. *Muscle Nerve* 2003;27:142–56.
4. Lane RJ, Mastaglia FL. Drug-induced myopathies in man. *Lancet* 1978;2:562–6.
5. Brunham LR, Baker S, Mammen A, Mancini GBJ, Rosenson RS. Role of genetics in the prediction of statin-associated muscle symptoms and optimization of statin use and adherence. *Cardiovasc Res* 2018;114:1073–81.

6. Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585–90.
7. Mammen AL. Statin-Associated Autoimmune Myopathy. *N Engl J Med* 2016;374:664–9.
8. Banach M, Serban C, Ursoniu S, et al. Statin therapy and plasma coenzyme Q10 concentrations−A systematic review and meta-analysis of placebo-controlled trials. *Pharmacol Res* 2015;99:329–36.
9. Rundek T, Naini A, Sacco R, Coates K, Dimauro S. Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke. *Arch Neurol* 2004;61:889–92.
10. Ghirlanda G, Oradei A, Manto A, et al. Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study. *J Clin Pharmacol* 1993;33:226–9.
11. Bleske BE, Willis RA, Anthony M, et al. The effect of pravastatin and atorvastatin on coenzyme Q10. *Am Heart J* 2001;142:E2.
12. Laaksonen R, Jokelainen K, Laakso J, et al. The effect of simvastatin treatment on natural antioxidants in low-density lipoproteins and high-energy phosphates and ubiquinone in skeletal muscle. *Am J Cardiol* 1996;77:851–4.
13. Lamperti C, Naini AB, Lucchini V, et al. Muscle coenzyme Q10 level in statin-related myopathy. *Arch Neurol* 2005;62:1709–12.
14. Phillips PS, Ciaraldi TP, Kim DL, et al. Myotoxic reactions to lipid-lowering therapy are associated with altered oxidation of fatty acids. *Endocrine* 2009;35:38–46.
15. Iacobazzi V, Convertini P, Infantino V, Scarcia P, Todisco S, Palmieri F. Statins, fibrates and retinoic acid upregulate mitochondrial acylcarnitine carrier gene expression. *Biochem Biophys Res Commun* 2009;388:643–7.
16. Hanai J, Cao P, Tanksale P, et al. The muscle-specific ubiquitin ligase atrogin-1/MAFbx mediates statin-induced muscle toxicity. *J Clin Invest* 2007;117:3940–51.
17. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes* 2017;24:73–9.
18. Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. *Drugs* 2015;75:33–59.
19. Fitchett D, Inzucchi SE, Cannon CP, et al. Empagliflozin Reduced Mortality and Hospitalization for Heart Failure Across the Spectrum of Cardiovascular Risk in the EMPA-REG OUTCOME Trial. *Circulation* 2019;139:1384–95.
20. Inzucchi SE, Kosiborod M, Fitchett D, et al. Improvement in Cardiovascular Outcomes With Empagliflozin Is Independent of Glycemic Control. *Circulation* 2018;138:1904–7.
21. Kalra S, Shetty KK, Nagarajan VB, Ved JK. Basic and clinical pharmaco-therapeutics of SGLT2 inhibitors: a contemporary update. *Diabetes Ther* 2020;11:813–33.
22. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* 2020. https://doi.org/10.1056/NEJMoa2022190.

23. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* 2020. https://doi.org/10.1016/S0140-6736(20)31824-9.
24. Mcmurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;381:1995–2008.
25. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117–28.
26. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;380:2295–306.
27. Summary of Revisions: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020;43(Suppl 1):S4–6.
28. Herrington WG, Preiss D, Haynes R, et al. The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study. *Clin Kidney J* 2018;11:749–61.
29. Scheen AJ. Beneficial effects of SGLT2 inhibitors on fatty liver in type 2 diabetes: a common comorbidity associated with severe complications. *Diabetes Metab* 2019;45:213–23.
30. Kuchay MS, Krishan S, Mishra SK, et al. Effect of empagliflozin on liver fat in patients with type 2 diabetes and nonalcoholic fatty liver disease: a randomized controlled trial (E-LIFT Trial). *Diabetes Care* 2018;41:1801–8.
31. Akuta N, Watanabe C, Kawamura Y, et al. Effects of a sodium-glucose co-transporter 2 inhibitor in nonalcoholic fatty liver disease complicated by diabetes mellitus: Preliminary prospective study based on serial liver biopsies. *Hepatol Commun* 2017;1:46–52.
32. Riddle MC, Cefalu WT. SGLT inhibitors for type 1 diabetes: an obvious choice or too good to be true? *Diabetes Care* 2018;41:2444–7.
33. Mccrimmon RJ, Henry RR. SGLT inhibitor adjunct therapy in type 1 diabetes. *Diabetologia* 2018;61:2126–33.
34. Henry RR, Thakkar P, Tong C, Polidori D, Alba M. Efficacy and safety of canagliflozin, a sodium-glucose co-transporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. *Diabetes Care* 2015;38:2258–65.
35. Refardt J, Winzeler B, Meienberg F, Vogt DR, Christ-Crain M. Empagliflozin increases short-term urinary volume output in artificially induced syndrome of inappropriate antidiuresis. *Int J Endocrinol* 2017;2017:7815690.
36. Javed Z, Papageorgiou M, Deshmukh H, et al. Effects of empagliflozin on metabolic parameters in polycystic ovary syndrome: a randomized controlled study. *Clin Endocrinol (Oxf)* 2019;90:805–13.
37. Tang Y, Sun Q, Bai XY, Zhou YF, Zhou QL, Zhang M. Effect of dapagliflozin on obstructive sleep apnea in patients with type 2 diabetes: a preliminary study. *Nutr Diabetes* 2019;9:32.
38. Shi FH, Li H, Shen L, et al. Appraisal of non-cardiovascular safety for sodium-glucose co-transporter 2 inhibitors: a systematic review and meta-analysis of placebo-controlled randomized clinical trials. *Front Pharmacol* 2019;10:1066.

39. Sakaeda T, Kobuchi S, Yoshioka R, et al. Susceptibility to serious skin and subcutaneous tissue disorders and skin tissue distribution of sodium-dependent glucose cotransporter type 2 (SGLT2) inhibitors. *Int J Med Sci* 2018;15:937–43.
40. Katsiki N, Dimitriadis G, Hahalis G, et al. Sodium-glucose co-transporter-2 inhibitors (SGLT2i) use and risk of amputation: an expert panel overview of the evidence. *Metabolism* 2019;96:92–100.
41. Ruanpeng D, Ungprasert P, Sangtian J, Harindhanavudhi T. Sodium-glucose co-transporter 2 (SGLT2) inhibitors and fracture risk in patients with type 2 diabetes mellitus: a meta-analysis. *Diabetes Metab Res Rev* 2017;33:e2903.
42. Wu CN, Tien KJ. The impact of antidiabetic agents on sarcopenia in type 2 diabetes: a literature review. *J Diabetes Res* 2020;2020:9368583.
43. Campins L, Camps M, Riera A, Pleguezuelos E, Yebenes JC, Serra-Prat M. Oral drugs related with muscle wasting and sarcopenia. A review. *Pharmacology* 2017;99:1–8.
44. Marty E, Liu Y, Samuel A, Or O, Lane J. A review of sarcopenia: enhancing awareness of an increasingly prevalent disease. *Bone* 2017;105:276–86.
45. Kim TN, Park MS, Yang SJ, et al. Prevalence and determinant factors of sarcopenia in patients with type 2 diabetes: the Korean Sarcopenic Obesity Study (KSOS). *Diabetes Care* 2010;33:1497–9.
46. Murata Y, Kadoya Y, Yamada S, Sanke T. Sarcopenia in elderly patients with type 2 diabetes mellitus: prevalence and related clinical factors. *Diabetol Int* 2018;9:136–42.
47. Ogama N, Sakurai T, Kawashima S, et al. Association of glucose fluctuations with sarcopenia in older adults with type 2 diabetes mellitus. *J Clin Med* 2019;8(3):319.
48. Abbatecola AM, Ferrucci L, Ceda G, et al. Insulin resistance and muscle strength in older persons. *J Gerontol A Biol Sci Med Sci* 2005;60:1278–82.
49. Abbatecola AM, Paolisso G. Is there a relationship between insulin resistance and frailty syndrome? *Curr Pharm Des* 2008;14:405–10.
50. Mori H, Kuroda A, Ishizu M, et al. Association of accumulated advanced glycation end-products with a high prevalence of sarcopenia and dynapenia in patients with type 2 diabetes. *J Diabetes Investig* 2019;10:1332–40.
51. Yabe D, Nishikino R, Kaneko M, Iwasaki M, Seino Y. Short-term impacts of sodium/glucose co-transporter 2 inhibitors in Japanese clinical practice: considerations for their appropriate use to avoid serious adverse events. *Expert Opin Drug Saf* 2015;14:795–800.
52. Yasuda M, Iizuka K, Kato T, et al. Sodium-glucose co-transporter 2 inhibitor and sarcopenia in a lean elderly adult with type 2 diabetes: a case report. *J Diabetes Investig* 2020;11:745–7.
53. Osonoi T, Nakamoto S, Saito M, Tamasawa A, Ishida H, Osonoi Y. Efficacy of ipragliflozin as monotherapy or as add-on therapy with other oral antidiabetic medications for treating type 2 diabetes in Japanese patients with inadequate glycemic control: a subgroup analysis based on patient characteristics. *J Diabetes Investig* 2018;9:341–53.
54. Tsurutani Y, Nakai K, Inoue K, et al. Comparative study of the effects of ipragliflozin and sitagliptin on multiple metabolic variables in Japanese patients with type 2 diabetes: a multicentre, randomized, prospective, open-label, active-controlled study. *Diabetes Obes Metab* 2018;20:2675–9.

55. Sugizaki T, Zhu S, Guo G, et al. treatment of diabetic mice with the SGLT2 inhibitor TA-1887 antagonizes diabetic cachexia and decreases mortality. *NPJ Aging Mech Dis* 2017;3:12.
56. Sano M, Meguro S, Kawai T, Suzuki Y. Increased grip strength with sodium-glucose co-transporter 2. *J Diabetes* 2016;8:736–7.
57. Bolinder J, Ljunggren O, Johansson L, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. *Diabetes Obes Metab* 2014;16:159–69.
58. Sugiyama S, Jinnouchi H, Kurinami N, et al. Dapagliflozin reduces fat mass without affecting muscle mass in type 2 diabetes. *J Atheroscler Thromb* 2018;25:467–76.
59. Inoue M, Hayashi A, Taguchi T, et al. Effects of canagliflozin on body composition and hepatic fat content in type 2 diabetes patients with non-alcoholic fatty liver disease. *J Diabetes Investig* 2019;10:1004–11.
60. Dalakas MC. Toxic and drug-induced myopathies. *J Neurol Neurosurg Psychiatry* 2009;80:832–8.
61. Valiyil R, Christopher-Stine L. Drug-related myopathies of which the clinician should be aware. *Curr Rheumatol Rep* 2010;12:213–20.
62. Gao F, Hall S, Bach LA. Myopathy secondary to empagliflozin therapy in type 2 diabetes. *Endocrinol Diabetes Metab Case Rep* 2020;2020.
63. Kabadi UM. Marked weight loss, muscle wasting and fatigue on administration of empagliflozin in a subject withtype 2 diabetes. *Br J Med Med Rese* 2017;21:1–7.
64. Degorter MK, Tirona RG, Schwarz UI, et al. Clinical and pharmacogenetic predictors of circulating atorvastatin and rosuvastatin concentrations in routine clinical care. *Circ Cardiovasc Genet* 2013;6:400–8.
65. Brailovski E, Kim RB, Juurlink D. Rosuvastatin myotoxicity after starting canagliflozin treatment: a case report. *Ann Intern Med* 2020. https://doi.org/10.7326/L20-0549.
66. Mamidi R, Dallas S, Sensenhauser C, et al. In vitro and physiologically-based pharmacokinetic based assessment of drug-drug interaction potential of canagliflozin. *Br J Clin Pharmacol* 2017;83:1082–96.
67. Empagliflozin. *Aust Prescr* 2015;38:64–6.