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DIABETES PHARMACOTHERAPY AND EFFECTS ON THE MUSCULOSKELETAL SYSTEM

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Abstract

Persons with type 1 or type 2 diabetes (T1D, T2D) have a significantly higher fracture risk than age-matched persons without diabetes, attributed to disease-specific deficits in the microarchitecture and material properties of bone tissue. Therefore, independent effects of diabetes drugs on skeletal integrity are vitally important. Studies of incretin-based therapies have shown divergent effects of different agents on fracture risk, including detrimental, beneficial and neutral effects. The sulfonylurea class of drugs, owing to its hypoglycemic potential, is thought to amplify the risk of fall-related fractures, particularly in the elderly. Other agents such as the biguanides may, in fact, be osteo-anabolic. In contrast, despite similarly expected anabolic properties of insulin, data suggests that insulin pharmacotherapy itself, particularly in T2D, may be a risk factor for fracture, negatively associated with determinants of bone quality and bone strength. Finally, sodium-dependent glucose co-transporter 2 inhibitors have been associated with an increased risk of atypical fractures in select populations, and possibly with an increase in lower extremity amputation with specific SGLT2I drugs. The role of skeletal muscle, as a potential mediator and determinant of bone quality, is also a relevant area of exploration. Currently, data regarding the impact of glucose lowering medications on diabetes-related muscle atrophy is more limited, although preclinical studies suggest that various hypoglycemic agents may have either aggravating (sulfonylureas, glinides) or repairing (thiazolidinediones, biguanides, incretins) effects on skeletal muscle atrophy, thereby influencing bone quality. Hence, the therapeutic efficacy of each hypoglycemic agent must also be evaluated in light of its impact, alone or in combination, on musculoskeletal health, when determining an individualized treatment approach. Moreover, the effect of newer medications (potentially seeking expanded clinical indication into the pediatric age range) on the growing skeleton is largely unknown. Herein we review the available literature regarding effects of diabetes pharmacotherapy, by drug class and/or by clinical indication, on the musculoskeletal health of persons with diabetes.

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Keywords

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INTRODUCTION

The incidence of both type 1 diabetes (T1D) and type 2 diabetes (T2D) is increasing steadily, both in the United States (US) and worldwide (1–7). The National Diabetes Statistics report, 2017 (www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf) (8) estimates that as of 2015, 30.3 million people in the US have diabetes (T1D or T2D), with 23.1 million being diagnosed and 7.2 million being undiagnosed; ~90–95% of these have T2D. In China, where diabetes prevalence is the highest worldwide, an estimated 110 million adults have diabetes (1). Globally, the International Diabetes Federation estimates that the diabetes pandemic encompasses 8.8% of the global population; and, in 2017, worldwide healthcare expenditure for diabetes exceeded 800 billion US dollars (www.diabetesatlas.org) (9). The economic burden of diabetes in the US alone in 2017 has been estimated at $327 billion, both in direct medical care costs and in reduced productivity, representing a 26% inflation-adjusted cost increase from just 5 years earlier (10).

While insulin replacement therapy remains the mainstay of therapy for T1D, the expanding armamentarium of medications for treatment of T2D now includes 11 distinct classes of glucose lowering oral or injectable medications, including insulin (11) (Table 1). Consensus guidelines of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (12) recommend a HbA1c treatment target of <7% for most patients with T2D, and multicomponent therapy [along with lifestyle management and diabetes self-management education and support (DSMES)] is indicated if this HbA1c target is not achieved within ~3 months from start of treatment (11). As such, it can be anticipated that a multitude of individuals will, at some point in their lifetime, be exposed to diabetes pharmacotherapy, and very often requiring polypharmacy.

Osteoporosis is also an increasingly common skeletal disorder affecting an estimated 75 million people in Europe, Japan and the Unites States; it is a condition which increases with aging, and is the predominant contributor to fracture in the elderly (www.iofbonehealth.org/facts-statistics) (13). Worldwide, osteoporosis contributes annually to >8.9 million fractures. Prevalence rates for osteoporotic vertebral fracture, in particular, are highest in North American and in Asia, geographically mirroring areas that also exhibit a high prevalence of diabetes (14). At the same time, non-osteoporotic fall-related fractures are also becoming increasingly common at all ages (15).

Persons with either T1D or T2D are at relatively greater risk for fracture, when compared with age-matched persons without diabetes, potentially compounding these two independent public health concerns (16, 17). In those with T1D, fracture risk is increased across the

lifespan including in childhood (18), with relative risk for any osteoporotic fracture increasing 3-fold (19), and for hip fracture in particular increasing between 4-fold and 6-fold (19, 20). In those with T2D, fracture risk increases with longer duration of diabetes (21) and with poorer glycemic control (22, 23); but, for any given femoral neck bone mineral density (BMD) T-score or individual FRAX (World Health Organization Fracture Risk Algorithm) score, fracture risk is greater in those with T2D than in those without diabetes mellitus (24). Moreover, complications of fracture, such as delayed healing and secondary infection, as well as consequences of fracture, such as prolonged hospitalization and economic burden, are even more detrimental in the diabetic population, compared with the general population (25, 26).

The elevated propensity for fracture in persons with diabetes is not predictable by bone BMD measurements, which are typically only modestly decreased in T1D (27, 28), and normal or increased in T2D (29, 30). Instead, elevated fracture risk is attributed to secondary deficits in the microarchitecture (31, 32) and in the material properties of the bone tissue (33), along with pathophysiological and genetic factors intrinsic to diabetes itself (32). Variables inherent to both T1D and T2D, including chronic hyperglycemia and glycemic variation (23), tissue-specific accumulation of advanced glycation end-products (AGEs) (34, 35), dysregulation of insulin-like growth factor 1 (IGF-1) bioavailability (36, 37), variable insulin exposure (endogenous or exogenous), enhanced oxidative stress, changes in bone mineral and vitamin D homeostasis (38), and regional diabetic microvascular disease, undoubtedly all impact the skeletal quality in diabetes (3). Added to these variables is an increased propensity to falling, whether attributable to acute hypoglycemia, peripheral neuropathy, decreased visual acuity, or postural instability (39). Finally, the impact of diabetes-related muscle atrophy, as a determinant of both bone quality and individual stability, is relevant to the understanding of skeletal health in these disorders.

A decade ago, diabetes therapy using select thiazolidinedione (TZD) medications was first shown to further increase fracture risk in women with T2D (40), by accelerating bone loss (41), and activating osteoclastogenesis (42). This warning prompted a comprehensive and ongoing evaluation of the effects, both direct and indirect, of diabetes pharmacotherapy on bone health and fracture risk. While the impact of anti-diabetes medications on diabetes-related loss of muscle mass has not been as extensively investigated, preclinical studies suggest that various hypoglycemic agents may *also* have either harmful (sulfonylureas, glinides) or beneficial (TZDs, biguanides, incretins) effects on muscle, thereby also influencing bone quality. Hence, when determining individualized treatment strategies for persons with diabetes, the therapeutic efficacy of each hypoglycemic agent must also be evaluated in light of its impact, alone or in combination, on the bone and muscle health of each individual.

The intent of this review is to provide a comprehensive overview of known preclinical and clinical effects of diabetes pharmacotherapy, by drug class and/or by clinical indication, on the musculoskeletal system in diabetes (summarized in Table 2). This chapter is considered a comprehensive review and discussion of the literature, but is not intended as a clinical management guideline or recommendation. Recommendations regarding the personalized management of persons with both T2D and osteoporosis have recently been published (43).

A similar guideline for the T1D population with osteoporosis has not been established although co-therapy with insulin and various other drugs (SGLT2 inhibitors, amylin mimetics) is on the rise, suggesting that similar recommendations will be needed in the future.

DRUGS AND BONE

Insulin Action

1. Insulin

Mechanism of Action: Insulin is a peptide hormone (~7.5 kD), produced by the β-cell of the pancreas and highly regulated by systemic glucose concentrations (44). Insulin signals primarily through the insulin receptor, a hetero-tetramer made up of two extracellular α-subunits and two transmembrane β-subunits, which is present on most cell-types (45). Insulin-mediated signaling can occur through phosphorylation of insulin receptor substrate (IRS)-1 and IRS-2 and subsequent activation of phosphatidylinositol (PI) 3-kinase or by activation of the mitogen-activated protein (MAP)/ERK kinase pathway (46–48). Insulin can mediate various cellular events including glucose uptake and promotion of mitogenesis (49).

In T1D, insulin production is reduced and therefore inadequate to control blood glucose levels due to impairment and destruction of pancreatic β-cells. In T2D, insulin production may actually be exaggerated, due to insulin resistance. However, in later stages of T2D, insulin production typically declines as β-cell failure ensues (50, 51). Thus, those with T1D are uniformly treated with insulin, while many individuals with T2D may eventually need to be treated with insulin (51). It is estimated that approximately 100 million people world-wide require insulin therapy and that between 10–25% of those individuals have T2D (52). Despite its significant clinical utilization, the role that insulin therapy may play in modulating bone homeostasis in the context of diabetes is not well understood. Most clinical studies in diabetes examining insulin-bone interactions have been correlative in nature only, and not prospective, double-blinded or placebo-controlled.

Skeletal effects: In vitro: The insulin receptor is expressed by osteoblasts *in vitro* and *in vivo* (16, 53–56). Insulin receptor expression is detected in early bone progenitor cells as well as in primary bone cell cultures. Its expression is detected throughout differentiation, from pre-osteoblast to mature osteoblast, suggesting that insulin signaling is important in promoting all stages of osteogenesis (54). *In vitro*, insulin promotes osteoblast proliferation and increases type 1 collagen synthesis and alkaline phosphatase production by osteoblasts (57–63). Physiologic doses of insulin enhance glucose uptake by osteoblasts and recent data show that Glucose transporter type 4 (Glut-4) is the primary glucose transporter responsible for mediating insulin-stimulated glucose uptake by mature osteoblasts and osteocytes (64–66). Only very limited information is available on any direct effects that insulin may have on osteoclasts; however, insulin has been shown to decrease osteoclast activity in culture (67). Taken together, these *in vitro* studies suggest that insulin may have broad activity to promote bone formation by regulating various phases of osteoblast maturation and osteoblast metabolism, and by decreasing bone resorption through inhibition of osteoclast activity.

Skeletal effects: In vivo: In rodent models of type 1 diabetes, wherein significant pancreatic β-cell destruction has occurred and circulating insulin levels are very low to undetectable, skeletal micro-architecture, bone quality and fracture resistance are compromised and fracture healing and skeletal regeneration are impaired (53, 68). These skeletal deficits are in large part due to decreased bone formation and significant down-regulation of Runt related transcription factor 2 (RUNX2), a master regulator of osteogenesis, as well as important skeletal genes known to be targets of RUNX2 (69, 70). Insulin administration to rodent models of type 1 diabetes consistently demonstrates improvements in bone microarchitecture, bone quality and biomechanical properties of bone and in fracture healing (53, 71–73). Even at the molecular level, RUNX2 and RUNX2-regulated osteogenic genes are in large part normalized in insulin-treated diabetic rodents (70).

Debate continues as to whether insulin's ability to improve bone formation in the condition of diabetes is related to its glucose lowering effect and/or to its ability to directly impact osteoblastogenesis and bone formation. Advanced glycation end products (AGEs) are compounds generated through non-enzymatic reactions occurring between sugars and amine residues. In diabetes, where glucose levels are elevated, AGEs are deposited in many tissues, including bone (74). AGEs are associated with increased bone fragility in diabetes; thus, by lowering glucose levels, insulin may help to decrease accumulation of AGEs in bone (75, 76). Never-the-less, *in vivo* evidence also suggests that insulin has a direct effect on bone formation and osteogenesis, irrespective of its effect on glucose metabolism. For instance, several studies in mice have shown that impaired insulin signaling, via knock-down of the insulin receptor specifically in osteoblast progenitors and mature osteoblasts, results in impaired bone formation, abnormal trabecular architecture, smaller cortices, and increased fragility, dependent on the developmental stage in which the insulin receptor was eliminated and in a sex-specific manner (56, 77, 78). In other studies, exogenous insulin administration shows a dose-dependent ability to prevent diabetes-related skeletal changes in mice, even though glucose levels remain elevated (79). Similarly, systemic insulin treatment of diabetic male Wistar rats (alloxan-induced) has been shown to improve bone repair and osteo-integration around tibial titanium implants (80). Further support for a direct action of insulin on osteoblastogenesis in diabetes has come from fracture models in diabetic rodents, which demonstrate that insulin delivered locally to the fracture site results in normalization of mineralization, improved callus bone content, and enhanced biomechanical properties, despite persistent systemic hyperglycemia and systemic hypo-insulinemia (81). Together these preclinical data support a role for insulin to directly, and possibly indirectly, improve skeletal well-being in the context of active diabetes and persistent hyperglycemia.

Skeletal effects: Clinical investigation and fracture risk: Despite significant preclinical data to support a role for insulin in preventing skeletal consequences of diabetes, there is much less information about its role in skeletal preservation in humans with diabetes. Because all individuals with T1D are treated with insulin, it is impossible to carry out placebo-controlled studies. Nevertheless, in those with T1D, exogenous insulin dose and residual C-peptide production have been shown to positively correlate with the bone formation marker, osteocalcin (82). Also, inadequate glycemic control, potentially a

consequence of inadequate insulin administration, has been linked in some studies to low BMD in T1D [reviewed in (16)].

Studies in humans with T2D demonstrate a positive correlation between BMD by Dual X-ray Absorptiometry (DXA) and insulin dose (83, 84) or urinary C-peptide excretion (83), suggesting that insulin may positively impact the skeletal properties of those with T2D. This is in keeping with several studies demonstrating that insulin resistance, a common feature of T2D, is associated with greater volumetric BMD, yet smaller bone size and lower strength indices, suggesting that normal insulin sensitivity may be related to increased bone formation and better skeletal outcomes (85–88). Despite the correlative data suggesting that insulin is associated with improved bone parameters in T2D, several recent reports have demonstrated a more rapid BMD loss and an increased fracture risk in those with T2D treated with insulin (89–93). It is not clear why this apparent paradox exists in T2D, but it may be related to the fact that most individuals treated with insulin for T2D are more advanced in their disease process (94). As such, they may have additional complications, such as microvascular disease or peripheral neuropathy, and may be at a higher risk to fall, thus increasing their chances of fracture.

Conclusion: Insulin therapy is always used in the treatment of T1D and commonly used in the treatment of T2D. Many *in vitro*, pre-clinical and clinical studies support the view that insulin can function as an anabolic agent in bone, and when used in the condition of diabetes, it may provide beneficial effects on bone formation and in the prevention of diabetic-related bone disease and fractures. However, recent data, specifically related to T2D in humans, suggests that insulin treatment may be unexpectedly associated with higher fracture rates.

Insulin Sensitizers

2. Biguanides

Mechanism of Action: Biguanides, conjoined chemical derivatives of guanidine, were initially endorsed (95) for the treatment of T2D in the 1950s. Early derivatives (phenformin, buformin) were ultimately withdrawn from the pharmaceutical market due to toxicity concerns: Metformin (Glucophage®), however, received FDA approval in the US in 1994 and is now the principal biguanide used worldwide for its anti-hyperglycemic potential. Metformin is considered as the first line mono-therapy for most patients with T2D (12), both in adults (96, 97) and in children > 10 years of age (95). Recent recommendations of the ADA and EASD specifically state, *"Because of its high efficacy in lowering HbA1c, good safety profile and low cost, metformin remains the first-line medication for management of type 2 diabetes"* (12). While not fully elucidated, the anti-hyperglycemic effects of this drug class are attributable broadly to: 1) the inhibition of hepatic gluconeogenesis (98, 99); and 2) the enhancement of peripheral tissue insulin sensitization (95, 99), seemingly mediated via activation, albeit indirect, of adenosine monophosphate-activated protein kinase (AMPK) signaling pathways (100, 101). Recently identified and potentially beneficial *non-glycemic* effects of metformin, including resistance to cancer (102–106), aging (107, 108), infection (109), cognitive impairment (110), and cardiovascular disease (111) may further contribute to an increase in its overall use in the future.

Skeletal effects: In vitro: Examining both murine and human-derived mesenchymal stem cell cultures, metformin exposure has been shown in several studies to induce an overall shift in mesenchymal stem cell differentiation toward the osteogenic pathway and away from adipogenesis (112–115). Further evidence of the osteogenic potential of metformin comes from studies utilizing a variety of osteoblast-specific cell cultures, including UMR106 cells, MC3T3–E1 cells, primary mouse calvarial cultures, and primary rat osteoblast cultures. Using these *in vitro* models, metformin-mediated increases in: 1) cell proliferation; 2) cell differentiation; 3) insulin-stimulated glucose uptake; 4) type 1 collagen production; 5) alkaline phosphatase activity; 6) extracellular matrix deposition and mineralization; along with 7) transcriptional up-regulation of pro-osteogenic genes [including *Runx2*, osteocalcin (*Ocn)*, bone morphogenic protein-2 *(Bmp-2)*, osteoprotegerin *(Opg), Igf-1*] have been demonstrated in cultured osteoblasts (116–120). *In vitro*, metformin also appears to protect against AGE-induced cellular injury and cell death in osteoblastic cells (121), similar to described effects in other human and rodent complication-affiliated cell types such as neurons (122), macrophages (123), cardiomyocytes (124), and renal tubular cells (125). In many cases, these effects are thought to be mediated by metformin activation of AMPK signaling pathways (112, 117, 126). Given that AMPK is a regulator of cellular energy sensing, a role for metformin in stimulating osteogenesis and inhibiting adipogenesis is conceptually consistent with its presumed systemic effects (127). Metformin is also hypothesized to be a negative regulator of Receptor Activator of Nuclear factor Kappa-B Ligand (RANKL), inhibiting the differentiation of osteoclasts (128, 129). Additionally, metformin has been shown to be a negative regulator of chondrocyte differentiation (130).

Never-the-less, not all *in vitro* studies support an anabolic role for metformin. Kasai, *et al* reported that metformin *inhibited* gene expression of *Runx2* and osteoblast differentiation markers such as *Ocn*, bone sialo-protein (*Bsp*), and osteopontin (*Opn*) in terminally differentiated osteoblasts (131). Others have reported simply the lack of metformin effect on osteogenic differentiation or osteoblast function *in vitro* (132, 133).

Skeletal effects: In vivo: Skeletal effects of metformin in preclinical models have been somewhat inconsistent, demonstrating both pro-osteogenic efficacy as well as the absence of effect. Pro-osteogenic benefits have been demonstrated *in vivo* in *non-diabetic* rodent models. In rats, metformin monotherapy was shown to increase bone regeneration, increase femoral trabecular area, increase osteoblastic and osteocytic density (134), and to stimulate the re-ossification of artificial bone defects (135). Likewise, in mice, metformin treatment was found to increase cortical bone density and decreased medullary volume (113). Finally, metformin has been shown to attenuate the expected bone loss which occurs under various conditions, including: 1) ovariectomized models of post-menopausal osteoporosis (128, 136); 2) experimental models of periodontitis-induced alveolar bone loss (137–140); and 3) pharmacotherapy-induced bone loss (134).

Studies utilizing various *in vivo* models of insulin resistance and/or hyperglycemia also generally confirm that metformin monotherapy is bone-friendly, with ability to counteract the detrimental effects of diabetes on bone. Specifically, metformin has been shown to prevent or correct the diabetes-induced alterations in bone microarchitecture and/or bone histology in models of partial insulin deficiency (141) and in models of insulin resistance,

diet-induced obesity or metabolic syndrome (142–145). At the same time, bone marrow adipose expansion, characteristic of mice fed a high-fat diet, was also correctible with metformin (143). Finally, metformin treatment appears to accelerate wound healing and angiogenesis in hyperglycemic rodents (146, 147). These findings, however, may be indirectly mediated by the insulin-sensitizing and/or glucose-lowering efficacy of metformin in these studies. As shown by Inouye *et al*, in Goto-Kakizaki (GK) spontaneously diabetic rats treated with metformin, the peri-implant wound healing around oral titanium implants was directly related to the glucose lowering success of the treatment (148).

In contrast, a lack of benefit has been seen in many other studies specifically examining bone regeneration or bone repair. In *non-diabetic* Wistar rats, metformin had a detrimental effect on osseointegration around titanium bone implants (149). In *non-diabetic* female rodents (either C57BL/6 ovariectomized mice or female Wistar rats), metformin treatment had no beneficial effect on fracture healing (150). In *diabetic* Zucker rats, metformin had a negative effect on fracture repair, despite successfully improving blood glucose (151); similarly, in a rat model of type 2 diabetes, metformin did not reverse the detrimental effects of hyperglycemia on bone healing around tibial titanium implants (152).

Skeletal effects: Clinical investigation and fracture risk: Investigation in humans more commonly supports the concept that metformin exposure has either a neutral or modestly beneficial effect on skeletal health and fracture occurrence. A neutral impact on fracture risk has been seen in studies examining metformin exposure and fracture incidence in a variety of T2D populations, often in comparison with other anti-diabetic medications. Specifically, data has indicated that metformin did *not* affect the risk of fracture in: 1) older adults with T2D (mean age ~ 69 years) living in the Tuscany region of Italy, and exposed to metformin for at least 36 months (153); 2) adults with T2D (mean age ~57 years) participating in the North American and European multisite ADOPT trial, with relatively recent onset T2D (< 3 years at randomization) and receiving ~ 4 years of metformin treatment (40); 3) adults with T2D living in the United Kingdom (mean age ~ 61 years), identified through a large general practitioner database, receiving standard-of-care metformin therapy for ≥12 months duration (154); 4) adults with T2D living in Scotland (mean age ~ 65 years) with any history of metformin exposure (155); and 5) elderly men with T2D (median age ~73 years) enrolled in the United States, multisite Osteoporotic Fractures in Men study (93). Several studies specifically comparing metformin with the thiazolidinediones (TZDs) have also supported a comparatively neutral impact of metformin exposure on bone health, bone density or fracture risk (40, 156–159).

In support of an osteo-anabolic impact of metformin, a large case-controlled Danish study of fracture risk in patients with both T1D and T2D demonstrated a significant reduction in relative risk of fracture, after adjustment for multiple co-variates, among patients treated with metformin (91). Similarly, in residents of Rochester, MN, the diabetes-associated increased risk for fracture was relatively reduced among those treated with biguanides (160). Biguanide-related benefits to bone repair have also been reported. Specifically, metformin usage appeared to improve healing of fixated femoral neck fractures in a small retrospective study of patients with T2D and displaced fractures (161). Additionally, anabolic benefits of metformin have been seen with localized drug delivery for the treatment of intrabony defects

in non-diabetic patients with chronic periodontitis (162–164). Finally, in rapidly maturing peri-pubertal girls, treatment with metformin for 4 years duration normalized the accelerated pace of skeletal maturation in these children (165). Metformin-treated girls gained more height, and less central adiposity, per bone age year, possibly confirming a shift away from adipogenesis, as is seen in *in vitro* studies.

The effects of metformin on systemic bone biomarker concentrations have also been investigated as an indirect assessment of its drug-related skeletal impact. Several studies in adults with T2D (166, 167), along with one study in adults with non-alcoholic fatty liver disease (NAFLD)(168) suggest that extended treatment with metformin results in a decrease in biomarkers of bone turnover including Procollagen type 1 amino-terminal propeptide (P1NP) and carboxy-terminal collagen crosslinks (CTX) (166, 167), related, in some studies, to the improvement in glycemic control (169). These changes are not necessarily confirmed, however, following shorter duration of metformin exposure (170).

Only a very few studies have definitively reported adverse outcomes of metformin treatment on skeletal health. In a study of 67 adults with T2D, each receiving 1 year of treatment with 1 of 6 distinct drug-treatments for T2D (n=8–13 per group), a significant treatment-emergent *decrease* in BMD of both spine and hip was seen in the metformin mono-therapy group (n=12), a finding which the authors acknowledge was clearly contrary to existing literature (171). However, this study was limited not only by the very small sample size of the metformin-treatment group, but by the finding that BMD *and* BMI (mean, 24.89±4.37) in the T2D patients as a whole were lower than BMD and BMI of their control subjects, suggesting that the diabetic cohort in this study was not typical of most T2D populations. Moreover, the relationship of these findings to any impact on fracture risk is not known, as BMD alone is expected to be a poor predictor of fracture risk in this population. In another study of exclusively postmenopausal women with T2D, 1 year of metformin therapy unexpectedly, but significantly, increased the percentage of circulating osteoclast precursor cells in peripheral blood (172), a finding which caused the authors to question the validity of their assay. Alternatively, this finding may be unique to postmenopausal women with T2D.

Conclusion: A number of preclinical studies infer a beneficial, osteogenic potential of metformin, including *in vitro, in vivo*, and *ex vivo* investigations. *In vitro* data generally demonstrate anabolic effects of metformin at the cellular level, while animal modeling has demonstrated both pro-osteogenic, as well as negative effects of drug exposure. Much of the pre-clinical data suggests, however, that metformin effects are perhaps most relevant in the context of diabetes, due to pharmacological mitigation of hyperglycemia. Clinical studies generally indicate that fractures are no more prevalent in patients treated with metformin, and fracture risk may in fact be reduced, perhaps attributable, again, to concurrent glycemic improvements. However, a direct comparison of patients treated with metformin monotherapy with other more intensified multicomponent therapies negates the contribution that diabetes severity itself may have on fracture risk assessment, limiting the relevance of these clinical conclusions. Never-the-less, metformin appears to be, at most, modestly anabolic and at least, neutral (i.e., not harmful) with respect to bone health.

3. Thiazolidinediones

Mechanism of Action: Thiazolidinediones (TZDs), including FDA-approved rosiglitazone and pioglitazone, are synthetic peroxisome proliferator-activated receptor gamma (PPARγ) agonists. They enhance hepatic and peripheral insulin sensitivity through PPARγ activation (173) which modulates the transcription of several genes involved in glucose and lipid metabolism (174). Furthermore, PPARγ activation has effects on bone marrow cells; specifically, it promotes adipocyte differentiation and limits osteoblastogenesis (175). TZDs were introduced in the late 1990s and have been considered an effective second-line option in the treatment of T2D (11, 173). Both rosiglitazone and pioglitazone were associated with increased risk of fluid retention and congestive heart failure (176), leading to certain restrictions on prescribing by the FDA (11, 173). PPARγ has been implicated in bone metabolism, with specific effects on osteoblasts, osteocytes and osteoclasts (177, 178); therefore, it is not surprising that TZDs have also been associated with an increased risk of bone fractures based on a plethora of preclinical and clinical studies (41, 179–185), although some have suggested that the fracture risk could be similar to the risk in patients with T2D receiving insulin treatment (186).

Skeletal effects: In vitro: TZDs cause an imbalance between adipocyte and osteoblast formation (187) and this imbalance has been proposed as a possible mechanism for impaired bone metabolism. Specifically, most studies on TZDs have shown inhibition of osteoblast differentiation and mineralization (134, 175), reduced collagen and osteocalcin levels (188), decreased expression of RUNX2 (134) and decreased mRNA levels of RUNX2 (175, 189, 190), osterix (190), type I collagen (188, 189) and osteocalcin (188). Additionally, TZDs inhibit alkaline phosphatase activity and osteocalcin production from murine osteoblasts (191), increase sclerostin levels (192), suppress Wnt signaling (187, 193), and induce osteoblast (191) and osteocyte (192, 194) death. One study showed no effects on osteoblast differentiation, alkaline phosphatase activity or mineralization *in vitro* when rosiglitazone or pioglitazone was added to human bone marrow stromal cells (195). This same study, however, reported a decrease in osteoblast precursors with an increase in adipocyte precursors in their *in vivo* studies, in cells harvested from humans treated with TZDs (195). Rosiglitazone has also been shown to suppress IGF-1 (196), which can negatively affect skeletal acquisition. A newer TZD, lobeglitazone (currently approved in South Korea) does not appear to have suppressive effects on osteoblast function when compared to rosiglitazone (197). Osteoclastogenesis is also affected by PPARγ (178); some studies have shown that TZDs promote osteoclastogenesis (198–200), whereas others have reported decreased bone resorption *in vitro* (201), reduced pit formation and a reduction in RANK expression and RANKL activation with TZDs (188).

Skeletal effects: In vivo: Numerous preclinical studies have been published on the effects of TZDs on bone. Studies involving rosiglitazone use in rodents found decreases in total body BMD (142, 189, 202–204) with a decrease in bone formation rate (189, 190, 198, 203), induction of osteoblast and osteocyte death (204), increased bone resorption/osteoclast activity (198, 203), and an increase in adipose content in the bone marrow (189, 190, 198, 202, 203). In younger mice, low bone formation is considered to be the cause of bone loss, whereas in older mice increased osteoclastogenesis has been thought to contribute

significantly to bone loss (198). Some of the adverse effects of rosiglitazone have been prevented in rats with co-treatment with metformin (134).

Studies in rodents exposed to pioglitazone have found either no adverse effects on bone (142, 205) or negative effects. Several studies found that pioglitazone resulted in decreases in BMD (199, 202, 206), decreased bone strength (199, 207), decreased osteoblast surface and mineralizing surface and increased osteoclast surface and number (199), supporting that pioglitazone suppresses bone formation and promotes bone resorption (207), predisposing to bone fragility. These effects have been reversible in certain studies (206, 207) with discontinuation of treatment. Interestingly, when pioglitazone treatment has been combined with fenofibrate (a PPARα agonist) administration, the negative effects on bone were either unaffected (207) or attenuated (206).

Lastly, lobeglitazone did not have any negative effect on whole body and femoral BMD in mice compared to vehicle (197).

Skeletal effects: Clinical investigation and fracture risk

Effects on BMD and bone turnover markers: Studies examining a change in systemic bone biomarker concentration during TZD exposure have been inconsistent. Measurement of markers of bone turnover in T2D patients treated with TZDs has shown no difference (208), a decrease (167, 209), or an increase (210) in P1NP, a decrease in alkaline phosphatase (167, 209–211), no difference (208, 209) or a decrease in osteocalcin (211) and an increase in sclerostin (166) levels. Likewise, a meta-analysis including 14 trials found considerable variation in bone turnover markers between studies (179). TZDs have also been shown to have no effect (209) or to increase CTX, a marker of bone resorption, compared to healthy controls (166, 208), or metformin or glyburide treatment (167, 212).

TZD effects on BMD, however, have been somewhat more consistent. TZDs have been associated with decreases in BMD, particularly in women (41, 179, 210, 211), although men with T2D on treatment with TZDs have been reported to have bone loss in both the spine and the hip (158, 213). Rosiglitazone has been associated with reductions in cortical thickness at the hip, as measured by QCT, in post-menopausal women with T2D when compared to metformin (214). One study reported that TZD use (troglitazone, pioglitazone, and/or rosiglitazone) was associated with significant bone loss in older women with T2D at multiple sites (215) and another study showed lower BMD of spine and total hip compared to metformin involving both men and women with T2D (158). However, when compared to insulin or exenatide treatment specifically, Li *et al* found no difference in BMD or bone turnover markers with pioglitazone (216). Grey *et al* found that pioglitazone when compared to control was associated with increased bone loss at the femur but no other sites (217). Finally, a recent meta-analysis on the effects of TZDs on bone reported decreases in BMD at the lumbar spine, total hip and forearm (179). Admittedly, however, effects of TZDs on BMD do not predict effects on the risk for fracture from TZD exposure.

Interestingly, the newer TZD, lobeglitazone, when compared with placebo over a 52-week treatment period, was not associated with a significant decrease in BMD (218) in 112 adults with T2D (mean age ~56 years; duration of T2D ~4 years); however, these relatively better

skeletal outcomes need to be confirmed with further studies, as there are no long-term data yet available.

Effects on fracture: TZDs have been explicitly associated with increased risk of fracture in several clinical studies. The ADOPT trial reported increased fracture risk in women with T2D treated with rosiglitazone compared to women taking metformin or glyburide (cumulative incidence of fractures was 15.1% with rosiglitazone vs 7.3% with metformin and 7.7% with glyburide) (40). Interestingly, in this study, men did not experience different fracture rates in the three treatment groups. The RECORD follow-up study reported that treatment of patients with T2D with a combination of metformin (M) + sulfonylurea (SU) demonstrated decreased fracture occurrence (6.8%), compared to rosiglitazone (R) (10.7%) (219). Fracture occurrence was more frequent in women (M + SU = 8.5% vs. R = 14.5%), compared with men (M + SU = 5.2% vs. R = 7.2%) (219). These findings have been confirmed in a meta-analysis involving patients with T2D treated with pioglitazone or rosiglitazone. All studies showed an overall increased risk of fractures with TZDs and half of them showed an increased risk in women with T2D (double risk of fracture), but not in men (220). A more recent meta-analysis of 22 randomized clinical trials using pioglitazone or rosiglitazone treatment for T2D patients (24,544 subjects) concluded that TZDs are associated with increased risk of fractures in women and that the fracture risk does not depend on age or duration of exposure to TZD (41). Other studies have also reported on increased risk, particularly in women treated with a TZD (220–223). Additionally, another study found that the fracture incidence in patients with T2D treated with a TZD was 39% higher compared to control patients, and that the risk was increased irrespective of gender after the age of 50 years (224). This risk was reported to be almost identical between rosiglitazone and pioglitazone (224). An increased prevalence of vertebral fractures was reported in male patients with T2D treated with TZD and metformin compared to metformin alone, supporting that men are also at risk of fractures when on TZDs (225). Other investigation supported the conclusion that fracture risk is independent of age and sex, with similar risk in both sexes (OR=2.5 for men, OR= 2.56 for women) (154). Few studies have found no increased risk of fractures with pioglitazone (226).

Based on the ACCORD Bone study, follow-up of female patients who had discontinued TZDs showed that fracture risk is reduced within 1–2 years of discontinuation (227). The increased fracture risk observed in patients with T2D treated with TZDs is likely multifactorial, and both the deleterious effects of diabetes on bone in combination with the exposure to a TZD contribute towards this increased risk. Although several studies have shown the negative effects of TZDs on bone even in healthy populations without diabetes (228) and in those with prediabetes (229), a study designed to treat women with impaired fasting glucose or impaired glucose tolerance testing with pioglitazone for 12 months showed that women treated with TZDs were found to have similar BMD and bone markers as the control group (230). This finding supports that pioglitazone alone might not be sufficient to cause bone loss, although BMD change, by itself, may not be an adequate marker for fracture risk in this population.

Conclusion: Review of the published clinical trials that have assessed TZDs and risk of fracture supports the concern that this class of medications, and especially rosiglitazone, is associated with a significantly higher risk of bone fracture compared to other available hypoglycemic agents. However, data indicate that pioglitazone may have fewer adverse effects on bone metabolism compared to rosiglitazone, and recent preclinical data suggest that lobeglitazone may avoid some of the TZD-associated skeletal concerns, although fracture data and long-term skeletal effects with lobeglitazone are still unavailable. Although achievement of glycemic control might be similar with TZDs as with other hypoglycemic agents, caution has been recommended in prescribing TZDs in populations at high risk for fracture (184), and specifically older women with T2D or other predisposing factors for osteoporosis.

Insulin Secretagogues

4. Sulfonylureas

Mechanism of Action: Glucose is the major trigger of insulin secretion in the pancreatic β-cell. The increase in glucose concentration is sensed by glucokinase (GCK), which initiates the glycolysis pathway, pyruvate synthesis and tricarboxylic acid (TCA) cycle reactions, finally resulting in ATP production. The increase in intracellular [ATP]/[ADP] ratio triggers, consecutively, closure of the ATP-sensitive potassium channels (KATP channels), membrane depolarization, opening of voltage-gated $Ca2^{+}$ channels, and ultimately $Ca2^{+}$-mediated activation of insulin exocytosis (231). KATP channels are hetero-octameric complexes composed of 2 tetrameric subunits: a SUR regulatory transmembrane subunit and a Kir6.*x* pore-forming subunit, which also contains an ATP-binding site for channel inhibition (232). Sulfonylureas (SUs) and meglitinides (glinides; GLDs) are oral hypoglycemic agents which bind to the regulatory SUR1 subunit of the β-cell KATP channel, resulting in channel closure, membrane depolarization and insulin release (233). Tolbutamide and gliclazide (a first and a second generation SU, respectively) block, specifically, KATP channels containing SUR1 subunits (present in the β-cell membrane) whereas glibenclamide and glimepiride (a second and a third generation SU respectively), along with repaglinide (GLD) block KATP channels containing both SUR1 and SUR2 subunits (cardiac, skeletal and smooth muscle) with different potencies (233, 234). The different affinities of SUs for different tissues at therapeutic doses relate to the differences in the adverse effects of these drugs in a specific tissue, *e.g.* the cardiovascular risk. Furthermore, variations in the composition of both SUR and Kir6.*x* subunits explain the differences between the electrophysiological and pharmacological properties of the KATP channels in different tissues. These variations in subunits are also observed in bone cells. For instance, human undifferentiated mesenchymal stem cells (MSC), the precursors of mesodermal cell types (i.e. osteoblasts, adipocytes, chondrocytes) express KATP channels containing Kir6.1, Kir6.2 and SUR2A subunits (235). However, upon osteogenic differentiation, Kir6.2 subunit expression increases significantly at both the mRNA and protein level, while no changes are observed in the other subunits (235). KATP channels have been identified in adult bone cells, including: primary rat osteoblasts (236); human periodontal ligament cells (237); as well as in human osteoblasts-like MG-63 cells (238), suggesting that SUs may have direct effects on bone cell physiology.

Skeletal effects: In vitro: KATP channels appear to have different sensitivities to channel blockers such as SUs: they can be responsive to glipizide or glibenclamide, as was described in the MG-63 osteoblast cell line (238), or insensitive to glibenclamide (but sensitive to ATP) as shown in human primary periodontal ligament cells (237). This might be due to different SUR subunits assembling to various Kir6.x subunits in a tissue-specific manner, resulting in different types of KATP channels. In primary osteoblasts, inhibition of KATP channels with glibenclamide showed no effect on osteogenic gene expression (238).

Hyperglycemia has been shown to suppress the PI3K/Akt/eNOS pathway in rat osteoblasts, and therefore interfere with osteoblast transcription factors, such as RUNX2, critical for their differentiation and proliferation (239–241). In addition, hyperglycemia-induced Reactive Oxygen Species (ROS) formation contributes to adipogenesis and inhibition of PI3K/Akt-mediated osteogenic differentiation (242). In rat osteoblasts, glimepiride activates the PI3K/Akt pathway (239, 240, 243) inducing the proliferation and differentiation of these cells *in vitro*. In other studies, glimepiride (10μM) induced the tyrosine phosphorylation of IRS1/2, accumulation of activated PI3K and Akt phosphorylated at Ser 473, and enhanced both total eNOS and eNOS phorphorylated at Ser 1177, a downstream regulator of the PI3K/Akt pathway and a cell survival signal (243). The eNOS activation by glimepiride (but not glibenclamide) was also described in human endothelial cells (244) and a role for eNOS in the regulation of bone development and metabolism has also been suggested by Saura *et al.* (245). In the context of diabetic bone disease, glimepiride reverses the inhibitory effect of high glucose on the PI3K/Akt/eNOS pathway, enhancing the expression of RUNX2, osteocalcin and alkaline phosphatase mRNA and significantly increasing the differentiation capability of osteoblasts. Glimepiride was also reported to enhance bone formation by osteoblasts in a high glucose (16.5mM) microenvironment (239, 240).

Recently, it was reported that the activation of the NLRP3 inflammasome in human MSCs, a major pathway involved in β-cell failure and multiple complications of T2D, also impairs osteogenic differentiation and promotes adipocyte differentiation (246). Therefore, new SU molecules have been designed to target both the KATP channels and NLRP3 activation (247), opening the way for a new generation of sulfonylureas that could act on both the pancreatic β-cell and on bone.

Skeletal effects: In vivo: *In vitro* data indicate a potential beneficial role for SUs in bone metabolism; however, only limited data exist on the impact of this class of drugs on bone health in animal models. Experiments in ovariectomized rats have demonstrated that glimepiride (given once daily, for 28 days) inhibited the changes in BMD and bone remodeling caused by estrogen deficiency; this beneficial effect was also observed in non-ovariectomized rats, albeit to a lesser extent (248). Therefore it was suggested that glimepiride may reduce the development of osteoporosis in post-menopausal women.

Skeletal effects: Clinical investigation and fracture risk: The sulfonylureas (SUs) have been widely prescribed since 1950 and 3 generations of compounds have emerged since then, for use as monotherapy or in association with other anti-diabetic drugs, such as metformin or insulin. Most of the primary outcomes of the pioneering clinical trials for these molecules were focused on cardiovascular or all-cause mortality, hypoglycemic events or

reduction of HbA1c, compared with other hypoglycemic agents (*i.e.*, metformin, TZDs). Most initial studies were not designed to evaluate their impact on the risk of falls and subsequent bone fracture (249–251). However, regarding bone integrity, one recent very small (n=61 patients) prospective sub-study (LEAD-3) comparing liraglutide [1.8 (n=20) or 1.2 (n=23) mg/day) with the SU glimepiride (n=18; 8 mg/day), each as monotherapy, demonstrated that total BMD remained stable from baseline following 52 or 104 weeks of treatment with either of these medications (252).

The risk of fracture from SUs has, to date, predominately been associated with the risk of falls due to hypoglycemia (253–256) with SU therapy, and not to a direct effect of the drugs on bone remodeling (bone turnover markers) or integrity (*i.e.*, BMD) (252, 257). Because SUs increase both first and second phase insulin release by β-cells (in a glycaemia-independent manner), hypoglycemia is a known risk factor of the SUs. This side-effect, although rarely occurring as 'symptomatic' (258), is more likely to appear at the beginning of treatment, mainly with the long-acting SUs (glyburide, glibenclamide) rather than with the short-acting medications (gliclazide, glipizide, tolbutamide), at higher doses, after exercise or a missed meal, and in patients with a higher risk for hypoglycemia (259–261). A 4 year head-to-head study [EMPA-REG H2H-SU], conducted in T2D patients inadequately controlled on metformin alone (baseline HbA1c 7–10%), looked specifically at the relationship between hypoglycemia and fracture risk, comparing the SGLT2 inhibitor empagliflozin (25mg) vs. glimepiride (1–4mg), as add-on to metformin. Hypoglycemic events occurred in 28% of patients on glimepiride vs. only 3% on empagliflozin (262); however, bone fracture occurrence was similar across the groups (4.1% in empagliflozin group; 4.2% in glimepiride group) (263). In the ACCORD BONE study, intensive glycemic control with any SU was not associated with a higher risk of falls or fracture, in spite of more hypoglycemic episodes (264). Thus, a direct relationship amongst SU use, hypoglycemia, falls, and fractures has yet to be fully established.

Subpopulation-based cohort studies are inconsistent regarding the use of SUs and the risk of fracture. For instance, commercial health data providing ~4 year follow-up of persons treated with SUs (>13,000 patients, compared to age-matched non-users) demonstrated an increased risk of hip fracture (aOR 1.46, 95% CI 1.17–1.82), in both elderly men and women (>65 years old) (256). The risk of major osteoporotic fractures, including hip, spine, proximal humerus and distal radius, was also increased in a relatively young population with T2D (median age 52 years) receiving SU treatment over ~ 2.2 years of follow-up (265). In contrast, Vestergaard *et al* (91) reported a decreased risk of hip fractures in SU-treated Danish patients, while concomitant use of metformin and SUs was associated with decreased risk of any fracture (91). However, this study included a large number of subjects of variable age (43±27 years), with both T1D and T2D, and without adjustments for BMI or metabolic parameters. Exposure to SU use was also associated with decreased risk of vertebral fractures in postmenopausal Japanese women with T2D (90) but not with hip fracture incidence in a large cohort of Scottish population (155).

In other investigations, the skeletal effects of SUs have been compared to other anti-diabetic drug classes. The long-term clinical trial ADOPT was designed to compare the effects of rosiglitazone, glyburide, and metformin on glycemic control in patients with T2D. The study

confirmed that the TZD, rosiglitazone, produced more durable glycemic control than metformin or glyburide (measured by FPG and Hb1Ac), but also was associated with a doubling (9.3% of patients) of fracture occurrence in pre- and postmenopausal women even after only one year of therapy (40), compared to fracture occurrence with metformin and glyburide (5.1% and 3.5% of patients, respectively). The negative impact of rosiglitazone on bone in women was associated with increased bone resorption and osteoclast activity (CTX marker) (167); however, this circulating bone biomarker was significantly reduced by glyburide and metformin. Glyburide had the smallest effect on markers of osteoblast activity [P1NP and bone alkaline phosphatase (BAP)], in both women and men. Another randomized controlled trial, designed to compare the effects of one year treatment with gliclazide [modified release (MR); 73.3±25.7 mg] to a DPP-4 inhibitor (vidagliptin, 100 mg) on bone metabolism in 42 postmenopausal women with uncontrolled T2D, found no impact of the SU on bone formation (PINP, osteocalcin) or resorption (CTX, U-NTX) markers compared to baseline (257); in addition, gliclazide MR use did not affect lumbar spine, femoral neck or total hip BMD. Finally, a nested case-control study, examining any association between antidiabetic treatments (alone or in combination) in a “real-world” setting, demonstrated that the use of a SU combined with metformin modestly increased fracture risk compared to metformin alone; however, the causality for SU could not be established (89).

Conclusion: *In vitro* data suggest that SUs might directly impact bone *in vivo*. However, little preclinical data exists to explore this possibility. Overall, clinical studies of SUs in the setting of diabetes do not definitively establish this class of drugs as being harmful, or beneficial, in relationship to fracture risk. As monotherapy, SUs may have a neutral, if not beneficial, effect on bone health in patients with T2D. None-the-less, SUs have been associated with an increased risk of hypoglycemia, and related falls; coincidentally, they may predispose to fractures in specific populations. Consequently, for specific populations at higher risk for falls and/or fractures, such as the elderly and postmenopausal women, these pre-existing conditions are relevant when SU therapy is being considered for the management of T2D.

5. Meglitinides (Glinides)

Mechanism of Action: Glinides, including repaglinide and nateglinide, are a class of oral, meal-based medications intended for the control of post-prandial hyperglycemia. They stimulate insulin exocytosis by closure of the KATP channels of pancreatic β-cells, a mechanism of action they share with the SUs. Nateglinide binds the A-site on SUR1 subunit while repaglinide binds the B-site on both SUR1 and SUR2 subunits (234). In addition, glinides trigger intracellular Ca2+ release from the endoplasmic reticulum via ryanodine receptor activation, contributing to the enhancement of insulin secretion independently of KATP channel activity (266). However, long-term exposure to glinides (as well as to SUs) accelerates KATP channel dysfunction and pancreatic β-cell apoptosis and failure (‘secondary failure’) over time (267).

The glinides are rapid-onset and short-acting (T1/2 ~1 hour) insulinotropic drugs. They are prescribed in patients with significant post-prandial hyperglycemia (and are administered prior to meals), acting faster and with shorter duration than SUs and displaying less

propensity to elicit hypoglycemia (nateglinide < repaglinide) than SUs (268), except in patients with advanced chronic kidney disease, and in association with insulin (269) or in combination with TZDs (270).

Skeletal effects: In vitro: We have not identified any published information on the *in vitro* skeletal effects of the meglitinide class of anti-diabetic medications.

Skeletal effects: In vivo: The effects of repaglinide on fertility, on embryo- and fetogenesis and on peri- and postnatal development in rats were studied by Viertel *et al* (271). This study revealed skeletal changes in the extremities of the offspring when dams were exposed to repaglinide (30 and 80 mg/kg) during late pregnancy and/or lactation; these alterations included deformities of the scapula, of the proximal humeral epiphysis, and of the femur (271). However, these skeletal alterations appeared at very high plasma concentrations, outside of the concentration range reached with the human therapeutic dose.

Skeletal effects: Clinical investigation and fracture risk: By retrospective analysis of T2D patients in the Taiwanese National Health Insurance Claims Database from 2000–2010, an examination of bone fractures by medication category demonstrated that repaglinide (but not nateglinide), particularly when used in combination with TZDs, was shown to increase the risk of bone fracture, particularly in older female T2D patients between 65 and 74 years of age (aOR 1.83; 95% CI 1.19–2.79; adjusted for ESRD, stroke, osteoporosis) (272). Two other studies using repaglinide/troglitazone, specifically (273) or nateglinide/troglitazone, specifically (270) as combination therapy demonstrated better reduction in HbA1c in the combination groups compared to mono-therapy for both glinides. No bone fractures were reported as adverse events in these studies; however, treatment duration for these trials was ≤ 22 weeks.

Conclusion: Little scientific evidence is available regarding the effects of glinides on bone. Glinides seem to have a neutral effect on bone health, with low hypoglycemia and fracture risk, excepting repaglinide in combinations with TZDs, mostly in female patients over 65 years old. In addition, repaglinide can induce skeletal muscle atrophy and sarcopenia, as negative prognostic factors in the treatment of the diabetic aged-population (274).

Incretins

6. DPP4 Inhibitors

Mechanism of Action: Dipeptidyl peptidase-4 (DPP-4) is a peptidase that removes 2 amino acids (His-Ala) from the active glucagon-like peptide 1 [GLP-1 (7–37)] resulting in its bio-inactivation. The use of DPP-4 inhibitors, therefore, increases GLP-1 half-life and is an effective way to increase the endogenous effects of GLP-1 to enhance glucose-stimulated insulin secretion and to suppress glucagon secretion. Similarly, DPP-4 inhibitors enhance and promote the effects of glucose-dependent insulinotropic polypeptide (GIP), which also stimulates insulin secretion.

Current FDA-approved DPP-4 inhibitor medications include Sitagliptin (the first DPP-4 inhibitor to be approved for therapeutic use in T2D, approved in 2006), Saxagliptin (2009),

Linagliptin (2011) and Alogliptin (2013). Vildagliptin, a newer DPP-4 inhibitor marketed in the European Union, has been shown to increase the ability of both α and β cells to sense and respond to glucose and induce peripheral insulin sensitivity (275). DPP-4 inhibitors are effective and well tolerated when used as monotherapy, although when used in combination with other oral antidiabetic agents, such as metformin and sulfonylureas, their efficacy is improved (275, 276). Their mechanism of action on bone is still largely undiscovered but due to their effect on prolonging endogenous GLP-1 and GIP action, improved glucose tolerance and enhanced GLP-1 and GIP action on bone are two of the proposed mechanisms (277). GLP-1 has been shown to affect bone metabolism, specifically by promoting osteoblast proliferation and inhibiting osteoblast apoptosis in murine osteoblasts (278). GLP-1 has also been found to have indirect effects on inhibiting bone resorption by upregulation of calcitonin in mice (279). GIP has been shown to promote bone formation, partly through its direct action on osteoblasts where it improves collagen maturity (280) but also by inhibiting osteoblast apoptosis and by affecting calcium deposition in bone (281). Furthermore, GIP has been shown to inhibit the activity of mature osteoclasts (282). Moreover, a safety announcement by the US FDA was published regarding arthralgia reported with the use of DPP-4 inhibitors, introducing a potential musculoskeletal complication of mobility-limiting joint pain with these medications (283–285).

Skeletal effects: In vitro: A DPP-4 inhibitor, MK-0626, was shown to have no effect on osteoblast differentiation (286). Saxagliptin has been shown to inhibit *Runx2* and *Ocn* expression, as well as type-1 collagen production and mineralization, in bone marrow stromal cells from rats and in the MC3T3E1 cell-line (287). Sitagliptin reduced osteoclast-specific markers in murine macrophages and suppressed RANKL-mediated osteoclastogenesis (288).

Skeletal effects: In vivo: Animal studies comparing the effects of sitagliptin to a TZD have shown a protective or neutral effect of sitagliptin on the skeleton (202, 289, 290). Ambrosi *et al* reported that sitagliptin promotes bone healing by reducing adipocyte accumulation in the bone marrow (291). An attenuation of bone loss in diabetic rats along with lower CTX levels was also shown with sitagliptin treatment (290). Interestingly, pharmacologic reduction in DPP-4 showed an improvement in the bone phenotype of mice, whereas genetically induced reduction of DPP-4 (DPP-4 knockout mice) was not associated with such changes (289). Vildagliptin was also found to have beneficial effects on BMD and bone microacrchitecture (292) and has even been shown to restore bone changes induced by pioglitazone treatment in a type 2 diabetes animal model (293). Another DPP-4 inhibitor, MK-0626 had neutral effects on bone in a type 2 diabetes mouse model (286). Saxaglitpin, on the other hand, when administered to rats had a negative effect on osteoblast number and metaphyseal trabecular bone osteocytic density (287).

Skeletal effects: Clinical investigation and fracture risk: DPP-4 inhibitors have been mostly associated with either beneficial or neutral effects on the bone health of patients with diabetes (294, 295). A clinical trial involving patients with T2D did not show any changes in bone biomarkers after treatment with vildagliptin (296), whereas another trial reported lower alkaline phosphatase levels and urinary deoxypyridinoline, a urine marker of bone

resorption, in diabetic women treated with sitagliptin (170). Among 1536 participants of the Cardiovascular Health Study, a longitudinal study of community-based elderly adults, wherein approximately 10% of participants had a diagnosis of diabetes, DPP-4 plasma activity was not associated with individual BMD or with incident hip fractures (297). Vildagliptin had no effects on bone markers or BMD over a 12 month period of therapy in post-menopausal women with T2D (257), although effects on fracture risk were not an endpoint of this study.

Sitagliptin has *not* been associated with an increased risk of fracture based on published studies (265, 298) and a meta-analysis that included 27 trials evaluating sitagliptin use (299); however, a recent cohort study with 1578 participants concluded that sitagliptin use for longer than 250 days *was* associated with increased risk for fracture (aHR: 1.32) (300). The reason for these conflicting findings regarding sitagliptin therapy is unclear, but differences in compliance and duration of therapy, age, and glycemic control of subjects between these studies could account for some of the discrepancies.

Additionally, saxagliptin (as monotherapy or add-on therapy), in recent data from pooled analysis of 20 randomized control studies demonstrated a higher incidence of fracture with saxagliptin (301), a risk which was not, however, reported in the SAVOR-TIMI trial (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (302).

In support of a neutral effect of the DPP-4 inhibitors, two large meta-analyses, which included 51 and 62 clinical trials, reported no association between DPP-4 inhibitors and fractures in people with T2D (299, 303); this was followed by a recent cohort study confirming that there was no difference in fracture risk, compared to insulin or sulfonylurea amongst new users of DPP-4 inhibitors (304). Furthermore, Driessen *et al* evaluated long term use of DPP-4 inhibitors, and also concluded that there is no association between risk of fracture and DPP-4 use (305).

Conversely, a study in Germany showed a *decrease* in the risk of bone fracture with DPP-4 inhibitors *plus* metformin, when compared to metformin monotherapy (306) and a meta-analysis reported a beneficial reduction in risk of fractures with DPP-4 inhibitors compared to control or other treatments for type 2 diabetes (307); this reduction in fracture risk was specifically associated with alogliptin use when compared to control, linagliptin or saxagliptin in another meta-analysis (308). Finally, using a South Korean nationwide medical claims database for analysis of fracture risk by diabetes drug class, the combination of a DPP4 inhibitor, *added to* metformin had the lowest rate of fracture, compared with metformin alone vs. sulfonylurea alone vs. alpha-glucosidase inhibitor vs. metformin + sulfonylurea vs. metformin + TZD, and vs. sulfonylurea + TZD (309). These reported beneficial effects of DPP-4 inhibitors on bone, compared to those listed above showing no difference in fracture risk, could be attributed to small sample size of studies included in meta-analyses, a failure to fully identify incident fractures, or to concurrent use of other anti-hyperglycemic medications (i.e., metformin) that can independently affect risk for fracture by the majority of the participants.

Conclusion: DPP-4 inhibitors have been reported to have neutral or beneficial effects on bone by the majority of studies and have not been associated with increased risk of fracture, with the exception of sitagliptin and saxagliptin, for which contradictory clinical studies exist. Sitagliptin has been associated with greater therapeutic potential in bone metabolism compared to saxagliptin, based on pre-clinical data as it has been shown to promote bone formation, bone healing and suppress osteoclastogenesis in animal models (277). Clinical studies have shown that sitagliptin positively affects markers of bone turnover (170), but has a neutral or potentially harmful effect on fracture risk. On the other hand, saxagliptin has been shown to have negative effects on bone in both pre-clinical and clinical studies (277). Further prospective studies, designed specifically to evaluate fracture risk, are necessary to demonstrate the musculoskeletal safety of these drugs in persons with diabetes. Concerns regarding the risk for arthralgia with DPP-4 inhibitors should be taken into consideration when evaluating their effect on the musculoskeletal system and the underlying mechanisms and risk factors should also be evaluated in future studies.

7. GLP-1R agonists

Mechanism of Action: Incretin hormones have the ability to enhance insulin secretion in response to nutrient intake. GLP-1 receptor agonists slow down gastric emptying, suppress glucagon secretion and enhance glucose-induced insulin secretion. Glucagon-like peptide 1 Receptor agonists (GLP-1R agonists; or incretin mimetics) are widely used for the treatment of T2D and include exenatide (a synthetic form of exendin-4, which is found in the saliva of the Gila monster, *Heloderma suspectum*), liraglutide, lixisenatide, albiglutide, dulaglutide and semaglutide. Exenatide is 50% homologous to GLP-1; it exhibits a longer half-life ($t_{½}$ = 2.4 hours) than GLP-1 due to a difference in the second amino acid, which makes it resistant to degradation by DPP-4, without losing its biologic activity (275). Exenatide was approved by the US FDA in April of 2005 for treatment of T2D. Liraglutide is another GLP-1R agonist with delayed kidney clearance and considerably longer half-life compared to GLP-1 ($t_{½}$ = 11–13 hours) that has been approved for use in T2D. GLP-1 treatment has been associated with anabolic action on bone (294), and particularly, with increases in bone mass, improvement in the trabecular and cortical bone architecture, and enhancement of bone strength and is considered one of the most promising therapies for treating diabetes-associated bone disease (310). Although there are number of studies evaluating the potential effects of exenatide and liraglutide on the skeleton, there is very little data on the skeletal effects of the other GLP-1 agonists.

Skeletal effects: In vitro: GLP-1 receptors have been found on both human (311) and murine osteoblasts (312–314), suggesting a role for GLP-1 in bone formation. GLP-1 is considered to promote bone anabolism by stimulating osteoblast differentiation (315); activation of the GLP-1R by exendin-4 promotes the osteogenic differentiation of bone marrow stromal cells (316). *In vitro* studies have demonstrated that GLP-1 analogues lead to an increase of RUNX2 (317), alkaline phosphatase (317), collagen-1 (317) and osteocalcin expression in MC3T3 cells (278, 317) and most studies support that they promote proliferation and differentiation of these cells (317, 318). Liraglutide has also been shown to inhibit apoptosis of murine osteoblasts (319). A reduction in sclerostin in murine osteocytes and in diabetic rats treated with exendin-4 (312) suggests that an interaction between this

class of medications and the Wnt signaling pathway might be responsible for the bone promoting effects of GLP-1R agonists, a finding that has been suggested by other investigators (320). However, it is unclear whether the mechanism of action of GLP-1R agonists in murine bone is direct, or indirect, involving inhibition of bone resorption by calcitonin (279). The effects of GLP-1 on calcitonin secretion appear to be prominent in rodents as the concentration of the GLP-1R is higher in thyroid C cells from rodents compared to thyroid C cells from humans. In fact, human C cells have been shown to be less responsive to GLP-1-mediated calcitonin release (321).

Skeletal effects: In vivo: GLP-1R agonists have been shown to have anabolic effects on bone in animal models of T2D (322), T1D (323) and ovariectomized animal models without diabetes (324–326). Induction of RUNX2, alkaline phosphatase and collagen 1 expression as well as increased P1NP, alkaline phosphatase and osteocalcin serum levels (indicative of bone formation) have been reported with treatment with a GLP-1R agonist in ovariectomized rats (324). Both exenatide and liraglutide are associated with increases in bone mass, in both trabecular (313, 324–326) and cortical bone (325, 326). Additionally, CTX levels have been shown to decrease with GLP-1 analogue treatment in aged ovariectomized rats (324) and osteoclast number and surface area are increased in ovariectomized mice (313). Furthermore, GLP-1R knockout mice are characterized by reduced bone mass, with increased osteoclast numbers and bone resorption (279), whereas treatment of unloading-induced bone loss in rats with exendin-4 increases bone mass and bone quality (316) indicating a regulatory role of GLP-1 in bone resorption. Taken together, these findings support an overall beneficial impact of GLP-1R agonists on bone quality and microarchitecture.

Skeletal effects: Clinical investigation and fracture risk: There is no evidence currently to suggest that GLP-1R agonists are associated with increased fracture risk (183, 185, 294). Instead, similar to DPP-4 inhibitors, these agents are viewed as having beneficial or neutral effects on the skeleton of patients with diabetes.

Some data on bone biomarkers and/or BMD is available, although these findings would not directly predict fracture risk. Specifically, a recent, two-center, randomized, parallel-group clinical trial compared the effects of exenatide on BMD and bone turnover markers to insulin or pioglitazone treatment (n=62 newly diagnosed T2D patients) and did not find any improvement in either BMD or bone biomarkers after 24 weeks of treatment despite improvements in glycemic control (216). Similarly, exenatide did not affect BMD despite significant weight loss in a group of T2D patients, nor did it change alkaline phosphatase levels (327). Another study looking at the effects of liraglutide monotherapy (1.8 mg/day or 1.2 mg/day) compared with glimepiride (8 mg/day) on BMD of patients with T2D did not detect any differences in BMD change from baseline across treatment groups over 2 years of treatment (252). In comparison, liraglutide was shown to increase the bone formation marker P1NP, but in a group of weight-reduced obese, otherwise healthy (non-diabetic) women, while not affecting the bone resorption marker CTX-1 (328).

With respect to fracture risk, an early meta-analysis did not report an increased or decreased risk of fractures with GLP-1R agonists (329). This was followed by a meta-analysis

involving 14 randomized control trials that also did not provide any evidence of an effect on fracture risk (330). Liraglutide has been associated with decreased fracture risk (330) whereas exenatide with increased risk (330). This contrasts the findings by Zhang *et al*, who performed a meta-analysis including 57 clinical trials involving 49,602 participants of whom 28,353 were treated with exenatide, liraglutide, semaglutide, dulaglutide, albiglutide or lixisenatide (331). Comparators included GLP-1R agonists, other hypoglycemic drugs, or placebo. The authors concluded that exenatide was associated with a significantly lower risk for fracture compared to placebo and that other GLP-1R agonists showed a higher, but non-significant risk for fracture compared to exenatide and lower, but non-significant risk compared to placebo. Exenatide had higher probability of being the safest GLP-1R agonist with regard to the risk of fracture, followed by dulaglutide, liraglutide, albiglutide, lixisenatide, and semaglutide (331). Other studies have not found an association between GLP-1R agonists and fracture risk (332–334). These contradictory findings could be related to the difference in the number of trials included in the meta-analyses, different doses and duration of therapy with GLP-1R agonists and different analyses used to report comparisons between GLP-1R agonists. Additionally, recent studies have reported differences in the effects on the gastrointestinal and cardiovascular system with use of short-acting and long-acting GLP-1R agonists (335). Differential effects with the use of short-acting versus long-acting GLP-1R agonists on the musculoskeletal system could also be responsible for lack of consensus between studies.

Conclusion: Pre-clinical studies suggest that GLP-1R agonists are beneficial for the skeleton due to direct and indirect effects on bone. On the other hand, clinical studies have shown a neutral or weakly positive effect of exenatide and liraglutide on the human skeleton, making this category of medications an attractive therapy for patients with T2D. Due to the relatively short duration since the approval of this class of medications for use in patients with diabetes, additional studies are needed to identify any potential risks on bone fragility, including studies on lixisenatide, albiglutide, dulaglutide and semaglutide.

Glucosurics

8. SGLT2 Inhibitors

Mechanism of Action: Selective sodium-dependent glucose co-transporter 2 inhibitors (SGLT2Is) are one of the newest anti-hyperglycemic drug agents, with canagliflozin, dapagliflozin, empagliflozin and ertugliflozin currently FDA approved in the US. They exert glucose lowering effects by inhibiting renal glucose reabsorption and promoting glucosuria. Specifically, this class of drugs (“gliflozins”) inhibits the renal co-transport (i.e., reuptake) of glucose and sodium (Na^+) within the early proximal convoluted tubule, by blocking the SGLT2 co-transporter (336–340). In this way, enhanced glucose excretion leads to blood glucose lowering, through an insulin-independent mechanism. SGLT2Is are effective as monotherapy (341, 342), or as co-therapy, in combination with insulin (343, 344), or with a variety of oral hypoglycemic agents (345–348) in the treatment of T2D. Recent studies also suggest that SGLT2Is may be efficacious, as adjunct-to-insulin therapy, in the treatment of T1D (349, 350). In persons with T2D treated with SGLT2Is, net caloric loss attributable to glucosuria also contributes to a modest but beneficial weight loss (337, 339, 340). Additionally, cardiovascular risk reduction, including a reduction in cardiovascular death

and heart failure-related hospitalizations, has been documented in patients treated with empagliflozin and canagliflozin, increasing the appeal and utilization of this drug class in at-risk individuals (351, 352). Overall, these medications are considered highly efficacious in lowering glucose, particularly in T2D patients with normal renal function (12).

In conjunction with blockade of renal glucose reuptake, blockade of Na+ reuptake from the tubular lumen also results, which can alternatively be reabsorbed via the Sodium/Phosphate co-transporter; theoretically, the resulting secondary increase in serum phosphate concentration could induce a compensatory physiological increase in both parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23), to induce phosphaturia and maintain normal serum phosphorus concentration. Chronic glucosuria augmented by SGLT2I therapy could also contribute to diabetic hypercalciuria via osmotic diuresis (353–355). In total, blood glucose would decrease, but potentially accompanied by renal excretion of critical bone minerals. For this reason, both animal and human studies have investigated the possible impact of the “gliflozins” on skeletal heath. A comprehensive review of the effects of canagliflozin, specifically, on bone health in patients with T2D was published in 2016 (356).

Skeletal effects: In vitro and in vivo: Very little data has been reported, either by *in vitro* or pre-clinical *in vivo* investigation, on the *direct* effects of SGLT2-inhibitor drugs on bone cells or skeletal tissues. However, this is consistent with prevailing mechanistic concerns that any SGLT2I impact on skeletal health should occur from systemic metabolic or mineral dysregulation or restoration, rather than through cytotoxic or beneficial drug effects at the cellular level. In fact, the expression of SGLT2 and SGLT1 has been examined in a variety of bone cell types, including mouse calvarial osteoblasts, C3H10T½ mesenchymal stem cells, and MC3T3–E1 cells at various stage of differentiation, *in vitro* differentiated macrophages, and pre-osteoclasts as well as mature osteoclasts from mouse bone marrow. SGLT2 expression was not detected in cells of either the osteoblast or osteoclast lineages; SGLT1 was detected in MC3T3–E1 differentiating osteoblasts, albeit at levels < 1% of that observed in the kidney, but not in any cells of osteoclast lineage (357). Studies using radio-fluorinated labeling of dapagliflozin have also examined organ specific SGLT2-inhibitor binding in rat tissues and while skeletal binding was not assessed, no specific binding to skeletal muscle was observed (358). Similarly, mRNA expression of SGLT1 in muscle tissue of control and diabetic rats was found to be negligible (359). Taken together, these studies indicate that SGLT2-inhibitor drugs are unlikely to have a specific direct effect on musculoskeletal tissues at the cellular level.

When examined systemically, either pharmacologic or genetic inhibition of SGLT2 function appears to result in some disruption of bone mineral homeostasis in animal models. Theoretical mathematical modeling of Ca+ reabsorption in the renal proximal tubule predicts that SGLT2 blockade in the PT should contribute to hypercalciuria (360). Consistent with this concept, canagliflozin-treated diabetic mice (~10–20 mg/kg/day dose) exhibit persistently increased urine calcium excretion, along with increased serum FGF23 concentration, and biomarker evidence of bone resorption, despite a significant improvement in glycemic control compared with their untreated diabetic counterparts (357, 361). Increased urinary calcium excretion has also been reported in rats exposed to a supra-

physiological dose of canagliflozin (100 mg/kg/day) (362, 363), but this was jointly attributed to off-target effects, via SGLT1, to increase intestinal calcium absorption (362). The Sweet Pee mouse, however, which carries a nonsense mutation in the Slc5a2 gene resulting in genetic loss of SGLT2 protein function, also exhibits urinary calcium and magnesium wasting, along with growth retardation (364). In rats, again in toxicology studies, increases in serum phosphorus were also reported following supra-physiological exposure to empagliflozin (365).

Systemic effects of the SGLT2Is on bone mineral content have also been reported in animal models. Supra-physiological exposure to dapagliflozin at > 2000-fold MRHD resulted in trabecular bone accretion, and tissue mineralization, but again attributed to off-target effects to increase intestinal calcium absorption (366). In contrast, a 9-week study of the effects of ipragliflozin in the Goto-Kakizaki rat model of non-obese T2D found no change in bone mineral content compared with control mice although body fat mass was lowered by SGLT2I treatment (367).

Skeletal effects: Clinical investigation and fracture risk

Electrolyte vs. mineral abnormalities: Changes in serum electrolyte concentrations following SGLT2I exposure have been reported in a few publications, and a focused review of SGLT2I-induced electrolyte abnormalities, relative to cardiovascular health outcomes, has been published recently (368).

To more specifically evaluate serum bone mineral homeostasis, a single-blind, placebo-controlled, cross-over study conducted in 25 hospitalized patients, examining *short term* exposure to canagliflozin (300 mg/day for 5 days), demonstrated increases in serum phosphorus (+16%), plasma FGF23 (+20%), and PTH (+25%), while decreasing 1,25 $(OH)_2$ vitamin D (−10%) (369). Moreover, FGF23 and phosphorus levels were correlated (369). These data confirm an acute physiological impact of drug exposure (i.e. increased serum phosphorus, triggering downstream changes in other hormones), although physiological compensation to these acute changes could occur over time. To address the longer-term impact of SGLT2Is on serum electrolyte or bone mineral homeostasis, retrospective pooled dataset analysis from clinical trials has been conducted. Pooled data from placebo-controlled randomized controlled trials (RCTs) involving canagliflozin (NCT01081834, NCT01106625, NCT01106677, NCT01106690, NCT01032629, NCT01064414, NCT01106651) demonstrated small percentage increases in serum magnesium and phosphate in canagliflozin-treated patients compared with placebo (370). The newest FDA-approved SGLT2I, ertugliflozin, also appears to induce a small but significant increase in serum magnesium and phosphate concentrations, evident by 26 weeks of treatment and persistent at 52 weeks of treatment (371). Additional data provided by a meta-analysis of randomized controlled trials (including 18 RCTs with 15,309 patients, representing four SGLT2I drugs; canagliflozin, dapagliflozin, empagliflozin and ipragliflozin) found that all drugs significantly, but marginally, increased serum magnesium levels; additionally, magnesium changes with canagliflozin were dose-dependent (372). In this study, dapagliflozin alone increased serum phosphate concentrations, and none of these drugs significantly affected serum calcium (372). Consistent with the reported increase in serum

magnesium, a post-hoc analysis of 4 placebo-controlled RCTs (NCT01081834, NCT01106677, NCT01106625, NCT01106690) also found that hypomagnesemic T2D patients treated with canagliflozin experienced normalization of serum magnesium (373). In comparison, meta-analysis data specific to empagliflozin examining > 8500 T2D patients from 17 placebo-controlled Phase 1 to III trials plus 6 extension trials (study duration up to 104 weeks) found no significant change in serum calcium, phosphate, magnesium, or PTH, perhaps suggesting drug-specific differences in ultimate skeletal impact (374). Never-the-less, isolated case reports of severe mineral dysregulation (375) have prompted caution over the use of SGLT2I drugs in high-risk individuals. Taken together, clinical data generally confirm that SGLT2I medications are associated with small but reproducible increases in serum magnesium and phosphorus concentration, with the potential to induce pro-resorption secondary changes in PTH, and possibly FGF23, over time (368, 376).

Effects on BMD or bone turnover markers: The effects of SGLT2I exposure on changes in BMD or markers of bone turnover appear to differ between the various specific medications within this drug class. For example, in a multicenter, multinational, 26-week double-blind, placebo-controlled trial of canagliflozin in adults with T2D (which included a 78-week double-blind placebo-controlled extension), canagliflozin (100 mg vs. 300 mg daily) resulted in a small but significant decrease in total hip BMD at 104 weeks [−1.7% (100 mg) and −2.1% (300 mg) vs. −0.8% for placebo], but without BMD changes at the femoral neck, spine or radius (377). An increase in both osteocalcin, a marker of bone formation, and in CTX, a marker of bone resorption, suggested an increase in bone turnover, but attributed in part to treatment-related weight loss (377). Similarly, in a short duration, Phase 2b, 12 week, double-blind, study of canagliflozin (50 mg vs. 100 mg vs. 300 mg; once daily) given to overweight or obese subjects *without diabetes* (n=376 randomized), study participants achieved a 2.2–2.9% body weight reduction, again accompanied by a significant increase in CTX in the canagliflozin treatment groups. However, no change in bone formation markers (bone-specific alkaline phosphatase, osteocalcin, P1NP) or in urine N-telopeptides was observed. (378). In contrast, in adults with T2D inadequately controlled on metformin, dapagliflozin treatment (10 mg, once daily; NCT 00855166), whether analyzed at ~1 (379) or 2 years (337) of treatment, had no impact on bone biomarkers or on BMD. Also in patients with T2D, after 2 years of treatment empagliflozin exposure did not cause a significant change in alkaline phosphatase or urinary N-telopeptide compared with placebo (374, 380); and at 26 weeks of treatment ertugliflozin had no adverse effect on BMD (381).

Effects on Fracture: Early clinical investigation in T2D demonstrated a possible ~30% increase in bone fractures in patients receiving canagliflozin for a duration of 68 weeks (376); moreover, bone fractures were seen as early as 12 weeks after starting canagliflozin. Additionally, in patients with moderate renal impairment receiving dapagliflozin for 104 weeks, 7.7% of subjects experienced a bone fracture, compared with no fractures in the placebo group (382). In contrast, by cumulative meta-analyses of randomized controlled trials, along with systematic literature review, several later publications have subsequently demonstrated that the incidence of skeletal fracture, compared with placebo, does *not* appear to be increased across the currently available SGLT2 inhibitor drugs when used for the treatment of T2D (383–385). However, it is also recognized that the duration of treatment,

and duration of patient follow-up for most of these studies remains relatively short for evaluating any treatment-emergent effect on skeletal integrity and strength. Additionally, possible differences between individual medications within this drug class have been identified. Therefore, a discussion of available drug-specific findings is also included.

Canagliflozin: The increased incidence of fractures among T2D patients treated with canagliflozin has been reiterated by subsequent reports (356, 386, 387), but statistical analysis indicates that these findings were predominantly driven by the increase in fracture occurrence in one particular study (CANVAS, NCT01032629) of the CANVAS program of cardiovascular safety (including CANVAS and CANVAS-R, NCT01989754), in which the patients were older, had a prior history of cardiovascular diseases, and a higher use of concomitant diuretic therapy at baseline (386). Among these at-risk subjects, fractures were most common in distal extremities, perhaps mediated by falls related to volume-depletion (386). Additionally, the CANVAS trials demonstrated a ~2-fold greater risk of amputation with canagliflozin treatment (hazard ratio, 1.97; 95% CI, 1.41–2.75), occurring at the toe, metatarsal or leg (388), and most concerning for those with a history of peripheral vascular disease or neuropathy. In contrast, among eight other non-CANVAS comparator studies, pooled data did not signal an increase in fracture occurrence among canagliflozin-treated participants (386).

Dapagliflozin: As noted above, a study by Kohan, *et al* (NCT00663260) initially identified an increased fracture incidence among adults with T2D and moderate renal impairment, treated with dapagliflozin (5 mg or 10 mg) for 104 weeks (382). Specifically, 7.7% of dapagliflozin-treated subjects versus 0% of placebo-treated subjects experienced a fracture. However, all fractures occurred after trauma. Additionally, a greater incidence of hyperphosphatemia and PTH elevation was present in these patients with renal impairment; and, higher rates of peripheral neuropathy and orthostatic hypotension also existed, possibly contributing to fall risk (382). Together, these findings indicated that while fracture risk was increased, findings were again likely to be specific to the at-risk patient population studied in that trial.

In comparison, a randomized, double-blind, placebo-controlled trial of dapagliflozin (10 mg) treatment added to metformin in 140 adults with T2D (NCT00855166) found no change in fracture incidence or in BMD by DXA, after 102 weeks of treatment (337, 379). Similarly, a study of dapagliflozin (5 mg vs. 10 mg) given as add-on to insulin in Japanese patients with T2D (DAISY) reported no increased incidence of fracture after 52 weeks of treatment; additionally dapagliflozin was insulin-sparing (389). A population-based, open cohort study, using the Health Improvement Network (THIN), comparing 4548 T2D patients on dapagliflozin with 18,070 patients matched for age, sex, BMI, and diabetes duration, all on other standard-of-care diabetes drugs, also detected no increase in the primary outcome of fragility fracture, and no increase in any treatment-emergent fracture, even among patient at high risk for fracture (390). These findings were consistent with earlier data from a pooled safety analysis of 12 placebo-controlled Phase 2b/3 studies comparing dapagliflozin with placebo (encompassing 3281 participants); 1) as monotherapy; 2) as add-on therapy to other drugs; or 3) added to metformin; which also found no increase in fracture occurrence (391) with dapagliflozin. Finally, very recent data from the DERIVE study (NCT02413398),

following up on the findings of study NCT00663260 by comparing dapagliflozin (10 mg, for 24 weeks) versus placebo in patients with T2D and stage 3A chronic kidney disease reported no treatment emergent bone fractures or amputations in this population (392).

Empagliflozin: Pooled data from 15 phase 1–3 RCTs along with four extension trials, comparing Empagliflozin (10 or 25 mg) with placebo for the treatment of T2D, encompassing >4000 subjects per treatment group and > 15,000 combined patient-years of drug exposure, found no difference in the rates of fracture across treatment groups (374, 380).

Ertugliflozin: As yet, there are no published reports specifically comparing fracture risk among patients with T2D exposed to ertugliflozin. The VERTIS MONO clinical trial (NCT01958671) evaluating ertugliflozin monotherapy over 52 weeks (5 mg vs. 15 mg vs. placebo) in adults with T2D inadequately controlled on diet/exercise alone reported the occurrence of two adjudicated, non-serious hand fractures, both in the ertugliflozin 15 mg dose group, although the overall incidence of drug-related adverse events was otherwise similar across the treatment groups (371). However, the VERTIS SITA2 study (NCT02036515) again examining the efficacy of ertugliflozin (5 mg vs. 15 mg vs. placebo) in patients with T2D, but added to metformin and sitagliptin, reported one instance of adjudication-confirmed fracture in each of the 3 treatment groups (393). Despite a lack of association between ertugliflozin and either fracture or amputation risk, prescribing information provided by Merck & Co., Inc. for ertugliflozin (www.merck.com/product/usa/pi_circulars/s/steglatro/steglatro_pi.pdf) states that “Across seven Phase 3 clinical trials in the STEGLATRO® development program, non-traumatic lower limb amputations were reported in 1 (0.1%) patient in the comparator group, 3 (0.2%) patients in the STEGLATRO 5 mg group, and 8 (0.5%) patients in the STEGLATRO 15 mg group”, raising some concerns.

Conclusion: Exposure to most SGLT2I medications is associated with small but reproducible increases in serum magnesium and phosphorus concentrations, with the potential to induce pro-resorption secondary changes in PTH and FGF 23 secretion over time. Following 2 years of canagliflozin exposure, specifically, an increase in biomarkers of bone turnover has been reported, associated with a ~2% decrease in total hip BMD; however, these changes occurred in the context of beneficial weight loss, potentially confounding the interpretation of this data. Moreover, a relationship between these changes and fracture risk cannot be stated. However, among certain at-risk groups of T2D patients, including those with renal failure, cardiovascular disease, peripheral vascular diseases or neuropathy, specific SGLT2I medications may be associated with an increased risk for fracture or lower limb amputation, prompting caution in the use of SGLT2I drugs when these co-morbidities exist.

Glucose Uptake Inhibitors

9. Alpha glucosidase Inhibitors

Mechanism of Action: Membrane-bound alpha-glucoside hydrolase enzymes function in the intestinal brush border to hydrolyze oligosaccharides, trisaccharides and disaccharides to

glucose and other monosaccharides. Alpha-glucosidase inhibitors (α-GI) are reversible, competitive inhibitors of this enzyme, found in polyphenol extracts from medicinal plants, and initially manufactured in the early-mid 1990's as anti-diabetic pharmaceuticals. Physiological action of this drug class occurs by inhibiting the breakdown of these complex carbohydrates in the small intestine, thereby delaying glucose absorption from the gut, and mitigating the expected rise in blood glucose following a meal (394). These oral medications include acarbose (Precose®) and miglitol (Glyset®), currently FDA-approved in the US for treatment of adults with T2D. Because these drugs were considered of more modest efficacy for the treatment of T2D, their use has been less widespread and more recently intended as add-on therapy (11).

Skeletal effects: In vitro; In vivo; Clinical investigation and Fracture risk: The unique, non-insulinotropic mechanism of action of this drug class is to reduce blood glucose rise without stimulation of insulin synthesis (395). Despite a more than 20 year worldwide experience in the treatment of T2D, very little, if any, information is reported concerning specific effects of alpha-glucosidase inhibitors on skeletal health, beyond the generally anticipated beneficial impact of improved glucose control. To date, there are no reports of increased fracture risk or skeletal adverse events, either in early, extended-duration clinical trials (396–398), or in later post-marketing surveillance reports of α-GI drugs (399, 400). Moreover, when similar alpha-glucosidase inhibitory plant phenol extracts have been investigated in rodent models, we could not identify reports of skeletal toxicity or skeletal malformation in these preclinical studies (401). A more recent study utilizing the Goto-Kakizaki (GK) rat model of T2D found that treatment with voglibose, one of the newest α-GI drugs (approved for use in Asia), was insufficient to reverse the negative effects of diabetes on osteo-integration of dental implants (402). From this study, the authors inferred a detrimental effect of α-GI treatment on bone repair, although incomplete glycemic control could also account for their findings (402). Considering the longevity of this drug class, it is reasonable to assume that post-marketing surveillance would identify a serious musculoskeletal safety concern, although teasing out a class-specific contribution from these drugs could be difficult, considering that they are used less often and typically only in select multi-component therapy.

Conclusion: At present, there is little information available as to either the musculoskeletal benefit or harm from alpha glucosidase inhibitors.

Amylin Mimetics

10. Pramlintide

Mechanism of Action: Amylin (or islet amyloid polypeptide, IAPP) (403) is a pancreatic β-cell hormone that is co-localized and co-secreted with insulin, in response to food intake; as such, it acts synergistically with insulin to regulate blood glucose. In parallel with β-cell insulin status, amylin deficiency is characteristic of T1D and later stage T2D, whereas amylin excess is characteristic of hyperinsulinemic states such as obesity, prediabetes and early onset T2D. Pramlintide, a stable synthetic amylin analog with pharmacologic properties similar to the native peptide, was manufactured by introducing proline substitutions at positions 25, 26 and 29 of the amylin molecule, creating a non-

amyloidogenic analog. It was FDA approved in 2005, and is effective for adjuvant glucose-lowering treatment of both T1D (404) and T2D (405, 406), so as to restore amylin sufficiency. As an amylin mimetic, its mechanism of action is intended to reproduce the primary physiological actions of amylin, specifically to delay gastric emptying, suppress nutrient-stimulated glucagon secretion from islet α-cells and, via neuroendocrine effects, to promote satiety.

Interestingly, amylin is evolutionarily related to members of the calcitonin gene peptide superfamily, which includes calcitonin (CT) and calcitonin-gene related peptide (CGRP) (407). Amylin shares 20% amino acid sequence homology with CT, and mediates its effects through activation of amylin receptors (AMY_1, AMY_2, AMY_3) which are comprised of the CT receptor coupled to 1 of 3 receptor activity-modifying proteins ($RAMP_1$, $RAMP_2$, $RAMP_3$, respectively) which modify ligand affinity for the receptor. Similar to CT, amylin itself is a regulator of bone metabolism, although exhibiting a less potent inhibition of osteoclast activity. And, like amylin, pramlintide has been shown to activate not only the amylin receptors, but also the CT receptor, albeit with reduced potency (403, 408). Teleologically, the post-prandial co-secretion of amylin and insulin may, in fact, be coordinated so as to promote bone growth and mineral deposition, in concert with meal-based nutrient absorption.

Skeletal effects: In vitro; In vivo; Clinical investigation and Fracture risk: Effects of the native amylin hormone on bone physiology have been investigated; in contrast, very little is known about the skeletal effects of the pharmaceutical analog, pramlintide. Therefore, musculoskeletal effects of this drug class in diabetes, for the most part, can only be inferred from the native protein.

The anabolic potential of amylin has been demonstrated both *in vitro* and *in vivo*. Amylin stimulates osteoblast proliferation in rodent osteoblasts (409, 410), and increases cell proliferation and osteocalcin production in human primary osteoblast cultures (411). *In vivo*, animal studies further confirm that either local administration or systemic administration of full length amylin protein, or of fragment octapeptide (AMY 1–8), results in augmentation of bone volume [increased trabecular bone volume (Tb.BV), trabecular number (Tb.N), trabecular thickness (Tb.Th)], bone length and cortical thickness (Ct.Th), promotes an increase in bone formation indices, and improves bone strength (412–416). Together, an overall increase in bone mass and linear bone growth results from amylin exposure.

At the same time, amylin inhibits osteoclastic bone resorption and/or lowers plasma calcium as demonstrated in mice, rats and rabbits (417, 418). In rats specifically, an amylin-induced decrease in osteoclast surface (OcS/BS) and erosion surface (ES/BS) has been illustrated by dynamic histomorphometry (415). In humans, similar to CT, amylin also exhibits both hypocalcemic and osteoclast inhibitory properties (419, 420), although at a much reduced potency. As would be consistent with these anti-resorption effects, mice with targeted deletion of the amylin gene exhibit low bone mass, attributable to chronically unrestricted bone resorption (421, 422). Additionally, daily amylin treatment has been shown to inhibit ovariectomy-induced trabecular bone loss in rats, again by inhibiting bone resorption (423).

In preclinical investigation, somewhat conflicting results have been reported from studies examining the effects of amylin replacement on diabetic bone loss specifically. In streptozotocin (STZ)-induced diabetic Wistar rats (a model of T1D), 40 daily injections of amylin (1000 pmol/kg/day) resulted in improved bone strength and bone density to levels indistinguishable from nondiabetic control rats (424). Similarly, in a Wistar rat model of T2D, amylin treatment for only 3 days via continuous infusion (720 pmol/kg/day) resulted in an increase in osteoblast number and osteocalcin mRNA expression in long bones (415). However, in a study of STZ-induced diabetic Sprague-Dawley rats, 19 daily injections of amylin (45 ug/kg/day) did not rectify the low-turnover osteopenia which was characteristic of diabetic animals (425), but perhaps due to the supra-physiological, 1000-fold difference in treatment dose used in this study.

Altogether, the combination of generally pro-osteogenic and anti-resorptive effects of amylin infers that pramlintide might be similarly advantageous in diabetic bone disease. However, only one study has directly examined the skeletal effects of pramlintide therapy in humans. In a study of 23 non-osteoporotic T1D patients (mean age ~45 years; mean duration of T1D ~21 years), 12 months of treatment with pramlintide, as 4 injections per day, did not impart a significant change in BMD, or in bone biomarkers (calcium, PTH, osteocalcin, pyridinium cross-links) after 1 year (426). However, because these subjects were not osteoporotic at baseline, the implication of these findings may be limited; moreover, they do not provide any evidence of the impact of pramlintide on fracture risk, specifically.

Conclusion: At present, there is little information available as to either the musculoskeletal benefit or harm from amylin mimetics.

DRUGS AND MUSCLE

Overview

Diabetes mellitus is associated with muscle loss and atrophy, particularly in older individuals where age-related sarcopenia is also often observed (274, 427–431). Rodent models of type 1 diabetes and some rodent models of type 2 diabetes (db/db mice) are characterized by muscle atrophy and impaired muscle function (432). Muscle atrophy, weakness and functional impairment have also been documented in humans with T1D (429, 433–437) and T2D (430, 431, 433). Decreased physical activity or disability, aging, obesity, hyperglycemia, oxidative stress, mitochondrial dysfunction, inflammation, reduced insulin/IGF-1 signaling, and diabetic neuropathy are only some of the proposed mechanisms that contribute to diabetes-associated muscle wasting (274, 429, 433, 438). Skeletal muscle is considered the major site for insulin-mediated glucose disposal and energy metabolism. Therefore, its role in glucose homeostasis is crucial. Muscle wasting can exacerbate insulin resistance, which in turn can lead to further muscle loss (439). In addition to insulin, several anti-hyperglycemic medications act on skeletal muscle and, therefore, could affect diabetes-induced muscle loss.

Diabetic pharmacotherapy: effects on skeletal muscle

Insulin—Insulin is imperative for skeletal muscle metabolism. Several studies have shown that insulin promotes protein synthesis (440, 441), attenuates protein break-down (441–443), and improves mitochondrial capacity in skeletal muscle (444). Insulin resistance or insulin deficiency is associated with muscle wasting, partly due to increased protein degradation (445, 446). In an animal model of type 1 diabetes (90% partial pancreatectomy) impaired muscle growth and function was observed, secondary to impaired protein synthesis in Type II (fast twitch) fibers (447). Insulin withdrawal in insulin-deficient rats resulted in a decrease in protein synthesis and increase in protein degradation (448), while STZ-induced insulinopenia in mice resulted in an increase in protein degradation and decreased muscle mass (449), supporting the critical role of insulin in protein homeostasis.

Although in humans with T1D, inhibition of protein breakdown is observed with insulin treatment (446), protein synthesis is not consistently achieved with insulin administration (450, 451), and a relative resistance to the action of insulin has been observed (452, 453) affecting glucose, protein metabolism and mitochondrial function. In a study evaluating body composition in persons with T1D, only a small increase in lean body mass was observed during the first year of insulin therapy (454). However, another study comparing changes in body composition of newly diagnosed diabetic patients on insulin therapy revealed a significant increase in lean mass in patients with T1D within 6 months of treatment (455). Furthermore, patients with T1D assigned to intensive insulin therapy were noted to have greater weight gain and muscle mass compared to those on conventional therapy (456). These studies support that insulin is imperative for skeletal muscle mass and metabolism; some of the benefits on skeletal muscle associated with insulin therapy are likely indirect, due to insulin’s effect on glycemic control.

In humans with T2D, greater muscle mass due to larger body size may exist, compared to healthy adults; however, their muscle performance is negatively affected (457). Also, with age, muscle wasting in patients with T2D is evident (431). In certain animal models of type 2 diabetes, such as the db/db mice, decreased exercise capacity and muscle weight have been observed; however, other models of type 2 diabetes, such as the TallyHo mice, do not exhibit muscle atrophy and loss of muscle function (458). This indicates that additional factors to hyperglycemia and insulin resistance are necessary for muscle loss in T2D. In a rat model of type 2 diabetes, insulin therapy was shown to improve lean mass (459); however, in humans with T2D, insulin therapy is considered to be ineffective for improving muscle mitochondrial function (460), increasing protein synthesis (461), reversing skeletal muscle proteolysis (462) or improving muscle strength (463). Furthermore, insulin therapy in patients with newly diagnosed T2D was not associated with skeletal muscle gain (455, 464) contrary to patients with T1D (455). A study looking at skeletal muscle index (the ratio of appendicular muscle mass to total body weight, expressed as a percentage value) in T2D subjects treated with: oral hypoglycemic agents alone; insulin alone; or a combination of both; found higher skeletal muscle index in older patients (≥65 years) receiving insulin. Interestingly, the same study reported that endogenous insulin secretion, measured by stimulated C-peptide immunoreactivity, was negatively correlated with skeletal muscle index in T2D patients (465).

Future studies are needed to identify the risk factors associated with insulin resistance that predispose to muscle atrophy and dysfunction. The contribution of insulin therapy towards improvement in muscle mass and function is more evident in patients with T1D, whereas in patients with T2D, insulin therapy's benefits on skeletal muscle are not as promising due to insulin resistance.

Biguanides—Metformin activates AMPK, resulting in inhibition of protein and lipid synthesis and increased fatty acid oxidation and glucose uptake (466). Recent data suggests that skeletal muscle repair may be improved when AMPK is activated (467). Metformin has been proven beneficial for protein metabolism in a cachexia model of tumor-bearing rats (468). Metformin has also been shown to improve mitochondrial function in skeletal muscle (466) and induce irisin release, an exercise-induced myokine, with beneficial effects in adipose tissue metabolism in mice (469). A few clinical studies have shown effects of metformin in muscle morphology and muscle function. Muscle mass loss was significantly reduced in older diabetic men on insulin sensitizer therapy, with either metformin or TZD (470), while in another group of newly diagnosed patients with T2D, the skeletal muscle index was improved in men, but not in women, after 24 weeks of metformin treatment (471). Results from another study showed that the lipid content of vastus lateralis muscle in T2D patients was decreased with metformin therapy, although this decrease was not associated with improvement in the glucose-disposal rate (472). Another recent study from Indonesia reported improvement in gait speed but not grip strength in elderly patients treated with 1500 mg/day of metformin (473).

Although most of the studies have proposed that metformin is beneficial for muscle function, recent studies that have evaluated the effects of metformin on aerobic capacity have found a reduction in aerobic capacity with metformin treatment (474, 475), suggesting that metformin might be attenuating exercise-induced benefits on insulin sensitivity and cardio-metabolic health (476). Another study, however, noted that there was no metformin-mediated attenuation of exercise benefits on glycemic control (477).

Potential side effects of metformin involving the musculoskeletal system include myalgia and muscle weakness. Ongoing studies are evaluating the effects of metformin on muscle mass and physical performance in insulin resistant and older individuals (NCT01804049, NCT02308228).

Thiazolidinediones—Activation of PPARγ in muscle has proven to be protective against insulin resistance (478). TZDs in mice have shown promising results against muscle wasting. Rosiglitazone has been shown to reduce proteolysis and muscle atrophy in db/db mice by decreasing caspase-3 and proteasome activity (445) and decreasing cachexia markers, Atrogin-1 and Muscle RING-finger protein-1 (MuRF-1), in the skeletal muscle of mice with cancer cachexia (479). Pioglitazone was shown to suppress oxidative stress and inflammation in skeletal muscle of mice with spinal and bulbar muscular atrophy (480).

In patients with T2D, pioglitazone and troglitazone were found to improve myocellular lipid metabolism (472, 481, 482), without any changes in mitochondrial function in skeletal muscle (472, 481). In contrast, another study of subjects with T2D showed increased or

decreased mitochondrial respiration of skeletal muscle with pioglitazone or rosiglitazone, respectively (483). Additionally, pioglitazone treatment was shown to improve markers of inflammation in skeletal muscle of patients with PCOS (484). However, pioglitazone did not prevent skeletal muscle loss when compared to resistance training in a group of older, non-diabetic overweight or obese subjects enrolled in a hypocaloric weight-loss program (485). Evaluation of the transcriptome of skeletal muscle of subjects with impaired glucose tolerance on pioglitazone therapy did not reveal any metabolic pathways that were modulated by pioglitazone (486). TZDs appear to be relatively safe and although acute rhabdomyolysis after pioglitazone use has been reported (487), other skeletal muscle-related adverse events appear to be uncommon with TZD use (488). The majority of the studies support a positive or neutral effect of TZDs on skeletal muscle, however additional studies are required to confirm these effects, particularly in the diabetic population.

Sulfonylureas and Meglitinides—Sulfonylureas act on the plasma membrane KATP channel of different tissues causing changes in potassium intracellular flow. They have direct effects on muscle, affecting glucose uptake, glycogen synthase activity (489), protein degradation (490) and mitochondrial function in skeletal muscle (491, 492). Gliclazide can improve skeletal muscle glucose uptake and this effect appears to be mediated by action on the KATP channel (493) and associated with an increase in GLUT-1 membrane content and either no change (494, 495) or an increase (496) in the GLUT-4 expression and content in skeletal muscle. Recent studies suggest that sulfonylureas and glinides can induce muscle atrophy; reduced muscle protein content/muscle weight as well as reduced muscle fiber diameter was shown with sulfonylurea and glinide treatment in mice (497). Glibenclamide/glyburide, but not other sulfonylureas, has been associated with muscle atrophy in humans, based on reports in the FDA-Adverse Effects Reporting System (AERS) database over an observation period of 8 months (497). The underlying suggested mechanisms for muscle atrophy appear to be hypoglycemia and/or KATP channel blocking (497). Interestingly, glibenclamide has been shown to increase tension in fatigued slow muscle in mice (498) and in chickens (499) supporting a direct effect of sulfonylureas on the KATP channels of skeletal muscle.

Sulfonylurea and glinide use is rarely associated with skeletal muscle-related adverse events.

Incretins—Animal studies of GLP-1R agonists have shown beneficial effects on skeletal muscle, partly due to their insulin-like effects on glucose utilization in skeletal muscle (500). GLP-1 has been shown to increase glucose uptake in skeletal muscle (501, 502), an effect that is mediated by nitric oxide (501). Exendin-4 has been shown to enhance glucose transport in skeletal muscle of diabetic rats (502) and both exenatide and liraglutide promote glucose uptake in skeletal muscle through AMPK activation (503). Exendin-4 increases glycogen synthase activity and glucose incorporation into glycogen and stimulates glucose utilization and oxidation in muscle (504). Other effects are suggestive of glucose-independent effects of GLP-1R agonists on muscle. Colin *et al* showed that myocytes from obese, nondiabetic Zucker rates were significantly enlarged and depleted of lipid droplets with exendin-4 treatment, secondary to modulation of oxidative stress (505); Takada *et al* showed improved mitochondrial function and exercise capacity in mice receiving exendin-4

(506). Exenatide was reported to prevent sarcoma-induced cachexia in a mouse model (507), while liraglutide was shown to improve skeletal muscle capillary density in an animal model of insulin resistance, indicating a protective role against metabolic insulin resistance at the skeletal muscle level (508). Exenatide has also been shown to increase irisin, a myokine that is commonly induced by exercise, in patients with T2D (509). Furthermore, in a clinical study, liraglutide was associated with an increase in the skeletal muscle index in overweight and obese patients with T2D (510). Despite these positive reported actions of GLP-1R agonists on skeletal muscle, a very recent study from Japan evaluating changes in body composition of patients with T2D on hemodialysis showed decreases in skeletal muscle mass with six months of dulaglutide therapy, compared to teneligliptin therapy, raising some concern about dulaglutide-induced muscle loss (511).

Sitagliptin has been shown to increase GLUT-4 expression in skeletal muscle of type 2 diabetic rats (512) and hypertensive rats (513). MK-0626, a DPP-4 inhibitor was associated with improvements in mitochondrial biogenesis in skeletal muscle and improvement in exercise capacity of mice who had suffered recent myocardial infarction (506). In another study, the effects of linagliptin on an animal model of premature aging supported a positive role in preventing muscle loss, based on the larger size of the gastrocnemius muscle in linagliptin-treated mice compared to control (514). Teneligliptin, when compared to a GLP-1R agonist did not appear to have negative effects on skeletal muscle mass of patients with T2D on dialysis (511). However, with the recent increase in DPP-4 inhibitor use, there have been reports of this class of medications causing myalgia, extremity pain, muscle weakness and other musculoskeletal adverse events, such as arthralgia (284, 285, 515). Proposed mechanisms for these adverse events include a change in pain threshold or DPP4 inhibition in skeletal muscle (284). Additionally, case reports have been published describing that sitagliptin, when combined with a statin, is associated with rhabdomyolysis (516–518). Further studies are required to elucidate the underlying mechanisms and risk factors for these adverse events. Interestingly, acute toxicity associated with skeletal muscle necrosis has been reported with vildagliptin administration in monkeys, although the authors of this study reported that this is a monkey-specific phenomenon, with no relevance to humans (519).

SGLT2 inhibitors—Little is known about the effects of SGLT2Is on skeletal muscle. SGLT2Is have been shown to increase skeletal muscle glucose uptake (520) and reduce insulin resistance at the skeletal muscle (521). In an animal model of high fat, diet-induced obesity, canagliflozin was shown to induce expression of IGF-1, protect against muscle mass loss, and restore the contractile force of muscle (522), suggestive of a protective role for SGLT2Is on skeletal muscle. These findings have not been confirmed in humans. Contrary to the previously mentioned animal studies, a clinical trial in Japan showed a small but significant reduction in the skeletal muscle index with ipragliflozin (523) which was confirmed in a very recent clinical trial evaluating the effects of ipragliflozin compared to sitagliptin (524) on different metabolic variables in patients with T2D. Conversely, no changes in muscle mass were seen with dapagliflozin in patients with T2D (525). Adverse events, including musculoskeletal pain have been reported with ertugliflozin therapy, (526) but the underlying mechanisms for these events are not known. The data on the SGLT2I-

mediated effects on skeletal muscle are scarce and further studies are needed to reach conclusions regarding their direct action(s) on skeletal muscle.

Glucosidase Inhibitors—Acarbose's effects on skeletal muscle have been studied in genetically obese Zucker rats, a model of insulin resistance. Acarbose was found to induce GLUT-4 trafficking by inducing Akt activation in skeletal muscle (527). In a clinical study evaluating lipid deposition in skeletal muscle in individuals with metabolic syndrome, no changes in lipid metabolism in the muscle were observed with miglitol therapy (528). No adverse events of glucosidase inhibitors on skeletal muscle have been reported.

Amylin Mimetics—Amylin has been reported to decrease glycogen storage in skeletal muscle of rodents. A study evaluating the effects of the human amylin analog AC137 showed increased lactate release from skeletal muscle under hypoglycemic conditions in T1D patients (529). No other reports of amylin mimetic effects on skeletal muscle were found.

Conclusions—Skeletal muscle is negatively affected in diabetes due to multiple factors, and evaluating these factors in an environment of insulin resistance and/or deficiency is critical. There is an unmet need for studies assessing muscle morphology and function in diabetes, and for clinical trials focused on the anti-diabetic therapies and their role in preventing diabetes-associated muscle impairment.

FUTURE DIRECTIONS AND CONSIDERATIONS

In the future, as more pharmaceuticals become available to treat diabetes, and as combination therapy becomes more common practice for both T1D and T2D, the potential for these newer approaches in diabetes management to impact musculoskeletal health will require careful and ongoing evaluation. As an endpoint for fracture risk assessment, it is acknowledged that BMD measurement is not adequate, and other integrative determinations will be needed. At least, in instances in which an individual with diabetes has a history of fracture, a choice of treatment options should require the clinician to consider using medications with the least risk to musculoskeletal well-being. Finally, because a number of pharmaceuticals have been developed that have been shown to impact the musculoskeletal system, it is incumbent that clinicians be well informed about the association of diabetes with increased fracture risk and muscle atrophy, and that they recognize that certain anti-diabetes medications can predispose to musculoskeletal co-morbidities in those with diabetes, despite improving their glycemic control.

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REFERENCES

1. Hu C, Jia W. Diabetes in China: Epidemiology and Genetic Risk Factors and Their Clinical Utility in Personalized Medication. Diabetes. 2018;67(1):3–11. [PubMed: 29263166]
2. Alotaibi A, Perry L, Gholizadeh L, Al-Ganmi A. Incidence and prevalence rates of diabetes mellitus in Saudi Arabia: An overview. Journal of epidemiology and global health. 2017;7(4):211–8. [PubMed: 29110860]
3. Vehik K, Hamman RF, Lezotte D, Norris JM, Klingensmith G, Bloch C, et al. Increasing incidence of type 1 diabetes in 0- to 17-year-old Colorado youth. Diabetes care. 2007;30(3):503–9. [PubMed: 17327312]
4. Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G, Group ES. Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005–20: a multicentre prospective registration study. Lancet. 2009;373(9680):2027–33. [PubMed: 19481249]
5. Lawrence JM, Imperatore G, Dabelea D, Mayer-Davis EJ, Linder B, Saydah S, et al. Trends in incidence of type 1 diabetes among non-Hispanic white youth in the U.S., 2002–2009. Diabetes. 2014;63(11):3938–45. [PubMed: 24898146]
6. Bello-Chavolla OY, Rojas-Martinez R, Aguilar-Salinas CA, Hernandez-Avila M. Epidemiology of diabetes mellitus in Mexico. Nutrition reviews. 2017;75(suppl 1):4–12. [PubMed: 28049745]
7. Herman WH. The global agenda for the prevention of type 2 diabetes. Nutrition reviews. 2017;75(suppl 1):13–8. [PubMed: 28049746]
8. National Diabetes Statistics Report, 2017: Estimates of Diabetes and its burden in the United States.
9. IDF Diabetes Atlas - 8th Edition.
10. American Diabetes A. Economic Costs of Diabetes in the U.S. in 2017. Diabetes care. 2018;41(5): 917–28. [PubMed: 29567642]
11. American Diabetes A. 8. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2018. Diabetes care. 2018;41(Suppl 1):S73–S85. [PubMed: 29222379]
12. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2018.
13. International Osteoporosis Foundation - Facts and Statistics.
14. Ballane G, Cauley JA, Luckey MM, El-Hajj Fuleihan G. Worldwide prevalence and incidence of osteoporotic vertebral fractures. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2017;28(5):1531–42.
15. Court-Brown CM, Clement ND, Duckworth AD, Biant LC, McQueen MM. The changing epidemiology of fall-related fractures in adults. Injury. 2017;48(4):819–24. [PubMed: 28283181]
16. Thrailkill KM, Lumpkin CK, Jr., Bunn RC, Kemp SF, Fowlkes JL. Is insulin an anabolic agent in bone? Dissecting the diabetic bone for clues. American journal of physiology Endocrinology and metabolism. 2005;289(5):E735–45. [PubMed: 16215165]
17. Sellmeyer DE, Civitelli R, Hofbauer LC, Khosla S, Lecka-Czernik B, Schwartz AV. Skeletal Metabolism, Fracture Risk, and Fracture Outcomes in Type 1 and Type 2 Diabetes. Diabetes. 2016;65(7):1757–66. [PubMed: 27329951]
18. Weber DR, Haynes K, Leonard MB, Willi SM, Denburg MR. Type 1 Diabetes Is Associated With an Increased Risk of Fracture Across the Life Span: A Population-Based Cohort Study Using The Health Improvement Network (THIN). Diabetes care. 2015.
19. Shah VN, Shah CS, Snell-Bergeon JK. Type 1 diabetes and risk of fracture: meta-analysis and review of the literature. Diabetic medicine : a journal of the British Diabetic Association. 2015;32(9):1134–42. [PubMed: 26096918]
20. Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. American journal of epidemiology. 2007;166(5):495–505. [PubMed: 17575306]

21. Majumdar SR, Leslie WD, Lix LM, Morin SN, Johansson H, Oden A, et al. Longer Duration of Diabetes Strongly Impacts Fracture Risk Assessment: The Manitoba BMD Cohort. The Journal of clinical endocrinology and metabolism. 2016;101(11):4489–96. [PubMed: 27603908]
22. Li CI, Liu CS, Lin WY, Meng NH, Chen CC, Yang SY, et al. Glycated Hemoglobin Level and Risk of Hip Fracture in Older People with Type 2 Diabetes: A Competing Risk Analysis of Taiwan Diabetes Cohort Study. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2015;30(7):1338–46.
23. Oei L, Zillikens MC, Dehghan A, Buitendijk GH, Castano-Betancourt MC, Estrada K, et al. High bone mineral density and fracture risk in type 2 diabetes as skeletal complications of inadequate glucose control: the Rotterdam Study. Diabetes care. 2013;36(6):1619–28. [PubMed: 23315602]
24. Schwartz AV, Vittinghoff E, Bauer DC, Hillier TA, Strotmeyer ES, Ensrud KE, et al. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. Jama. 2011;305(21):2184–92. [PubMed: 21632482]
25. Toor AS, Jiang JJ, Shi LL, Koh JL. Comparison of perioperative complications after total elbow arthroplasty in patients with and without diabetes. Journal of shoulder and elbow surgery. 2014;23(11):1599–606. [PubMed: 25213826]
26. Basques BA, Webb ML, Bohl DD, Golinvaux NS, Grauer JN. Adverse events, length of stay, and readmission after surgery for tibial plateau fractures. Journal of orthopaedic trauma. 2015;29(3):e121–6. [PubMed: 25162975]
27. Mastrandrea LD, Wactawski-Wende J, Donahue RP, Hovey KM, Clark A, Quattrin T. Young women with type 1 diabetes have lower bone mineral density that persists over time. Diabetes care. 2008;31(9):1729–35. [PubMed: 18591404]
28. Shah VN, Harrall KK, Shah CS, Gallo TL, Joshee P, Snell-Bergeon JK, et al. Bone mineral density at femoral neck and lumbar spine in adults with type 1 diabetes: a meta-analysis and review of the literature. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2017;28(9):2601–10.
29. Hofbauer LC, Brueck CC, Singh SK, Dobnig H. Osteoporosis in patients with diabetes mellitus. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2007;22(9):1317–28.
30. Ma L, Oei L, Jiang L, Estrada K, Chen H, Wang Z, et al. Association between bone mineral density and type 2 diabetes mellitus: a meta-analysis of observational studies. European journal of epidemiology. 2012;27(5):319–32. [PubMed: 22451239]
31. Burghardt AJ, Issever AS, Schwartz AV, Davis KA, Masharani U, Majumdar S, et al. High-resolution peripheral quantitative computed tomographic imaging of cortical and trabecular bone microarchitecture in patients with type 2 diabetes mellitus. The Journal of clinical endocrinology and metabolism. 2010;95(11):5045–55. [PubMed: 20719835]
32. Diabetic Bone Disease. 1 ed Lecka-Czernik B, Fowlkes J, editor: Springer International Publishing; 2016 230 p.
33. Farr JN, Drake MT, Amin S, Melton LJ, 3rd, McCready LK, Khosla S. In vivo assessment of bone quality in postmenopausal women with type 2 diabetes. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2014;29(4):787–95.
34. Vashishth D The role of the collagen matrix in skeletal fragility. Current osteoporosis reports. 2007;5(2):62–6. [PubMed: 17521507]
35. Furst JR, Bandeira LC, Fan WW, Agarwal S, Nishiyama KK, McMahon DJ, et al. Advanced Glycation Endproducts and Bone Material Strength in Type 2 Diabetes. The Journal of clinical endocrinology and metabolism. 2016;101(6):2502–10. [PubMed: 27115060]
36. Thrailkill KM. Insulin-like growth factor-I in diabetes mellitus: its physiology, metabolic effects, and potential clinical utility. Diabetes technology & therapeutics. 2000;2(1):69–80. [PubMed: 11467325]
37. Moyer-Mileur LJ, Slater H, Jordan KC, Murray MA. IGF-1 and IGF-binding proteins and bone mass, geometry, and strength: relation to metabolic control in adolescent girls with type 1 diabetes. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2008;23(12):1884–91.

38. Thrailkill KM, Fowlkes JL. The role of vitamin D in the metabolic homeostasis of diabetic bone. Clinical reviews in bone and mineral metabolism. 2013;11(1):28–37. [PubMed: 23620712]
39. Schwartz AV, Hillier TA, Sellmeyer DE, Resnick HE, Gregg E, Ensrud KE, et al. Older women with diabetes have a higher risk of falls: a prospective study. Diabetes care. 2002;25(10):1749–54. [PubMed: 12351472]
40. Kahn SE, Zinman B, Lachin JM, Haffner SM, Herman WH, Holman RR, et al. Rosiglitazone-associated fractures in type 2 diabetes: an Analysis from A Diabetes Outcome Progression Trial (ADOPT). Diabetes care. 2008;31(5):845–51. [PubMed: 18223031]
41. Zhu ZN, Jiang YF, Ding T. Risk of fracture with thiazolidinediones: an updated meta-analysis of randomized clinical trials. Bone. 2014;68:115–23. [PubMed: 25173606]
42. Meier C, Schwartz AV, Egger A, Lecka-Czernik B. Effects of diabetes drugs on the skeleton. Bone. 2015.
43. Paschou SA, Dede AD, Anagnostis PG, Vryonidou A, Morganstein D, Goulis DG. Type 2 Diabetes and Osteoporosis: A Guide to Optimal Management. The Journal of clinical endocrinology and metabolism. 2017;102(10):3621–34. [PubMed: 28938433]
44. Wajchenberg BL. beta-cell failure in diabetes and preservation by clinical treatment. Endocrine reviews. 2007;28(2):187–218. [PubMed: 17353295]
45. Belfiore A, Frasca F, Pandini G, Sciacca L, Vigneri R. Insulin receptor isoforms and insulin receptor/insulin-like growth factor receptor hybrids in physiology and disease. Endocrine reviews. 2009;30(6):586–623. [PubMed: 19752219]
46. Shepherd PR, Kahn BB. Glucose transporters and insulin action--implications for insulin resistance and diabetes mellitus. The New England journal of medicine. 1999;341(4):248–57. [PubMed: 10413738]
47. Sasaoka T, Rose DW, Jhun BH, Saltiel AR, Draznin B, Olefsky JM. Evidence for a functional role of Shc proteins in mitogenic signaling induced by insulin, insulin-like growth factor-1, and epidermal growth factor. The Journal of biological chemistry. 1994;269(18):13689–94. [PubMed: 7513704]
48. Escribano O, Beneit N, Rubio-Longas C, Lopez-Pastor AR, Gomez-Hernandez A. The Role of Insulin Receptor Isoforms in Diabetes and Its Metabolic and Vascular Complications. Journal of diabetes research. 2017;2017:1403206. [PubMed: 29201918]
49. Knudsen L, Hansen BF, Jensen P, Pedersen TA, Vestergaard K, Schaffer L, et al. Agonism and antagonism at the insulin receptor. PloS one. 2012;7(12):e51972. [PubMed: 23300584]
50. Skyler JS, Bakris GL, Bonifacio E, Darsow T, Eckel RH, Groop L, et al. Differentiation of Diabetes by Pathophysiology, Natural History, and Prognosis. Diabetes. 2017;66(2):241–55. [PubMed: 27980006]
51. Home P, Riddle M, Cefalu WT, Bailey CJ, Bretzel RG, Del Prato S, et al. Insulin therapy in people with type 2 diabetes: opportunities and challenges? Diabetes care. 2014;37(6):1499–508. [PubMed: 24855154]
52. Holden SE, Gale EA, Jenkins-Jones S, Currie CJ. How many people inject insulin? UK estimates from 1991 to 2010. Diabetes, obesity & metabolism. 2014;16(6):553–9.
53. Thrailkill KM, Liu L, Wahl EC, Bunn RC, Perrien DS, Cockrell GE, et al. Bone formation is impaired in a model of type 1 diabetes. Diabetes. 2005;54(10):2875–81. [PubMed: 16186388]
54. Fowlkes JL, Bunn RC, Thrailkill KM. Contributions of the Insulin/Insulin-Like Growth Factor-1 Axis to Diabetic Osteopathy. Journal of diabetes & metabolism. 2011;1(3).
55. Fulzele K, DiGirolamo DJ, Liu Z, Xu J, Messina JL, Clemens TL. Disruption of the insulin-like growth factor type 1 receptor in osteoblasts enhances insulin signaling and action. The Journal of biological chemistry. 2007;282(35):25649–58. [PubMed: 17553792]
56. Fulzele K, Riddle RC, DiGirolamo DJ, Cao X, Wan C, Chen D, et al. Insulin receptor signaling in osteoblasts regulates postnatal bone acquisition and body composition. Cell. 2010;142(2):309–19. [PubMed: 20655471]
57. Hashizume M, Yamaguchi M. Stimulatory effect of beta-alanyl-L-histidinato zinc on cell proliferation is dependent on protein synthesis in osteoblastic MC3T3–E1 cells. Molecular and cellular biochemistry. 1993;122(1):59–64. [PubMed: 8350864]

58. Wergedal JE, Baylink DJ. Characterization of cells isolated and cultured from human bone. Proceedings of the Society for Experimental Biology and Medicine Society for Experimental Biology and Medicine. 1984;176(1):60–9.

59. Canalis EM, Dietrich JW, Maina DM, Raisz LG. Hormonal control of bone collagen synthesis in vitro. Effects of insulin and glucagon. Endocrinology. 1977;100(3):668–74. [PubMed: 401359]

60. Pun KK, Lau P, Ho PW. The characterization, regulation, and function of insulin receptors on osteoblast-like clonal osteosarcoma cell line. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 1989;4(6):853–62.

61. Rosen DM, Luben RA. Multiple hormonal mechanisms for the control of collagen synthesis in an osteoblast-like cell line, MMB-1. Endocrinology. 1983;112(3):992–9. [PubMed: 6337052]

62. Canalis E Effect of hormones and growth factors on alkaline phosphatase activity and collagen synthesis in cultured rat calvariae. Metabolism: clinical and experimental. 1983;32(1):14–20. [PubMed: 6217395]

63. Kream BE, Smith MD, Canalis E, Raisz LG. Characterization of the effect of insulin on collagen synthesis in fetal rat bone. Endocrinology. 1985;116(1):296–302. [PubMed: 3880543]

64. Hahn TJ, Westbrook SL, Sullivan TL, Goodman WG, Halstead LR. Glucose transport in osteoblast-enriched bone explants: characterization and insulin regulation. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 1988;3(3):359–65.

65. Ituarte EA, Halstead LR, Iida-Klein A, Ituarte HG, Hahn TJ. Glucose transport system in UMR-106–01 osteoblastic osteosarcoma cells: regulation by insulin. Calcified tissue international. 1989;45(1):27–33. [PubMed: 2504460]

66. Li Z, Frey JL, Wong GW, Faugere MC, Wolfgang MJ, Kim JK, et al. Glucose Transporter-4 Facilitates Insulin-Stimulated Glucose Uptake in Osteoblasts. Endocrinology. 2016;157(11):4094–103. [PubMed: 27689415]

67. Thomas DM, Udagawa N, Hards DK, Quinn JM, Moseley JM, Findlay DM, et al. Insulin receptor expression in primary and cultured osteoclast-like cells. Bone. 1998;23(3):181–6. [PubMed: 9737339]

68. Nyman JS, Even JL, Jo CH, Herbert EG, Murry MR, Cockrell GE, et al. Increasing duration of type 1 diabetes perturbs the strength-structure relationship and increases brittleness of bone. Bone. 2011;48(4):733–40. [PubMed: 21185416]

69. Lu H, Kraut D, Gerstenfeld LC, Graves DT. Diabetes interferes with the bone formation by affecting the expression of transcription factors that regulate osteoblast differentiation. Endocrinology. 2003;144(1):346–52. [PubMed: 12488363]

70. Fowlkes JL, Bunn RC, Liu L, Wahl EC, Coleman HN, Cockrell GE, et al. Runt-related transcription factor 2 (RUNX2) and RUNX2-related osteogenic genes are down-regulated throughout osteogenesis in type 1 diabetes mellitus. Endocrinology. 2008;149(4):1697–704. [PubMed: 18162513]

71. Follak N, Kloting I, Merk H. Influence of diabetic metabolic state on fracture healing in spontaneously diabetic rats. Diabetes/metabolism research and reviews. 2005;21(3):288–96. [PubMed: 15693070]

72. Follak N, Kloting L, Wolf E, Merk H. Delayed remodeling in the early period of fracture healing in spontaneously diabetic BB/OK rats depending on the diabetic metabolic state. Histology and histopathology. 2004;19(2):473–86. [PubMed: 15024708]

73. Hou JC, Zernicke RF, Barnard RJ. Effects of severe diabetes and insulin on the femoral neck of the immature rat. Journal of orthopaedic research : official publication of the Orthopaedic Research Society. 1993;11(2):263–71.

74. Yamamoto M, Sugimoto T. Advanced Glycation End Products, Diabetes, and Bone Strength. Current osteoporosis reports. 2016;14(6):320–6. [PubMed: 27704396]

75. Creecy A, Uppuganti S, Merkel AR, O'Neal D, Makowski AJ, Granke M, et al. Changes in the Fracture Resistance of Bone with the Progression of Type 2 Diabetes in the ZDSD Rat. Calcified tissue international. 2016;99(3):289–301. [PubMed: 27209312]

76. Silva MJ, Brodt MD, Lynch MA, McKenzie JA, Tanouye KM, Nyman JS, et al. Type 1 diabetes in young rats leads to progressive trabecular bone loss, cessation of cortical bone growth, and

diminished whole bone strength and fatigue life. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2009;24(9):1618–27.

77. Ferron M, Wei J, Yoshizawa T, Del Fattore A, DePinho RA, Teti A, et al. Insulin signaling in osteoblasts integrates bone remodeling and energy metabolism. Cell. 2010;142(2):296–308. [PubMed: 20655470]
78. Thrailkill K, Bunn RC, Lumpkin C, Jr., Wahl E, Cockrell G, Morris L, et al. Loss of insulin receptor in osteoprogenitor cells impairs structural strength of bone. Journal of diabetes research. 2014;2014:703589. [PubMed: 24963495]
79. Nyman JS, Kalaitzoglou E, Clay Bunn R, Uppuganti S, Thrailkill KM, Fowlkes JL. Preserving and restoring bone with continuous insulin infusion therapy in a mouse model of type 1 diabetes. Bone reports. 2017;7:1–8. [PubMed: 28736738]
80. Siqueira JT, Cavalher-Machado SC, Arana-Chavez VE, Sannomiya P. Bone formation around titanium implants in the rat tibia: role of insulin. Implant dentistry. 2003;12(3):242–51. [PubMed: 14560485]
81. Gandhi A, Beam HA, O'Connor JP, Parsons JR, Lin SS. The effects of local insulin delivery on diabetic fracture healing. Bone. 2005;37(4):482–90. [PubMed: 16027060]
82. Thrailkill KM, Jo CH, Cockrell GE, Moreau CS, Lumpkin CK, Jr., Fowlkes JL. Determinants of undercarboxylated and carboxylated osteocalcin concentrations in type 1 diabetes. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2012;23(6):1799–806.
83. Fukunaga Y, Minamikawa J, Inoue D, Koshiyama H. Does insulin use increase bone mineral density in patients with non-insulin-dependent diabetes mellitus? Archives of internal medicine. 1997;157(22):2668–9.
84. Weinstock RS, Goland RS, Shane E, Clemens TL, Lindsay R, Bilezikian JP. Bone mineral density in women with type II diabetes mellitus. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 1989;4(1):97–101.
85. Yang J, Hong N, Shim JS, Rhee Y, Kim HC. Association of Insulin Resistance with Lower Bone Volume and Strength Index of the Proximal Femur in Nondiabetic Postmenopausal Women. Journal of bone metabolism. 2018;25(2):123–32. [PubMed: 29900162]
86. Shanbhogue VV, Finkelstein JS, Bouxsein ML, Yu EW. Association Between Insulin Resistance and Bone Structure in Nondiabetic Postmenopausal Women. The Journal of clinical endocrinology and metabolism. 2016;101(8):3114–22. [PubMed: 27243136]
87. Srikanthan P, Crandall CJ, Miller-Martinez D, Seeman TE, Greendale GA, Binkley N, et al. Insulin resistance and bone strength: findings from the study of midlife in the United States. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2014;29(4):796–803.
88. Kanazawa I, Yamaguchi T, Tada Y, Yamauchi M, Yano S, Sugimoto T. Serum osteocalcin level is positively associated with insulin sensitivity and secretion in patients with type 2 diabetes. Bone. 2011;48(4):720–5. [PubMed: 21185419]
89. Losada E, Soldevila B, Ali MS, Martinez-Laguna D, Nogues X, Puig-Domingo M, et al. Real-world antidiabetic drug use and fracture risk in 12,277 patients with type 2 diabetes mellitus: a nested case-control study. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2018;29(9):2079–86.
90. Kanazawa I, Yamaguchi T, Yamamoto M, Sugimoto T. Relationship between treatments with insulin and oral hypoglycemic agents versus the presence of vertebral fractures in type 2 diabetes mellitus. Journal of bone and mineral metabolism. 2010;28(5):554–60. [PubMed: 20177722]
91. Vestergaard P, Rejnmark L, Mosekilde L. Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. Diabetologia. 2005;48(7):1292–9. [PubMed: 15909154]
92. Ruppert K, Cauley J, Lian Y, Zgibor JC, Derby C, Solomon DH. The effect of insulin on bone mineral density among women with type 2 diabetes: a SWAN Pharmacoepidemiology study. Osteoporosis international : a journal established as result of cooperation between the European

Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2018;29(2): 347–54.

93. Napoli N, Strotmeyer ES, Ensrud KE, Sellmeyer DE, Bauer DC, Hoffman AR, et al. Fracture risk in diabetic elderly men: the MrOS study. Diabetologia. 2014;57(10):2057–65. [PubMed: 24908567]
94. Asche CV, Bode B, Busk AK, Nair SR. The economic and clinical benefits of adequate insulin initiation and intensification in people with type 2 diabetes mellitus. Diabetes, obesity & metabolism. 2012;14(1):47–57.
95. Thomas I, Gregg B. Metformin; a review of its history and future: from lilac to longevity. Pediatric diabetes. 2017;18(1):10–6. [PubMed: 28052534]
96. Maruthur NM, Tseng E, Hutfless S, Wilson LM, Suarez-Cuervo C, Berger Z, et al. Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis. Annals of internal medicine. 2016;164(11):740–51. [PubMed: 27088241]
97. Bennett WL, Maruthur NM, Singh S, Segal JB, Wilson LM, Chatterjee R, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Annals of internal medicine. 2011;154(9):602–13. [PubMed: 21403054]
98. Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. The New England journal of medicine. 1995;333(9):550–4. [PubMed: 7623903]
99. An H, He L. Current understanding of metformin effect on the control of hyperglycemia in diabetes. The Journal of endocrinology. 2016;228(3):R97–106. [PubMed: 26743209]
100. McCarthy AD, Cortizo AM, Sedlinsky C. Metformin revisited: Does this regulator of AMP-activated protein kinase secondarily affect bone metabolism and prevent diabetic osteopathy. World journal of diabetes. 2016;7(6):122–33. [PubMed: 27022443]
101. Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, et al. Role of AMP-activated protein kinase in mechanism of metformin action. The Journal of clinical investigation. 2001;108(8): 1167–74. [PubMed: 11602624]
102. Coyle C, Cafferty FH, Vale C, Langley RE. Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis. Annals of oncology : official journal of the European Society for Medical Oncology. 2016;27(12):2184–95. [PubMed: 27681864]
103. Chae YK, Arya A, Malecek MK, Shin DS, Carneiro B, Chandra S, et al. Repurposing metformin for cancer treatment: current clinical studies. Oncotarget. 2016;7(26):40767–80. [PubMed: 27004404]
104. Landman GW, Kleefstra N, van Hateren KJ, Groenier KH, Gans RO, Bilo HJ. Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. Diabetes care. 2010;33(2):322–6. [PubMed: 19918015]
105. Daugan M, Dufay Wojcicki A, d'Hayer B, Boudy V. Metformin: An anti-diabetic drug to fight cancer. Pharmacological research. 2016;113(Pt A):675–85. [PubMed: 27720766]
106. Paiva-Oliveira DI, Martins-Neves SR, Abrunhosa AJ, Fontes-Ribeiro C, Gomes CMF. Therapeutic potential of the metabolic modulator Metformin on osteosarcoma cancer stem-like cells. Cancer chemotherapy and pharmacology. 2018;81(1):49–63. [PubMed: 29086064]
107. Barzilai N, Crandall JP, Kritchevsky SB, Espeland MA. Metformin as a Tool to Target Aging. Cell metabolism. 2016;23(6):1060–5. [PubMed: 27304507]
108. Bannister CA, Holden SE, Jenkins-Jones S, Morgan CL, Halcox JP, Schernthaner G, et al. Can people with type 2 diabetes live longer than those without? A comparison of mortality in people initiated with metformin or sulphonylurea monotherapy and matched, non-diabetic controls. Diabetes, obesity & metabolism. 2014;16(11):1165–73.
109. Kajiwara C, Kusaka Y, Kimura S, Yamaguchi T, Nanjo Y, Ishii Y, et al. Metformin Mediates Protection against Legionella Pneumonia through Activation of AMPK and Mitochondrial Reactive Oxygen Species. Journal of immunology. 2018;200(2):623–31.
110. Alagiakrishnan K, Sankaralingam S, Ghosh M, Mereu L, Senior P. Antidiabetic drugs and their potential role in treating mild cognitive impairment and Alzheimer's disease. Discovery medicine. 2013;16(90):277–86. [PubMed: 24333407]

111. Anabtawi A, Miles JM. Metformin: Nonglycemic Effects and Potential Novel Indications. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2016;22(8):999–1007.

112. Chen SC, Brooks R, Houskeeper J, Bremner SK, Dunlop J, Viollet B, et al. Metformin suppresses adipogenesis through both AMP-activated protein kinase (AMPK)-dependent and AMPK-independent mechanisms. Molecular and cellular endocrinology. 2017;440:57–68. [PubMed: 27856330]

113. Marycz K, Tomaszewski KA, Kornicka K, Henry BM, Wronski S, Tarasiuk J, et al. Metformin Decreases Reactive Oxygen Species, Enhances Osteogenic Properties of Adipose-Derived Multipotent Mesenchymal Stem Cells In Vitro, and Increases Bone Density In Vivo. Oxidative medicine and cellular longevity. 2016;2016:9785890. [PubMed: 27195075]

114. Wang P, Ma T, Guo D, Hu K, Shu Y, Xu HHK, et al. Metformin induces osteoblastic differentiation of human induced pluripotent stem cell-derived mesenchymal stem cells. Journal of tissue engineering and regenerative medicine. 2018;12(2):437–46. [PubMed: 28494141]

115. Gu Q, Gu Y, Yang H, Shi Q. Metformin Enhances Osteogenesis and Suppresses Adipogenesis of Human Chorionic Villous Mesenchymal Stem Cells. The Tohoku journal of experimental medicine. 2017;241(1):13–9. [PubMed: 28025449]

116. Cortizo AM, Sedlinsky C, McCarthy AD, Blanco A, Schurman L. Osteogenic actions of the anti-diabetic drug metformin on osteoblasts in culture. European journal of pharmacology. 2006;536(1–2):38–46. [PubMed: 16564524]

117. Kanazawa I, Yamaguchi T, Yano S, Yamauchi M, Sugimoto T. Metformin enhances the differentiation and mineralization of osteoblastic MC3T3–E1 cells via AMP kinase activation as well as eNOS and BMP-2 expression. Biochemical and biophysical research communications. 2008;375(3):414–9. [PubMed: 18721796]

118. Mu W, Wang Z, Ma C, Jiang Y, Zhang N, Hu K, et al. Metformin promotes the proliferation and differentiation of murine preosteoblast by regulating the expression of sirt6 and oct4. Pharmacological research. 2017.

119. Zhen D, Chen Y, Tang X. Metformin reverses the deleterious effects of high glucose on osteoblast function. Journal of diabetes and its complications. 2010;24(5):334–44. [PubMed: 19628413]

120. Jang WG, Kim EJ, Bae IH, Lee KN, Kim YD, Kim DK, et al. Metformin induces osteoblast differentiation via orphan nuclear receptor SHP-mediated transactivation of Runx2. Bone. 2011;48(4):885–93. [PubMed: 21147283]

121. Schurman L, McCarthy AD, Sedlinsky C, Gangoiti MV, Arnol V, Bruzzone L, et al. Metformin reverts deleterious effects of advanced glycation end-products (AGEs) on osteoblastic cells. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association. 2008;116(6):333–40.

122. Lin CH, Cheng YC, Nicol CJ, Lin KH, Yen CH, Chiang MC. Activation of AMPK is neuroprotective in the oxidative stress by advanced glycosylation end products in human neural stem cells. Experimental cell research. 2017;359(2):367–73. [PubMed: 28821394]

123. Zhou Z, Tang Y, Jin X, Chen C, Lu Y, Liu L, et al. Metformin Inhibits Advanced Glycation End Products-Induced Inflammatory Response in Murine Macrophages Partly through AMPK Activation and RAGE/NFkappaB Pathway Suppression. Journal of diabetes research. 2016;2016:4847812. [PubMed: 27761470]

124. Zhang T, Hu X, Cai Y, Yi B, Wen Z. Metformin protects against hyperglycemia-induced cardiomyocytes injury by inhibiting the expressions of receptor for advanced glycation end products and high mobility group box 1 protein. Molecular biology reports. 2014;41(3):1335–40. [PubMed: 24420848]

125. Ishibashi Y, Matsui T, Takeuchi M, Yamagishi S. Metformin inhibits advanced glycation end products (AGEs)-induced renal tubular cell injury by suppressing reactive oxygen species generation via reducing receptor for AGEs (RAGE) expression. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 2012;44(12):891–5. [PubMed: 22864903]

126. Jang WG, Kim EJ, Lee KN, Son HJ, Koh JT. AMP-activated protein kinase (AMPK) positively regulates osteoblast differentiation via induction of Dlx5-dependent Runx2 expression in

MC3T3E1 cells. Biochemical and biophysical research communications. 2011;404(4):1004–9. [PubMed: 21187071]

127. Wang YG, Qu XH, Yang Y, Han XG, Wang L, Qiao H, et al. AMPK promotes osteogenesis and inhibits adipogenesis through AMPK-Gfi1-OPN axis. Cellular signalling. 2016;28(9):1270–82. [PubMed: 27283242]
128. Mai QG, Zhang ZM, Xu S, Lu M, Zhou RP, Zhao L, et al. Metformin stimulates osteoprotegerin and reduces RANKL expression in osteoblasts and ovariectomized rats. Journal of cellular biochemistry. 2011;112(10):2902–9. [PubMed: 21618594]
129. Wang J, Chen TY, Qin S, Duan Y, Wang G. Inhibitory effect of metformin on bone metastasis of cancer via OPG/RANKL/RANK system. Medical hypotheses. 2013;81(5):805–6. [PubMed: 24074896]
130. Bandow K, Kusuyama J, Kakimoto K, Ohnishi T, Matsuguchi T. AMP-activated protein kinase (AMPK) activity negatively regulates chondrogenic differentiation. Bone. 2015;74:125–33. [PubMed: 25497570]
131. Kasai T, Bandow K, Suzuki H, Chiba N, Kakimoto K, Ohnishi T, et al. Osteoblast differentiation is functionally associated with decreased AMP kinase activity. Journal of cellular physiology. 2009;221(3):740–9. [PubMed: 19725053]
132. Wu W, Ye Z, Zhou Y, Tan WS. AICAR, a small chemical molecule, primes osteogenic differentiation of adult mesenchymal stem cells. The International journal of artificial organs. 2011;34(12):1128–36. [PubMed: 22198598]
133. Patel JJ, Butters OR, Arnett TR. PPAR agonists stimulate adipogenesis at the expense of osteoblast differentiation while inhibiting osteoclast formation and activity. Cell biochemistry and function. 2014;32(4):368–77. [PubMed: 24615887]
134. Sedlinsky C, Molinuevo MS, Cortizo AM, Tolosa MJ, Felice JI, Sbaraglini ML, et al. Metformin prevents anti-osteogenic in vivo and ex vivo effects of rosiglitazone in rats. European journal of pharmacology. 2011;668(3):477–85. [PubMed: 21839072]
135. Molinuevo MS, Schurman L, McCarthy AD, Cortizo AM, Tolosa MJ, Gangoiti MV, et al. Effect of metformin on bone marrow progenitor cell differentiation: in vivo and in vitro studies. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2010;25(2):211–21.
136. Gao Y, Li Y, Xue J, Jia Y, Hu J. Effect of the anti-diabetic drug metformin on bone mass in ovariectomized rats. European journal of pharmacology. 2010;635(1–3):231–6. [PubMed: 20307532]
137. Khajuria DK, Patil ON, Karasik D, Razdan R. Development and evaluation of novel biodegradable chitosan based metformin intrapocket dental film for the management of periodontitis and alveolar bone loss in a rat model. Archives of oral biology. 2018;85:120–9. [PubMed: 29055230]
138. Araujo AA, Pereira A, Medeiros C, Brito GAC, Leitao RFC, Araujo LS, et al. Effects of metformin on inflammation, oxidative stress, and bone loss in a rat model of periodontitis. PloS one. 2017;12(8):e0183506. [PubMed: 28847008]
139. Liu L, Zhang C, Hu Y, Peng B. Protective effect of metformin on periapical lesions in rats by decreasing the ratio of receptor activator of nuclear factor kappa B ligand/osteoprotegerin. Journal of endodontics. 2012;38(7):943–7. [PubMed: 22703658]
140. Bak EJ, Park HG, Kim M, Kim SW, Kim S, Choi SH, et al. The effect of metformin on alveolar bone in ligature-induced periodontitis in rats: a pilot study. Journal of periodontology. 2010;81(3):412–9. [PubMed: 20192868]
141. Tolosa MJ, Chuguransky SR, Sedlinsky C, Schurman L, McCarthy AD, Molinuevo MS, et al. Insulin-deficient diabetes-induced bone microarchitecture alterations are associated with a decrease in the osteogenic potential of bone marrow progenitor cells: preventive effects of metformin. Diabetes research and clinical practice. 2013;101(2):177–86. [PubMed: 23806481]
142. Wang C, Li H, Chen SG, He JW, Sheng CJ, Cheng XY, et al. The skeletal effects of thiazolidinedione and metformin on insulin-resistant mice. Journal of bone and mineral metabolism. 2012;30(6):630–7. [PubMed: 22886403]

143. Bornstein S, Moschetta M, Kawano Y, Sacco A, Huynh D, Brooks D, et al. Metformin Affects Cortical Bone Mass and Marrow Adiposity in Diet-Induced Obesity in Male Mice. Endocrinology. 2017;158(10):3369–85. [PubMed: 28977604]

144. Sun J, Du J, Feng W, Lu B, Liu H, Guo J, et al. Histological evidence that metformin reverses the adverse effects of diabetes on orthodontic tooth movement in rats. Journal of molecular histology. 2017;48(2):73–81. [PubMed: 27981392]

145. Felice JI, Schurman L, McCarthy AD, Sedlinsky C, Aguirre JI, Cortizo AM. Effects of fructose-induced metabolic syndrome on rat skeletal cells and tissue, and their responses to metformin treatment. Diabetes research and clinical practice. 2017;126:202–13. [PubMed: 28259010]

146. Han X, Tao Y, Deng Y, Yu J, Sun Y, Jiang G. Metformin accelerates wound healing in type 2 diabetic db/db mice. Molecular medicine reports. 2017;16(6):8691–8. [PubMed: 28990070]

147. Yu JW, Deng YP, Han X, Ren GF, Cai J, Jiang GJ. Metformin improves the angiogenic functions of endothelial progenitor cells via activating AMPK/eNOS pathway in diabetic mice. Cardiovascular diabetology. 2016;15:88. [PubMed: 27316923]

148. Inouye KA, Bisch FC, Elsalanty ME, Zakhary I, Khashaba RM, Borke JL. Effect of metformin on periimplant wound healing in a rat model of type 2 diabetes. Implant dentistry. 2014;23(3):319–27. [PubMed: 24776941]

149. Bastos MF, Serrao CR, Miranda TS, Cruz DF, de Souza Malta F, Duarte PM. Effects of metformin on bone healing around titanium implants inserted in non-diabetic rats. Clinical oral implants research. 2017;28(10):e146–e50. [PubMed: 27573975]

150. Jeyabalan J, Viollet B, Smitham P, Ellis SA, Zaman G, Bardin C, et al. The anti-diabetic drug metformin does not affect bone mass in vivo or fracture healing. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2013;24(10):2659–70.

151. La Fontaine J, Chen C, Hunt N, Jude E, Lavery L. Type 2 Diabetes and Metformin Influence on Fracture Healing in an Experimental Rat Model. The Journal of foot and ankle surgery : official publication of the American College of Foot and Ankle Surgeons. 2016;55(5):955–60.

152. Serrao CR, Bastos MF, Cruz DF, de Souza Malta F, Vallim PC, Duarte PM. Role of Metformin in Reversing the Negative Impact of Hyperglycemia on Bone Healing Around Implants Inserted in Type 2 Diabetic Rats. The International journal of oral & maxillofacial implants. 2017;32(3): 547–54. [PubMed: 28494038]

153. Monami M, Cresci B, Colombini A, Pala L, Balzi D, Gori F, et al. Bone fractures and hypoglycemic treatment in type 2 diabetic patients: a case-control study. Diabetes care. 2008;31(2):199–203. [PubMed: 18024851]

154. Meier C, Kraenzlin ME, Bodmer M, Jick SS, Jick H, Meier CR. Use of thiazolidinediones and fracture risk. Archives of internal medicine. 2008;168(8):820–5. [PubMed: 18443256]

155. Colhoun HM, Livingstone SJ, Looker HC, Morris AD, Wild SH, Lindsay RS, et al. Hospitalised hip fracture risk with rosiglitazone and pioglitazone use compared with other glucose-lowering drugs. Diabetologia. 2012;55(11):2929–37. [PubMed: 22945303]

156. Solomon DH, Cadarette SM, Choudhry NK, Canning C, Levin R, Sturmer T. A cohort study of thiazolidinediones and fractures in older adults with diabetes. The Journal of clinical endocrinology and metabolism. 2009;94(8):2792–8. [PubMed: 19470635]

157. Kanazawa I, Yamaguchi T, Yano S, Yamamoto M, Yamauchi M, Kurioka S, et al. Baseline atherosclerosis parameter could assess the risk of bone loss during pioglitazone treatment in type 2 diabetes mellitus. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2010;21(12):2013–8.

158. Borges JL, Bilezikian JP, Jones-Leone AR, Acusta AP, Ambery PD, Nino AJ, et al. A randomized, parallel group, double-blind, multicentre study comparing the efficacy and safety of Avandamet (rosiglitazone/metformin) and metformin on long-term glycaemic control and bone mineral density after 80 weeks of treatment in drug-naive type 2 diabetes mellitus patients. Diabetes, obesity & metabolism. 2011;13(11):1036–46.

159. Perez A, Zhao Z, Jacks R, Spanheimer R. Efficacy and safety of pioglitazone/metformin fixed-dose combination therapy compared with pioglitazone and metformin monotherapy in treating

patients with T2DM. Current medical research and opinion. 2009;25(12):2915–23. [PubMed: 19827910]

160. Melton LJ, 3rd, Leibson CL, Achenbach SJ, Therneau TM, Khosla S. Fracture risk in type 2 diabetes: update of a population-based study. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2008;23(8):1334–42.
161. Zhu XZ, Zheng XY. Metformin Prevents Nonunion after Three-Cannulated-Screw Fixation in Displaced Femoral Neck Fractures: A Retrospective Study. BioMed research international. 2016;2016:5682541. [PubMed: 27990430]
162. Pradeep AR, Patnaik K, Nagpal K, Karvekar S, Ramamurthy BL, Naik SB, et al. Efficacy of locally-delivered 1% metformin gel in the treatment of intrabony defects in patients with chronic periodontitis: a randomized, controlled clinical trial. Journal of investigative and clinical dentistry. 2016;7(3):239–45. [PubMed: 25787121]
163. Pradeep AR, Nagpal K, Karvekar S, Patnaik K, Naik SB, Guruprasad CN. Platelet-rich fibrin with 1% metformin for the treatment of intrabony defects in chronic periodontitis: a randomized controlled clinical trial. Journal of periodontology. 2015;86(6):729–37. [PubMed: 25762357]
164. Pradeep AR, Rao NS, Naik SB, Kumari M. Efficacy of varying concentrations of subgingivally delivered metformin in the treatment of chronic periodontitis: a randomized controlled clinical trial. Journal of periodontology. 2013;84(2):212–20. [PubMed: 22509750]
165. de Zegher F, Garcia Beltran C, Lopez-Bermejo A, Ibanez L. Metformin for Rapidly Maturing Girls with Central Adiposity: Less Liver Fat and Slower Bone Maturation. Hormone research in paediatrics. 2017.
166. van Lierop AH, Hamdy NA, van der Meer RW, Jonker JT, Lamb HJ, Rijzewijk LJ, et al. Distinct effects of pioglitazone and metformin on circulating sclerostin and biochemical markers of bone turnover in men with type 2 diabetes mellitus. European journal of endocrinology. 2012;166(4): 711–6. [PubMed: 22267280]
167. Zinman B, Haffner SM, Herman WH, Holman RR, Lachin JM, Kravitz BG, et al. Effect of rosiglitazone, metformin, and glyburide on bone biomarkers in patients with type 2 diabetes. The Journal of clinical endocrinology and metabolism. 2010;95(1):134–42. [PubMed: 19875477]
168. Soifer E, Gavish D, Shargorodsky M. Does metformin treatment influence bone formation in patients with nonalcoholic fatty liver disease? Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 2015;47(8):556–9. [PubMed: 25671801]
169. Capoglu I, Ozkan A, Ozkan B, Umudum Z. Bone turnover markers in patients with type 2 diabetes and their correlation with glycosylated haemoglobin levels. The Journal of international medical research. 2008;36(6):1392–8. [PubMed: 19094451]
170. Hegazy SK. Evaluation of the anti-osteoporotic effects of metformin and sitagliptin in postmenopausal diabetic women. Journal of bone and mineral metabolism. 2015;33(2):207–12. [PubMed: 24633493]
171. Dutta M, Pakhetra R, Garg M. Evaluation of bone mineral density in type 2 diabetes mellitus patients before and after treatment. Medical journal, Armed Forces India. 2012;68(1):48–52.
172. Rubin MR, Manavalan JS, Agarwal S, McMahon DJ, Nino A, Fitzpatrick LA, et al. Effects of rosiglitazone vs metformin on circulating osteoclast and osteogenic precursor cells in postmenopausal women with type 2 diabetes mellitus. The Journal of clinical endocrinology and metabolism. 2014;99(10):E1933–42. [PubMed: 24905061]
173. Nanjan MJ, Mohammed M, Prashantha Kumar BR, Chandrasekar MJN. Thiazolidinediones as antidiabetic agents: A critical review. Bioorganic chemistry. 2018;77:548–67. [PubMed: 29475164]
174. Hauner H The mode of action of thiazolidinediones. Diabetes/metabolism research and reviews. 2002;18 Suppl 2:S10–5. [PubMed: 11921433]
175. Benvenuti S, Cellai I, Luciani P, Deledda C, Baglioni S, Giuliani C, et al. Rosiglitazone stimulates adipogenesis and decreases osteoblastogenesis in human mesenchymal stem cells. Journal of endocrinological investigation. 2007;30(9):RC26–30. [PubMed: 17993761]
176. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al. Management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and

adjustment of therapy. Update regarding the thiazolidinediones. Diabetologia. 2008;51(1):8–11. [PubMed: 18026926]

177. Kawaguchi H, Akune T, Yamaguchi M, Ohba S, Ogata N, Chung UI, et al. Distinct effects of PPARgamma insufficiency on bone marrow cells, osteoblasts, and osteoclastic cells. Journal of bone and mineral metabolism. 2005;23(4):275–9. [PubMed: 15981022]
178. Wan Y, Chong LW, Evans RM. PPAR-gamma regulates osteoclastogenesis in mice. Nature medicine. 2007;13(12):1496–503.
179. Billington EO, Grey A, Bolland MJ. The effect of thiazolidinediones on bone mineral density and bone turnover: systematic review and meta-analysis. Diabetologia. 2015;58(10):2238–46. [PubMed: 26109213]
180. Palermo A, D'Onofrio L, Eastell R, Schwartz AV, Pozzilli P, Napoli N. Oral anti-diabetic drugs and fracture risk, cut to the bone: safe or dangerous? A narrative review. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2015;26(8):2073–89.
181. Betteridge DJ. Thiazolidinediones and fracture risk in patients with Type 2 diabetes. Diabetic medicine : a journal of the British Diabetic Association. 2011;28(7):759–71. [PubMed: 21672000]
182. Kheniser KG, Polanco Santos CM, Kashyap SR. The effects of diabetes therapy on bone: A clinical perspective. Journal of diabetes and its complications. 2018;32(7):713–9. [PubMed: 29747995]
183. Adil M, Khan RA, Kalam A, Venkata SK, Kandhare AD, Ghosh P, et al. Effect of anti-diabetic drugs on bone metabolism: Evidence from preclinical and clinical studies. Pharmacological reports : PR. 2017;69(6):1328–40. [PubMed: 29132091]
184. Wolverton D, Blair MM. Fracture risk associated with common medications used in treating type 2 diabetes mellitus. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists. 2017;74(15):1143–51. [PubMed: 28743778]
185. Chandran M Diabetes Drug Effects on the Skeleton. Calcified tissue international. 2017;100(2): 133–49. [PubMed: 27815568]
186. Bazelier MT, Vestergaard P, Gallagher AM, van Staa TP, Cooper C, Leufkens HG, et al. Risk of fracture with thiazolidinediones: disease or drugs? Calcified tissue international. 2012;90(6):450–7. [PubMed: 22488176]
187. Duan M, Zhou B, Zhou X, Yuan G. Thiazolidinediones Inhibit Mouse Osteoblastic MC3T3–E1 Cell Proliferation in Part Through the Wnt Signaling Pathway. Journal of investigative medicine : the official publication of the American Federation for Clinical Research. 2015;63(5):758–64. [PubMed: 25756249]
188. Cho ES, Kim MK, Son YO, Lee KS, Park SM, Lee JC. The effects of rosiglitazone on osteoblastic differentiation, osteoclast formation and bone resorption. Molecules and cells. 2012;33(2):173–81. [PubMed: 22286232]
189. Rzonca SO, Suva LJ, Gaddy D, Montague DC, Lecka-Czernik B. Bone is a target for the antidiabetic compound rosiglitazone. Endocrinology. 2004;145(1):401–6. [PubMed: 14500573]
190. Ali AA, Weinstein RS, Stewart SA, Parfitt AM, Manolagas SC, Jilka RL. Rosiglitazone causes bone loss in mice by suppressing osteoblast differentiation and bone formation. Endocrinology. 2005;146(3):1226–35. [PubMed: 15591153]
191. Seth A, Sy V, Pareek A, Suwandhi P, Rosenwaks Z, Poretsky L, et al. Thiazolidinediones (TZDs) affect osteoblast viability and biomarkers independently of the TZD effects on aromatase. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 2013;45(1):1–8. [PubMed: 22878908]
192. Mabilleau G, Mieczkowska A, Edmonds ME. Thiazolidinediones induce osteocyte apoptosis and increase sclerostin expression. Diabetic medicine : a journal of the British Diabetic Association. 2010;27(8):925–32. [PubMed: 20653751]
193. Avtanski D, Hirth Y, Babushkin N, Sy V, Sharma D, Poretsky L, et al. In Vitro Effects of Pioglitazone on the Expression of Components of Wnt Signaling Pathway and Markers of Bone Mineralization. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 2016;48(7):468–75. [PubMed: 26849824]

194. Mieczkowska A, Basle MF, Chappard D, Mabilleau G. Thiazolidinediones induce osteocyte apoptosis by a G protein-coupled receptor 40-dependent mechanism. The Journal of biological chemistry. 2012;287(28):23517–26. [PubMed: 22593579]

195. Beck GR, Jr., Khazai NB, Bouloux GF, Camalier CE, Lin Y, Garneys LM, et al. The effects of thiazolidinediones on human bone marrow stromal cell differentiation in vitro and in thiazolidinedione-treated patients with type 2 diabetes. Translational research : the journal of laboratory and clinical medicine. 2013;161(3):145–55. [PubMed: 23022285]

196. Lecka-Czernik B, Moerman EJ, Grant DF, Lehmann JM, Manolagas SC, Jilka RL. Divergent effects of selective peroxisome proliferator-activated receptor-gamma 2 ligands on adipocyte versus osteoblast differentiation. Endocrinology. 2002;143(6):2376–84. [PubMed: 12021203]

197. Kim KM, Jin HJ, Lee SY, Maeng HJ, Lee GY, Oh TJ, et al. Effects of Lobeglitazone, a New Thiazolidinedione, on Osteoblastogenesis and Bone Mineral Density in Mice. Endocrinology and metabolism. 2017;32(3):389–95. [PubMed: 28956370]

198. Lazarenko OP, Rzonca SO, Hogue WR, Swain FL, Suva LJ, Lecka-Czernik B. Rosiglitazone induces decreases in bone mass and strength that are reminiscent of aged bone. Endocrinology. 2007;148(6):2669–80. [PubMed: 17332064]

199. Kanda J, Izumo N, Kobayashi Y, Onodera K, Shimakura T, Yamamoto N, et al. Effect of the antidiabetic agent pioglitazone on bone metabolism in rats. Journal of pharmacological sciences. 2017;135(1):22–8. [PubMed: 28928054]

200. Xu F, Dong Y, Huang X, Chen P, Guo F, Chen A, et al. Pioglitazone affects the OPG/RANKL/RANK system and increase osteoclastogenesis. Molecular medicine reports. 2016;14(3):2289–96. [PubMed: 27430581]

201. Okazaki R, Toriumi M, Fukumoto S, Miyamoto M, Fujita T, Tanaka K, et al. Thiazolidinediones inhibit osteoclast-like cell formation and bone resorption in vitro. Endocrinology. 1999;140(11):5060–5. [PubMed: 10537132]

202. Cusick T, Mu J, Pennypacker BL, Li Z, Scott KR, Shen X, et al. Bone loss in the oestrogen-depleted rat is not exacerbated by sitagliptin, either alone or in combination with a thiazolidinedione. Diabetes, obesity & metabolism. 2013;15(10):954–7.

203. Sardone LD, Renlund R, Willett TL, Fantus IG, Grynpas MD. Effect of rosiglitazone on bone quality in a rat model of insulin resistance and osteoporosis. Diabetes. 2011;60(12):3271–8. [PubMed: 21998400]

204. Soroceanu MA, Miao D, Bai XY, Su H, Goltzman D, Karaplis AC. Rosiglitazone impacts negatively on bone by promoting osteoblast/osteocyte apoptosis. The Journal of endocrinology. 2004;183(1):203–16. [PubMed: 15525588]

205. Tsirella E, Mavrakanas T, Rager O, Tsartsalis S, Kallaras K, Kokkas B, et al. Low dose pioglitazone does not affect bone formation and resorption markers or bone mineral density in streptozocin-induced diabetic rats. Journal of physiology and pharmacology : an official journal of the Polish Physiological Society. 2012;63(2):201–4. [PubMed: 22653908]

206. Samadfam R, Awori M, Benardeau A, Bauss F, Sebokova E, Wright M, et al. Combination treatment with pioglitazone and fenofibrate attenuates pioglitazone-mediated acceleration of bone loss in ovariectomized rats. The Journal of endocrinology. 2012;212(2):179–86. [PubMed: 22062085]

207. Smith SY, Samadfam R, Chouinard L, Awori M, Benardeau A, Bauss F, et al. Effects of pioglitazone and fenofibrate co-administration on bone biomechanics and histomorphometry in ovariectomized rats. Journal of bone and mineral metabolism. 2015;33(6):625–41. [PubMed: 25534548]

208. Gruntmanis U, Fordan S, Ghayee HK, Abdullah SM, See R, Ayers CR, et al. The peroxisome proliferator-activated receptor-gamma agonist rosiglitazone increases bone resorption in women with type 2 diabetes: a randomized, controlled trial. Calcified tissue international. 2010;86(5):343–9. [PubMed: 20354684]

209. Xiao WH, Wang YR, Hou WF, Xie C, Wang HN, Hong TP, et al. The effects of pioglitazone on biochemical markers of bone turnover in the patients with type 2 diabetes. International journal of endocrinology. 2013;2013:290734. [PubMed: 23843787]

210. Bilezikian JP, Josse RG, Eastell R, Lewiecki EM, Miller CG, Wooddell M, et al. Rosiglitazone decreases bone mineral density and increases bone turnover in postmenopausal women with type 2 diabetes mellitus. The Journal of clinical endocrinology and metabolism. 2013;98(4):1519–28. [PubMed: 23450056]
211. Berberoglu Z, Yazici AC, Demirag NG. Effects of rosiglitazone on bone mineral density and remodelling parameters in Postmenopausal diabetic women: a 2-year follow-up study. Clinical endocrinology. 2010;73(3):305–12. [PubMed: 20148906]
212. Mori H, Okada Y, Tanaka Y. The Effects of Pioglitazone on Bone Formation and Resorption Markers in Type 2 Diabetes Mellitus. Internal medicine. 2017;56(11):1301–6. [PubMed: 28566590]
213. Yaturu S, Bryant B, Jain SK. Thiazolidinedione treatment decreases bone mineral density in type 2 diabetic men. Diabetes care. 2007;30(6):1574–6. [PubMed: 17363747]
214. Miller CG, Bogado CC, Nino AJ, Northcutt AR, Yu HJ, Lewiecki EM, et al. Evaluation of Quantitative Computed Tomography Cortical Hip Quadrant in a Clinical Trial With Rosiglitazone: A Potential New Study Endpoint. Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry. 2016;19(4):485–91. [PubMed: 27052635]
215. Schwartz AV, Sellmeyer DE, Vittinghoff E, Palermo L, Lecka-Czernik B, Feingold KR, et al. Thiazolidinedione use and bone loss in older diabetic adults. The Journal of clinical endocrinology and metabolism. 2006;91(9):3349–54. [PubMed: 16608888]
216. Li R, Xu W, Luo S, Xu H, Tong G, Zeng L, et al. Effect of exenatide, insulin and pioglitazone on bone metabolism in patients with newly diagnosed type 2 diabetes. Acta diabetologica. 2015;52(6):1083–91. [PubMed: 26249206]
217. Grey A, Bolland M, Fenwick S, Horne A, Gamble G, Drury PL, et al. The skeletal effects of pioglitazone in type 2 diabetes or impaired glucose tolerance: a randomized controlled trial. European journal of endocrinology. 2014;170(2):255–62. [PubMed: 24217934]
218. Lim S, Kim KM, Kim SG, Kim DM, Woo JT, Chung CH, et al. Effects of Lobeglitazone, a Novel Thiazolidinedione, on Bone Mineral Density in Patients with Type 2 Diabetes Mellitus over 52 Weeks. Diabetes & metabolism journal. 2017;41(5):377–85. [PubMed: 29086536]
219. Jones NP, Curtis PS, Home PD. Cancer and bone fractures in observational follow-up of the RECORD study. Acta diabetologica. 2015;52(3):539–46. [PubMed: 25524432]
220. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2009;180(1):32–9.
221. Jones SG, Momin SR, Good MW, Shea TK, Patric K. Distal upper and lower limb fractures associated with thiazolidinedione use. The American journal of managed care. 2009;15(8):491–6. [PubMed: 19670952]
222. Dormuth CR, Carney G, Carleton B, Bassett K, Wright JM. Thiazolidinediones and fractures in men and women. Archives of internal medicine. 2009;169(15):1395–402. [PubMed: 19667303]
223. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009;373(9681):2125–35. [PubMed: 19501900]
224. Aubert RE, Herrera V, Chen W, Haffner SM, Pendergrass M. Rosiglitazone and pioglitazone increase fracture risk in women and men with type 2 diabetes. Diabetes, obesity & metabolism. 2010;12(8):716–21.
225. Mancini T, Mazziotti G, Doga M, Carpinteri R, Simetovic N, Vescovi PP, et al. Vertebral fractures in males with type 2 diabetes treated with rosiglitazone. Bone. 2009;45(4):784–8. [PubMed: 19527806]
226. Pavlova V, Filipova E, Uzunova K, Kalinov K, Vekov T. Pioglitazone Therapy and Fractures: Systematic Review and Meta-Analysis. Endocrine, metabolic & immune disorders drug targets. 2018.

227. Schwartz AV, Chen H, Ambrosius WT, Sood A, Josse RG, Bonds DE, et al. Effects of TZD Use and Discontinuation on Fracture Rates in ACCORD Bone Study. The Journal of clinical endocrinology and metabolism. 2015;100(11):4059–66. [PubMed: 26305617]
228. Harslof T, Wamberg L, Moller L, Stodkilde-Jorgensen H, Ringgaard S, Pedersen SB, et al. Rosiglitazone decreases bone mass and bone marrow fat. The Journal of clinical endocrinology and metabolism. 2011;96(5):1541–8. [PubMed: 21367933]
229. Bray GA, Smith SR, Banerji MA, Tripathy D, Clement SC, Buchanan TA, et al. Effect of pioglitazone on body composition and bone density in subjects with prediabetes in the ACT NOW trial. Diabetes, obesity & metabolism. 2013;15(10):931–7.
230. Bone HG, Lindsay R, McClung MR, Perez AT, Raanan MG, Spanheimer RG. Effects of pioglitazone on bone in postmenopausal women with impaired fasting glucose or impaired glucose tolerance: a randomized, double-blind, placebo-controlled study. The Journal of clinical endocrinology and metabolism. 2013;98(12):4691–701. [PubMed: 24057294]
231. Koster JC, Permutt MA, Nichols CG. Diabetes and insulin secretion: the ATP-sensitive K+ channel (K ATP) connection. Diabetes. 2005;54(11):3065–72. [PubMed: 16249427]
232. Li N, Wu JX, Ding D, Cheng J, Gao N, Chen L. Structure of a Pancreatic ATP-Sensitive Potassium Channel. Cell. 2017;168(1–2):101–10e10. [PubMed: 28086082]
233. Proks P, Reimann F, Green N, Gribble F, Ashcroft F. Sulfonylurea stimulation of insulin secretion. Diabetes. 2002;51 Suppl 3:S368–76. [PubMed: 12475777]
234. Hu S, Wang S, Fanelli B, Bell PA, Dunning BE, Geisse S, et al. Pancreatic beta-cell K(ATP) channel activity and membrane-binding studies with nateglinide: A comparison with sulfonylureas and repaglinide. The Journal of pharmacology and experimental therapeutics. 2000;293(2):444–52. [PubMed: 10773014]
235. Diehlmann A, Bork S, Saffrich R, Veh RW, Wagner W, Derst C. KATP channels in mesenchymal stromal stem cells: strong up-regulation of Kir6.2 subunits upon osteogenic differentiation. Tissue & cell. 2011;43(5):331–6. [PubMed: 21820692]
236. Liu Y, Liu J, Li X, Wang F, Xu X, Wang C. Exogenous H2S prevents high glucose-induced damage to osteoblasts through regulation of KATP channels. Biochimie. 2017;137:151–7. [PubMed: 28322929]
237. Tran PT, Lee YH, Bhattarai JP, Park SJ, Yi HK, Han SK. Existence of ATP sensitive potassium currents on human periodontal ligament cells. Archives of oral biology. 2017;76:48–54. [PubMed: 28119170]
238. Moreau R, Aubin R, Lapointe JY, Lajeunesse D. Pharmacological and biochemical evidence for the regulation of osteocalcin secretion by potassium channels in human osteoblast-like MG-63 cells. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 1997;12(12):1984–92.
239. Ma P, Xiong W, Liu H, Ma J, Gu B, Wu X. Extrapancreatic roles of glimepiride on osteoblasts from rat manibular bone in vitro: Regulation of cytodifferentiation through PI3-kinases/Akt signalling pathway. Archives of oral biology. 2011;56(4):307–16. [PubMed: 21055727]
240. Ma P, Gu B, Xiong W, Tan B, Geng W, Li J, et al. Glimepiride promotes osteogenic differentiation in rat osteoblasts via the PI3K/Akt/eNOS pathway in a high glucose microenvironment. PloS one. 2014;9(11):e112243. [PubMed: 25391146]
241. Chen Y, Hu Y, Yang L, Zhou J, Tang Y, Zheng L, et al. Runx2 alleviates high glucose-suppressed osteogenic differentiation via PI3K/AKT/GSK3beta/beta-catenin pathway. Cell biology international. 2017;41(8):822–32. [PubMed: 28462510]
242. Zhang Y, Yang JH. Activation of the PI3K/Akt pathway by oxidative stress mediates high glucose-induced increase of adipogenic differentiation in primary rat osteoblasts. Journal of cellular biochemistry. 2013;114(11):2595–602. [PubMed: 23757055]
243. Ma P, Gu B, Ma J, E L, Wu X, Cao J, et al. Glimepiride induces proliferation and differentiation of rat osteoblasts via the PI3-kinase/Akt pathway. Metabolism: clinical and experimental. 2010;59(3):359–66. [PubMed: 19800638]
244. Ueba H, Kuroki M, Hashimoto S, Umemoto T, Yasu T, Ishikawa SE, et al. Glimepiride induces nitric oxide production in human coronary artery endothelial cells via a PI3-kinase-Akt dependent pathway. Atherosclerosis. 2005;183(1):35–9. [PubMed: 16216590]

245. Saura M, Tarin C, Zaragoza C. Recent insights into the implication of nitric oxide in osteoblast differentiation and proliferation during bone development. TheScientificWorldJournal. 2010;10:624–32.

246. Wang L, Chen K, Wan X, Wang F, Guo Z, Mo Z. NLRP3 inflammasome activation in mesenchymal stem cells inhibits osteogenic differentiation and enhances adipogenic differentiation. Biochemical and biophysical research communications. 2017;484(4):871–7. [PubMed: 28167279]

247. Hill JR, Coll RC, Sue N, Reid JC, Dou J, Holley CL, et al. Sulfonylureas as Concomitant Insulin Secretagogues and NLRP3 Inflammasome Inhibitors. ChemMedChem. 2017;12(17):1449–57. [PubMed: 28703484]

248. Fronczek-Sokol J, Pytlik M. Effect of glimepiride on the skeletal system of ovariectomized and non-ovariectomized rats. Pharmacological reports : PR. 2014;66(3):412–7. [PubMed: 24905517]

249. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. The New England journal of medicine. 2006;355(23):2427–43. [PubMed: 17145742]

250. Khunti K, Chatterjee S, Gerstein HC, Zoungas S, Davies MJ. Do sulphonylureas still have a place in clinical practice? The lancet Diabetes & endocrinology. 2018.

251. Lapane KL, Yang S, Brown MJ, Jawahar R, Pagliasotti C, Rajpathak S. Sulfonylureas and risk of falls and fractures: a systematic review. Drugs & aging. 2013;30(7):527–47. [PubMed: 23609875]

252. Gilbert MP, Marre M, Holst JJ, Garber A, Baeres FM, Thomsen H, et al. Comparison of the Long-Term Effects of Liraglutide and Glimepiride Monotherapy on Bone Mineral Density in Patients with Type 2 Diabetes. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2016;22(4):406–11.

253. Johnston SS, Conner C, Aagren M, Ruiz K, Bouchard J. Association between hypoglycaemic events and fall-related fractures in Medicare-covered patients with type 2 diabetes. Diabetes, obesity & metabolism. 2012;14(7):634–43.

254. Starup-Linde J, Gregersen S, Frost M, Vestergaard P. Use of glucose-lowering drugs and risk of fracture in patients with type 2 diabetes. Bone. 2017;95:136–42. [PubMed: 27890548]

255. Lapane KL, Jesdale BM, Dube CE, Pimentel CB, Rajpathak SN. Sulfonylureas and risk of falls and fractures among nursing home residents with type 2 diabetes mellitus. Diabetes research and clinical practice. 2015;109(2):411–9. [PubMed: 26008723]

256. Rajpathak SN, Fu C, Brodovicz KG, Engel SS, Lapane K. Sulfonylurea use and risk of hip fractures among elderly men and women with type 2 diabetes. Drugs & aging. 2015;32(4):321–7. [PubMed: 25825122]

257. Vianna AGD, de Lacerda CS, Pechmann LM, Polesel MG, Marino EC, Borba VZC, et al. Vildagliptin has the same safety profile as a sulfonylurea on bone metabolism and bone mineral density in post-menopausal women with type 2 diabetes: a randomized controlled trial. Diabetology & metabolic syndrome. 2017;9:35. [PubMed: 28515791]

258. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. Archives of internal medicine. 1997;157(15):1681–6. [PubMed: 9250229]

259. Sola D, Rossi L, Schianca GP, Maffioli P, Bigliocca M, Mella R, et al. Sulfonylureas and their use in clinical practice. Archives of medical science : AMS. 2015;11(4):840–8. [PubMed: 26322096]

260. Douros A, Yin H, Yu OHY, Filion KB, Azoulay L, Suissa S. Pharmacologic Differences of Sulfonylureas and the Risk of Adverse Cardiovascular and Hypoglycemic Events. Diabetes care. 2017;40(11):1506–13. [PubMed: 28864502]

261. Leonard CE, Han X, Brensinger CM, Bilker WB, Cardillo S, Flory JH, et al. Comparative risk of serious hypoglycemia with oral antidiabetic monotherapy: A retrospective cohort study. Pharmacoepidemiology and drug safety. 2018;27(1):9–18. [PubMed: 29108130]

262. Ridderstrale M, Rosenstock J, Andersen KR, Woerle HJ, Salsali A, investigators E-RHHSt. Empagliflozin compared with glimepiride in metformin-treated patients with type 2 diabetes: 208-week data from a masked randomized controlled trial. Diabetes, obesity & metabolism. 2018.

263. Kohler S, Kaspers S, Salsali A, Zeller C, Woerle HJ. Analysis of Fractures in Patients With Type 2 Diabetes Treated With Empagliflozin in Pooled Data From Placebo-Controlled Trials and a Head-to-Head Study Versus Glimepiride. Diabetes care. 2018;41(8):1809–16. [PubMed: 29907581]

264. Schwartz AV, Margolis KL, Sellmeyer DE, Vittinghoff E, Ambrosius WT, Bonds DE, et al. Intensive glycemic control is not associated with fractures or falls in the ACCORD randomized trial. Diabetes care. 2012;35(7):1525–31. [PubMed: 22723583]

265. Majumdar SR, Josse RG, Lin M, Eurich DT. Does Sitagliptin Affect the Rate of Osteoporotic Fractures in Type 2 Diabetes? Population-Based Cohort Study. The Journal of clinical endocrinology and metabolism. 2016;101(5):1963–9. [PubMed: 26930183]

266. Shigeto M, Katsura M, Matsuda M, Ohkuma S, Kaku K. Nateglinide and mitiglinide, but not sulfonylureas, induce insulin secretion through a mechanism mediated by calcium release from endoplasmic reticulum. The Journal of pharmacology and experimental therapeutics. 2007;322(1):1–7. [PubMed: 17409272]

267. Takahashi A, Nagashima K, Hamasaki A, Kuwamura N, Kawasaki Y, Ikeda H, et al. Sulfonylurea and glinide reduce insulin content, functional expression of K(ATP) channels, and accelerate apoptotic beta-cell death in the chronic phase. Diabetes research and clinical practice. 2007;77(3):343–50. [PubMed: 17316868]

268. Jovanovic L, Dailey G, Huang WC, Strange P, Goldstein BJ. Repaglinide in type 2 diabetes: a 24-week, fixed-dose efficacy and safety study. Journal of clinical pharmacology. 2000;40(1):49–57. [PubMed: 10631622]

269. Wu PC, Wu VC, Lin CJ, Pan CF, Chen CY, Huang TM, et al. Meglitinides increase the risk of hypoglycemia in diabetic patients with advanced chronic kidney disease: a nationwide, population-based study. Oncotarget. 2017;8(44):78086–95. [PubMed: 29100450]

270. Rosenstock J, Shen SG, Gatlin MR, Foley JE. Combination therapy with nateglinide and a thiazolidinedione improves glycemic control in type 2 diabetes. Diabetes care. 2002;25(9):1529–33. [PubMed: 12196422]

271. Viertel B, Guttner J. Effects of the oral antidiabetic repaglinide on the reproduction of rats. Arzneimittel-Forschung. 2000;50(5):425–40. [PubMed: 10858870]

272. Chen HH, Horng MH, Yeh SY, Lin IC, Yeh CJ, Muo CH, et al. Glycemic Control with Thiazolidinedione Is Associated with Fracture of T2DM Patients. PloS one. 2015;10(8):e0135530. [PubMed: 26317995]

273. Raskin P, Jovanovic L, Berger S, Schwartz S, Woo V, Ratner R. Repaglinide/troglitazone combination therapy: improved glycemic control in type 2 diabetes. Diabetes care. 2000;23(7): 979–83. [PubMed: 10895850]

274. Cetrone M, Mele A, Tricarico D. Effects of the antidiabetic drugs on the age-related atrophy and sarcopenia associated with diabetes type II. Current diabetes reviews. 2014;10(4):231–7. [PubMed: 25245021]

275. Tasyurek HM, Altunbas HA, Balci MK, Sanlioglu S. Incretins: their physiology and application in the treatment of diabetes mellitus. Diabetes/metabolism research and reviews. 2014;30(5):354–71. [PubMed: 24989141]

276. Gerich J DPP-4 inhibitors: what may be the clinical differentiators? Diabetes research and clinical practice. 2010;90(2):131–40. [PubMed: 20708812]

277. Yang Y, Zhao C, Liang J, Yu M, Qu X. Effect of Dipeptidyl Peptidase-4 Inhibitors on Bone Metabolism and the Possible Underlying Mechanisms. Frontiers in pharmacology. 2017;8:487. [PubMed: 28790917]

278. Nuche-Berenguer B, Portal-Nunez S, Moreno P, Gonzalez N, Acitores A, Lopez-Herradon A, et al. Presence of a functional receptor for GLP-1 in osteoblastic cells, independent of the cAMP-linked GLP-1 receptor. Journal of cellular physiology. 2010;225(2):585–92. [PubMed: 20506394]

279. Yamada C, Yamada Y, Tsukiyama K, Yamada K, Udagawa N, Takahashi N, et al. The murine glucagon-like peptide-1 receptor is essential for control of bone resorption. Endocrinology. 2008;149(2):574–9. [PubMed: 18039776]

280. Mieczkowska A, Bouvard B, Chappard D, Mabilleau G. Glucose-dependent insulinotropic polypeptide (GIP) directly affects collagen fibril diameter and collagen cross-linking in osteoblast cultures. Bone. 2015;74:29–36. [PubMed: 25582623]

281. Tsukiyama K, Yamada Y, Yamada C, Harada N, Kawasaki Y, Ogura M, et al. Gastric inhibitory polypeptide as an endogenous factor promoting new bone formation after food ingestion. Molecular endocrinology. 2006;20(7):1644–51. [PubMed: 16469773]

282. Zhong Q, Itokawa T, Sridhar S, Ding KH, Xie D, Kang B, et al. Effects of glucose-dependent insulinotropic peptide on osteoclast function. American journal of physiology Endocrinology and metabolism. 2007;292(2):E543–8. [PubMed: 17003233]

283. Scheen AJ. The safety of gliptins : updated data in 2018. Expert opinion on drug safety. 2018;17(4):387–405. [PubMed: 29468916]

284. Tarapues M, Cereza G, Figueras A. Association of musculoskeletal complaints and gliptin use: review of spontaneous reports. Pharmacoepidemiology and drug safety. 2013;22(10):1115–8. [PubMed: 23960039]

285. Men P, He N, Song C, Zhai S. Dipeptidyl peptidase-4 inhibitors and risk of arthralgia: A systematic review and meta-analysis. Diabetes & metabolism. 2017;43(6):493–500. [PubMed: 28778563]

286. Gallagher EJ, Sun H, Kornhauser C, Tobin-Hess A, Epstein S, Yakar S, et al. The effect of dipeptidyl peptidase-IV inhibition on bone in a mouse model of type 2 diabetes. Diabetes/metabolism research and reviews. 2014;30(3):191–200. [PubMed: 24023014]

287. Sbaraglini ML, Molinuevo MS, Sedlinsky C, Schurman L, McCarthy AD. Saxagliptin affects long-bone microarchitecture and decreases the osteogenic potential of bone marrow stromal cells. European journal of pharmacology. 2014;727:8–14. [PubMed: 24485890]

288. Wang C, Xiao F, Qu X, Zhai Z, Hu G, Chen X, et al. Sitagliptin, An Anti-diabetic Drug, Suppresses Estrogen Deficiency-Induced OsteoporosisIn Vivo and Inhibits RANKL-Induced Osteoclast Formation and Bone Resorption In Vitro. Frontiers in pharmacology. 2017;8:407. [PubMed: 28713268]

289. Kyle KA, Willett TL, Baggio LL, Drucker DJ, Grynpas MD. Differential effects of PPAR-{gamma} activation versus chemical or genetic reduction of DPP-4 activity on bone quality in mice. Endocrinology. 2011;152(2):457–67. [PubMed: 21177828]

290. Glorie L, Behets GJ, Baerts L, De Meester I, D'Haese PC, Verhulst A. DPP IV inhibitor treatment attenuates bone loss and improves mechanical bone strength in male diabetic rats. American journal of physiology Endocrinology and metabolism. 2014;307(5):E447–55. [PubMed: 25053403]

291. Ambrosi TH, Scialdone A, Graja A, Gohlke S, Jank AM, Bocian C, et al. Adipocyte Accumulation in the Bone Marrow during Obesity and Aging Impairs Stem Cell-Based Hematopoietic and Bone Regeneration. Cell stem cell. 2017;20(6):771–84e6. [PubMed: 28330582]

292. Charoenphandhu N, Suntornsaratoon P, Sa-Nguanmoo P, Tanajak P, Teerapornpuntakit J, Aeimlapa R, et al. Dipeptidyl Peptidase-4 Inhibitor, Vildagliptin, Improves Trabecular Bone Mineral Density and Microstructure in Obese, Insulin-Resistant, Pre-diabetic Rats. Canadian journal of diabetes. 2018.

293. Eom YS, Gwon AR, Kwak KM, Kim JY, Yu SH, Lee S, et al. Protective Effects of Vildagliptin against Pioglitazone-Induced Bone Loss in Type 2 Diabetic Rats. PloS one. 2016;11(12):e0168569. [PubMed: 27997588]

294. Egger A, Kraenzlin ME, Meier C. Effects of Incretin-Based Therapies and SGLT2 Inhibitors on Skeletal Health. Current osteoporosis reports. 2016;14(6):345–50. [PubMed: 27709509]

295. Meier C, Schwartz AV, Egger A, Lecka-Czernik B. Effects of diabetes drugs on the skeleton. Bone. 2016;82:93–100. [PubMed: 25913633]

296. Bunck MC, Poelma M, Eekhoff EM, Schweizer A, Heine RJ, Nijpels G, et al. Effects of vildagliptin on postprandial markers of bone resorption and calcium homeostasis in recently diagnosed, well-controlled type 2 diabetes patients. Journal of diabetes. 2012;4(2):181–5. [PubMed: 22051153]

297. Carbone LD, Buzkova P, Fink HA, Robbins JA, Bethel M, Isales CM, et al. Association of DPP-4 activity with BMD, body composition, and incident hip fracture: the Cardiovascular Health Study. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2017;28(5):1631–40.

298. Josse RG, Majumdar SR, Zheng Y, Adler A, Bethel MA, Buse JB, et al. Sitagliptin and risk of fractures in type 2 diabetes: Results from the TECOS trial. Diabetes, obesity & metabolism. 2017;19(1):78–86.

299. Fu J, Zhu J, Hao Y, Guo C, Zhou Z. Dipeptidyl peptidase-4 inhibitors and fracture risk: an updated meta-analysis of randomized clinical trials. Scientific reports. 2016;6:29104. [PubMed: 27384445]

300. Lin SY, Hsu WH, Lin CC, Lin CL, Tsai CH, Yeh HC, et al. Sitagliptin and Fractures in Type 2 Diabetes: A Nationwide Population-Based Propensity-Matching Study. Frontiers in pharmacology. 2018;9:677. [PubMed: 29988467]

301. Hirshberg B, Parker A, Edelberg H, Donovan M, Iqbal N. Safety of saxagliptin: events of special interest in 9156 patients with type 2 diabetes mellitus. Diabetes/metabolism research and reviews. 2014;30(7):556–69. [PubMed: 24376173]

302. Mosenzon O, Wei C, Davidson J, Scirica BM, Yanuv I, Rozenberg A, et al. Incidence of Fractures in Patients With Type 2 Diabetes in the SAVOR-TIMI 53 Trial. Diabetes care. 2015;38(11): 2142–50. [PubMed: 26358285]

303. Mamza J, Marlin C, Wang C, Chokkalingam K, Idris I. DPP-4 inhibitor therapy and bone fractures in people with Type 2 diabetes - A systematic review and meta-analysis. Diabetes research and clinical practice. 2016;116:288–98. [PubMed: 27321347]

304. Gamble JM, Donnan JR, Chibrikov E, Twells LK, Midodzi WK, Majumdar SR. The risk of fragility fractures in new users of dipeptidyl peptidase-4 inhibitors compared to sulfonylureas and other anti-diabetic drugs: A cohort study. Diabetes research and clinical practice. 2018;136:159–67. [PubMed: 29258886]

305. Driessen JH, van den Bergh JP, van Onzenoort HA, Henry RM, Leufkens HG, de Vries F. Long-term use of dipeptidyl peptidase-4 inhibitors and risk of fracture: A retrospective population-based cohort study. Diabetes, obesity & metabolism. 2017;19(3):421–8.

306. Dombrowski S, Kostev K, Jacob L. Use of dipeptidyl peptidase-4 inhibitors and risk of bone fracture in patients with type 2 diabetes in Germany-A retrospective analysis of real-world data. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2017;28(8): 2421–8.

307. Monami M, Dicembrini I, Antenore A, Mannucci E. Dipeptidyl peptidase-4 inhibitors and bone fractures: a meta-analysis of randomized clinical trials. Diabetes care. 2011;34(11):2474–6. [PubMed: 22025784]

308. Yang J, Huang C, Wu S, Xu Y, Cai T, Chai S, et al. The effects of dipeptidyl peptidase-4 inhibitors on bone fracture among patients with type 2 diabetes mellitus: A network meta-analysis of randomized controlled trials. PloS one. 2017;12(12):e0187537. [PubMed: 29206832]

309. Choi HJ, Park C, Lee YK, Ha YC, Jang S, Shin CS. Risk of fractures and diabetes medications: a nationwide cohort study. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2016;27(9):2709–15.

310. Mabilleau G, Pereira M, Chenu C. Novel skeletal effects of glucagon-like peptide-1 (GLP-1) receptor agonists. The Journal of endocrinology. 2018;236(1):R29–R42. [PubMed: 28855317]

311. Pacheco-Pantoja EL, Ranganath LR, Gallagher JA, Wilson PJ, Fraser WD. Receptors and effects of gut hormones in three osteoblastic cell lines. BMC physiology. 2011;11:12. [PubMed: 21801348]

312. Kim JY, Lee SK, Jo KJ, Song DY, Lim DM, Park KY, et al. Exendin-4 increases bone mineral density in type 2 diabetic OLETF rats potentially through the down-regulation of SOST/sclerostin in osteocytes. Life sciences. 2013;92(10):533–40. [PubMed: 23357248]

313. Pereira M, Jeyabalan J, Jorgensen CS, Hopkinson M, Al-Jazzar A, Roux JP, et al. Chronic administration of Glucagon-like peptide-1 receptor agonists improves trabecular bone mass and architecture in ovariectomised mice. Bone. 2015;81:459–67. [PubMed: 26314515]

314. Aoyama E, Watari I, Podyma-Inoue KA, Yanagishita M, Ono T. Expression of glucagon-like peptide-1 receptor and glucosedependent insulinotropic polypeptide receptor is regulated by the glucose concentration in mouse osteoblastic MC3T3–E1 cells. International journal of molecular medicine. 2014;34(2):475–82. [PubMed: 24866833]

315. Ramsey W, Isales CM. Intestinal Incretins and the Regulation of Bone Physiology. Advances in experimental medicine and biology. 2017;1033:13–33. [PubMed: 29101649]

316. Meng J, Ma X, Wang N, Jia M, Bi L, Wang Y, et al. Activation of GLP-1 Receptor Promotes Bone Marrow Stromal Cell Osteogenic Differentiation through beta-Catenin. Stem cell reports. 2016;6(4):633. [PubMed: 27074552]

317. Feng Y, Su L, Zhong X, Guohong W, Xiao H, Li Y, et al. Exendin-4 promotes proliferation and differentiation of MC3T3–E1 osteoblasts by MAPKs activation. Journal of molecular endocrinology. 2016;56(3):189–99. [PubMed: 26647389]

318. Wu X, Li S, Xue P, Li Y. Liraglutide, a glucagon-like peptide-1 receptor agonist, facilitates osteogenic proliferation and differentiation in MC3T3–E1 cells through phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT), extracellular signal-related kinase (ERK)1/2, and cAMP/protein kinase A (PKA) signaling pathways involving beta-catenin. Experimental cell research. 2017;360(2):281–91. [PubMed: 28919123]

319. Wu X, Li S, Xue P, Li Y. Liraglutide Inhibits the Apoptosis of MC3T3–E1 Cells Induced by Serum Deprivation through cAMP/PKA/beta-Catenin and PI3K/AKT/GSK3beta Signaling Pathways. Molecules and cells. 2018;41(3):234–43. [PubMed: 29463067]

320. Nuche-Berenguer B, Moreno P, Portal-Nunez S, Dapia S, Esbrit P, Villanueva-Penacarrillo ML. Exendin-4 exerts osteogenic actions in insulin-resistant and type 2 diabetic states. Regulatory peptides. 2010;159(1–3):61–6. [PubMed: 19586609]

321. Zhao C, Liang J, Yang Y, Yu M, Qu X. The Impact of Glucagon-Like Peptide-1 on Bone Metabolism and Its Possible Mechanisms. Frontiers in endocrinology. 2017;8:98. [PubMed: 28515711]

322. Nuche-Berenguer B, Moreno P, Esbrit P, Dapia S, Caeiro JR, Cancelas J, et al. Effect of GLP-1 treatment on bone turnover in normal, type 2 diabetic, and insulin-resistant states. Calcified tissue international. 2009;84(6):453–61. [PubMed: 19219381]

323. Mansur SA, Mieczkowska A, Bouvard B, Flatt PR, Chappard D, Irwin N, et al. Stable Incretin Mimetics Counter Rapid Deterioration of Bone Quality in Type 1 Diabetes Mellitus. Journal of cellular physiology. 2015;230(12):3009–18. [PubMed: 26016732]

324. Ma X, Meng J, Jia M, Bi L, Zhou Y, Wang Y, et al. Exendin-4, a glucagon-like peptide-1 receptor agonist, prevents osteopenia by promoting bone formation and suppressing bone resorption in aged ovariectomized rats. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2013;28(7):1641–52.

325. Lu N, Sun H, Yu J, Wang X, Liu D, Zhao L, et al. Glucagon-like peptide-1 receptor agonist Liraglutide has anabolic bone effects in ovariectomized rats without diabetes. PloS one. 2015;10(7):e0132744. [PubMed: 26177280]

326. Sun HX, Lu N, Liu DM, Zhao L, Sun LH, Zhao HY, et al. The bone-preserving effects of exendin-4 in ovariectomized rats. Endocrine. 2016;51(2):323–32. [PubMed: 26109471]

327. Bunck MC, Eliasson B, Corner A, Heine RJ, Shaginian RM, Taskinen MR, et al. Exenatide treatment did not affect bone mineral density despite body weight reduction in patients with type 2 diabetes. Diabetes, obesity & metabolism. 2011;13(4):374–7.

328. Iepsen EW, Lundgren JR, Hartmann B, Pedersen O, Hansen T, Jorgensen NR, et al. GLP-1 Receptor Agonist Treatment Increases Bone Formation and Prevents Bone Loss in Weight-Reduced Obese Women. The Journal of clinical endocrinology and metabolism. 2015;100(8):2909–17. [PubMed: 26043228]

329. Mabilleau G, Mieczkowska A, Chappard D. Use of glucagon-like peptide-1 receptor agonists and bone fractures: a meta-analysis of randomized clinical trials. Journal of diabetes. 2014;6(3):260–6. [PubMed: 24164867]

330. Su B, Sheng H, Zhang M, Bu L, Yang P, Li L, et al. Risk of bone fractures associated with glucagon-like peptide-1 receptor agonists' treatment: a meta-analysis of randomized controlled trials. Endocrine. 2015;48(1):107–15. [PubMed: 25074632]

331. Zhang YS, Weng WY, Xie BC, Meng Y, Hao YH, Liang YM, et al. Glucagon-like peptide-1 receptor agonists and fracture risk: a network meta-analysis of randomized clinical trials. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2018.

332. Driessen JH, Henry RM, van Onzenoort HA, Lalmohamed A, Burden AM, Prieto-Alhambra D, et al. Bone fracture risk is not associated with the use of glucagon-like peptide-1 receptor agonists: a population-based cohort analysis. Calcified tissue international. 2015;97(2):104–12. [PubMed: 25894068]

333. Driessen JH, van Onzenoort HA, Starup-Linde J, Henry R, Burden AM, Neef C, et al. Use of Glucagon-Like-Peptide 1 Receptor Agonists and Risk of Fracture as Compared to Use of Other Anti-hyperglycemic Drugs. Calcified tissue international. 2015;97(5):506–15. [PubMed: 26184119]

334. Driessen JH, de Vries F, van Onzenoort H, Harvey NC, Neef C, van den Bergh JP, et al. The use of incretins and fractures - a meta-analysis on population-based real life data. British journal of clinical pharmacology. 2017;83(4):923–6. [PubMed: 27780288]

335. Gentilella R, Pechtner V, Corcos A, Consoli A. Glucagon-like peptide-1 receptor agonists in type 2 diabetes treatment: are they all the same? Diabetes/metabolism research and reviews. 2018:e3070. [PubMed: 30156747]

336. Nigro SC, Riche DM, Pheng M, Baker WL. Canagliflozin, a novel SGLT2 inhibitor for treatment of type 2 diabetes. The Annals of pharmacotherapy. 2013;47(10):1301–11. [PubMed: 24259694]

337. Bolinder J, Ljunggren O, Johansson L, Wilding J, Langkilde AM, Sjostrom CD, 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, obesity & metabolism. 2014;16(2):159–69.

338. Hedrington MS, Davis SN. The role of empagliflozin in the management of type 2 diabetes by patient profile. Therapeutics and clinical risk management. 2015;11:739–49. [PubMed: 25999725]

339. Liakos A, Karagiannis T, Athanasiadou E, Sarigianni M, Mainou M, Papatheodorou K, et al. Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis. Diabetes, obesity & metabolism. 2014;16(10):984–93.

340. Monami M, Nardini C, Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. Diabetes, obesity & metabolism. 2014;16(5):457–66.

341. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes care. 2010;33(10):2217–24. [PubMed: 20566676]

342. Kaku K, Watada H, Iwamoto Y, Utsunomiya K, Terauchi Y, Tobe K, et al. Efficacy and safety of monotherapy with the novel sodium/glucose cotransporter-2 inhibitor tofogliflozin in Japanese patients with type 2 diabetes mellitus: a combined Phase 2 and 3 randomized, placebo-controlled, double-blind, parallel-group comparative study. Cardiovascular diabetology. 2014;13:65. [PubMed: 24678906]

343. Wilding JP, Woo V, Soler NG, Pahor A, Sugg J, Rohwedder K, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. Annals of internal medicine. 2012;156(6):405–15. [PubMed: 22431673]

344. Rosenstock J, Jelaska A, Frappin G, Salsali A, Kim G, Woerle HJ, et al. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. Diabetes care. 2014;37(7):1815–23. [PubMed: 24929430]

345. DeFronzo RA, Lewin A, Patel S, Liu D, Kaste R, Woerle HJ, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes care. 2015;38(3):384–93. [PubMed: 25583754]

346. Guthrie RM. Clinical use of dipeptidyl peptidase-4 and sodium-glucose cotransporter 2 inhibitors in combination therapy for type 2 diabetes mellitus. Postgraduate medicine. 2015;127(5):463–79. [PubMed: 25956345]

347. Kovacs CS, Seshiah V, Merker L, Christiansen AV, Roux F, Salsali A, et al. Empagliflozin as Add-on Therapy to Pioglitazone With or Without Metformin in Patients With Type 2 Diabetes Mellitus. Clinical therapeutics. 2015.

348. Mathieu C, Ranetti AE, Li D, Ekholm E, Cook W, Hirshberg B, et al. A Randomized, Double-Blind, Phase 3 Trial of Triple Therapy With Dapagliflozin Add-on to Saxagliptin Plus Metformin in Type 2 Diabetes. Diabetes care. 2015.

349. Perkins BA, Cherney DZ, Partridge H, Soleymanlou N, Tschirhart H, Zinman B, et al. Sodium-glucose cotransporter 2 inhibition and glycemic control in type 1 diabetes: results of an 8-week open-label proof-of-concept trial. Diabetes care. 2014;37(5):1480–3. [PubMed: 24595630]

350. Argento NB, Nakamura K. Glycemic Effects of Sglt-2 Inhibitor Canagliflozin in Type 1 Diabetes Patients Using the Dexcom G4 Platinum Cgm. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2016;22(3):315–22.

351. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine. 2015;373(22):2117–28. [PubMed: 26378978]

352. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. The New England journal of medicine. 2017;377(7):644–57. [PubMed: 28605608]

353. Brown IR, McBain AM, Chalmers J, Campbell IW, Brown ER, Lewis MJ. Sex difference in the relationship of calcium and magnesium excretion to glycaemic control in type 1 diabetes mellitus. Clinica chimica acta; international journal of clinical chemistry. 1999;283(1–2):119–28. [PubMed: 10404736]

354. Isidro ML, Ruano B. Bone disease in diabetes. Current diabetes reviews. 2010;6(3):144–55. [PubMed: 20380629]

355. Malone JI, Lowitt S, Duncan JA, Shah SC, Vargas A, Root AW. Hypercalciuria, hyperphosphaturia, and growth retardation in children with diabetes mellitus. Pediatrics. 1986;78(2):298–304. [PubMed: 3488537]

356. Alba M, Xie J, Fung A, Desai M. The effects of canagliflozin, a sodium glucose co-transporter 2 inhibitor, on mineral metabolism and bone in patients with type 2 diabetes mellitus. Current medical research and opinion. 2016;32(8):1375–85. [PubMed: 27046479]

357. Thrailkill KM, Nyman JS, Bunn RC, Uppuganti S, Thompson KL, Lumpkin CK, Jr., et al. The impact of SGLT2 inhibitors, compared with insulin, on diabetic bone disease in a mouse model of type 1 diabetes. Bone. 2016.

358. Ghezzi C, Yu AS, Hirayama BA, Kepe V, Liu J, Scafoglio C, et al. Dapagliflozin Binds Specifically to Sodium-Glucose Cotransporter 2 in the Proximal Renal Tubule. Journal of the American Society of Nephrology : JASN. 2017;28(3):802–10. [PubMed: 27620988]

359. Jurysta C, Nicaise C, Giroix MH, Cetik S, Malaisse WJ, Sener A. Comparison of GLUT1, GLUT2, GLUT4 and SGLT1 mRNA expression in the salivary glands and six other organs of control, streptozotocin-induced and Goto-Kakizaki diabetic rats. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology. 2013;31(1):37–43.

360. Edwards A, Bonny O. A Model of Calcium Transport and Regulation in the Proximal Tubule. American journal of physiology Renal physiology. 2018.

361. Thrailkill KM, Clay Bunn R, Nyman JS, Rettiganti MR, Cockrell GE, Wahl EC, et al. SGLT2 inhibitor therapy improves blood glucose but does not prevent diabetic bone disease in diabetic DBA/2J male mice. Bone. 2015.

362. Mamidi RN, Proctor J, De Jonghe S, Feyen B, Moesen E, Vinken P, et al. Carbohydrate malabsorption mechanism for tumor formation in rats treated with the SGLT2 inhibitor canagliflozin. Chemico-biological interactions. 2014;221:109–18. [PubMed: 25130857]

363. De Jonghe S, Proctor J, Vinken P, Feyen B, Wynant I, Marien D, et al. Carcinogenicity in rats of the SGLT2 inhibitor canagliflozin. Chemico-biological interactions. 2014;224:1–12. [PubMed: 25289773]
364. Ly JP, Onay T, Sison K, Sivaskandarajah G, Sabbisetti V, Li L, et al. The Sweet Pee model for Sglt2 mutation. Journal of the American Society of Nephrology : JASN. 2011;22(1):113–23. [PubMed: 21209254]
365. Bogdanffy MS, Stachlewitz RF, van Tongeren S, Knight B, Sharp DE, Ku W, et al. Nonclinical safety of the sodium-glucose cotransporter 2 inhibitor empagliflozin. International journal of toxicology. 2014;33(6):436–49. [PubMed: 25260362]
366. Tirmenstein M, Dorr TE, Janovitz EB, Hagan D, Abell LM, Onorato JM, et al. Nonclinical toxicology assessments support the chronic safety of dapagliflozin, a first-in-class sodium-glucose cotransporter 2 inhibitor. International journal of toxicology. 2013;32(5):336–50. [PubMed: 24097127]
367. Takasu T, Hayashizaki Y, Hirosumi J, Minoura H, Amino N, Kurosaki E, et al. The Sodium Glucose Cotransporter 2 Inhibitor Ipragliflozin Promotes Preferential Loss of Fat Mass in Non-obese Diabetic Goto-Kakizaki Rats. Biological & pharmaceutical bulletin. 2017;40(5):675–80. [PubMed: 28458353]
368. Filippatos TD, Tsimihodimos V, Liamis G, Elisaf MS. SGLT2 inhibitors-induced electrolyte abnormalities: An analysis of the associated mechanisms. Diabetes & metabolic syndrome. 2018;12(1):59–63. [PubMed: 28826578]
369. Blau JE, Bauman V, Conway EM, Piaggi P, Walter MF, Wright EC, et al. Canagliflozin triggers the FGF23/1,25-dihydroxyvitamin D/PTH axis in healthy volunteers in a randomized crossover study. JCI insight. 2018;3(8).
370. Weir MR, Kline I, Xie J, Edwards R, Usiskin K. Effect of canagliflozin on serum electrolytes in patients with type 2 diabetes in relation to estimated glomerular filtration rate (eGFR). Current medical research and opinion. 2014;30(9):1759–68. [PubMed: 24786834]
371. Aronson R, Frias J, Goldman A, Darekar A, Lauring B, Terra SG. Long-term efficacy and safety of ertugliflozin monotherapy in patients with inadequately controlled T2DM despite diet and exercise: VERTIS MONO extension study. Diabetes, obesity & metabolism. 2018;20(6):1453–60.
372. Tang H, Zhang X, Zhang J, Li Y, Del Gobbo LC, Zhai S, et al. Elevated serum magnesium associated with SGLT2 inhibitor use in type 2 diabetes patients: a meta-analysis of randomised controlled trials. Diabetologia. 2016;59(12):2546–51. [PubMed: 27628105]
373. Gilbert RE, Mende C, Vijapurkar U, Sha S, Davies MJ, Desai M. Effects of Canagliflozin on Serum Magnesium in Patients With Type 2 Diabetes Mellitus: A Post Hoc Analysis of Randomized Controlled Trials. Diabetes therapy : research, treatment and education of diabetes and related disorders. 2017;8(2):451–8.
374. Kohler S, Salsali A, Hantel S, Kaspers S, Woerle HJ, Kim G, et al. Safety and Tolerability of Empagliflozin in Patients with Type 2 Diabetes. Clinical therapeutics. 2016;38(6):1299–313. [PubMed: 27085585]
375. Kaur A, Winters SJ. Severe hypercalcemia and hypernatremia in a patient treated with canagliflozin. Endocrinology, diabetes & metabolism case reports. 2015;2015:150042.
376. Taylor SI, Blau JE, Rother KI. Possible adverse effects of SGLT2 inhibitors on bone. The lancet Diabetes & endocrinology. 2015;3(1):8–10. [PubMed: 25523498]
377. Bilezikian JP, Watts NB, Usiskin K, Polidori D, Fung A, Sullivan D, et al. Evaluation of Bone Mineral Density and Bone Biomarkers in Patients With Type 2 Diabetes Treated With Canagliflozin. The Journal of clinical endocrinology and metabolism. 2016;101(1):44–51. [PubMed: 26580234]
378. Bays HE, Weinstein R, Law G, Canovatchel W. Canagliflozin: effects in overweight and obese subjects without diabetes mellitus. Obesity. 2014;22(4):1042–9. [PubMed: 24227660]
379. Ljunggren O, Bolinder J, Johansson L, Wilding J, Langkilde AM, Sjostrom CD, et al. Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin. Diabetes, obesity & metabolism. 2012;14(11):990–9.

380. Kohler S, Zeller C, Iliev H, Kaspers S. Safety and Tolerability of Empagliflozin in Patients with Type 2 Diabetes: Pooled Analysis of Phase I-III Clinical Trials. Advances in therapy. 2017;34(7): 1707–26. [PubMed: 28631216]
381. Rosenstock J, Frias J, Pall D, Charbonnel B, Pascu R, Saur D, et al. Effect of ertugliflozin on glucose control, body weight, blood pressure and bone density in type 2 diabetes mellitus inadequately controlled on metformin monotherapy (VERTIS MET). Diabetes, obesity & metabolism. 2018;20(3):520–9.
382. Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney international. 2014;85(4):962–71. [PubMed: 24067431]
383. Tang HL, Li DD, Zhang JJ, Hsu YH, Wang TS, Zhai SD, et al. Lack of evidence for a harmful effect of sodium-glucose co-transporter 2 (SGLT2) inhibitors on fracture risk among type 2 diabetes patients: a network and cumulative meta-analysis of randomized controlled trials. Diabetes, obesity & metabolism. 2016;18(12):1199–206.
384. Wu JH, Foote C, Blomster J, Toyama T, Perkovic V, Sundstrom J, et al. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. The lancet Diabetes & endocrinology. 2016;4(5):411–9. [PubMed: 27009625]
385. Ruanpeng D, Ungprasert P, Sangtian J, Harindhanavudhi T. Sodium-glucose cotransporter 2 (SGLT2) inhibitors and fracture risk in patients with type 2 diabetes mellitus: A meta-analysis. Diabetes/metabolism research and reviews. 2017;33(6).
386. Watts NB, Bilezikian JP, Usiskin K, Edwards R, Desai M, Law G, et al. Effects of Canagliflozin on Fracture Risk in Patients With Type 2 Diabetes Mellitus. The Journal of clinical endocrinology and metabolism. 2016;101(1):157–66. [PubMed: 26580237]
387. Blevins TC, Farooki A. Bone effects of canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus. Postgraduate medicine. 2017;129(1):159–68. [PubMed: 27894216]
388. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. The New England journal of medicine. 2017.
389. Araki E, Onishi Y, Asano M, Kim H, Yajima T. Efficacy and safety of dapagliflozin over 1 year as add-on to insulin therapy in Japanese patients with type 2 diabetes: the DAISY (Dapagliflozin Added to patients under InSulin therapY) trial. Diabetes, obesity & metabolism. 2017;19(4):562–70.
390. Toulis KA, Bilezikian JP, Thomas GN, Hanif W, Kotsa K, Thayakaran R, et al. Initiation of dapagliflozin and treatment-emergent fractures. Diabetes, obesity & metabolism. 2018;20(4): 1070–4.
391. Ptaszynska A, Johnsson KM, Parikh SJ, de Bruin TW, Apanovitch AM, List JF. Safety profile of dapagliflozin for type 2 diabetes: pooled analysis of clinical studies for overall safety and rare events. Drug safety. 2014;37(10):815–29. [PubMed: 25096959]
392. Fioretto P, Del Prato S, Buse JB, Goldenberg R, Giorgino F, Reyner D, et al. Efficacy and Safety of Dapagliflozin in Patients with Type 2 Diabetes and Moderate Renal Impairment (Chronic Kidney Disease Stage 3A): The DERIVE Study. Diabetes, obesity & metabolism. 2018.
393. Dagogo-Jack S, Liu J, Eldor R, Amorin G, Johnson J, Hille D, et al. Efficacy and safety of the addition of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sitagliptin: The VERTIS SITA2 placebo-controlled randomized study. Diabetes, obesity & metabolism. 2018;20(3):530–40.
394. Balfour JA, McTavish D. Acarbose : An Update of its Pharmacology and Therapeutic Use in Diabetes Mellitus. Drugs. 1993;46(6):1025–54. [PubMed: 7510610]
395. Rosak C, Mertes G. Critical evaluation of the role of acarbose in the treatment of diabetes: patient considerations. Diabetes, metabolic syndrome and obesity : targets and therapy. 2012;5:357–67.
396. Holman RR, Cull CA, Turner RC. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44). Diabetes care. 1999;22(6):960–4. [PubMed: 10372249]

397. Coniff RF, Shapiro JA, Seaton TB. Long-term efficacy and safety of acarbose in the treatment of obese subjects with non-insulin-dependent diabetes mellitus. Archives of internal medicine. 1994;154(21):2442–8. [PubMed: 7979840]
398. Scorpiglione N, Belfiglio M, Carinci F, Cavaliere D, De Curtis A, Franciosi M, et al. The effectiveness, safety and epidemiology of the use of acarbose in the treatment of patients with type II diabetes mellitus. A model of medicine-based evidence. European journal of clinical pharmacology. 1999;55(4):239–49. [PubMed: 10424314]
399. Mertes G Safety and efficacy of acarbose in the treatment of Type 2 diabetes: data from a 5-year surveillance study. Diabetes research and clinical practice. 2001;52(3):193–204. [PubMed: 11323089]
400. He K, Shi JC, Mao XM. Safety and efficacy of acarbose in the treatment of diabetes in Chinese patients. Therapeutics and clinical risk management. 2014;10:505–11. [PubMed: 25061309]
401. Huang YN, Zhao YL, Gao XL, Zhao ZF, Jing Z, Zeng WC, et al. Intestinal alpha-glucosidase inhibitory activity and toxicological evaluation of Nymphaea stellata flowers extract. Journal of ethnopharmacology. 2010;131(2):306–12. [PubMed: 20600753]
402. Hashiguchi C, Kawamoto S, Kasai T, Nishi Y, Nagaoka E. Influence of an antidiabetic drug on biomechanical and histological parameters around implants in type 2 diabetic rats. Implant dentistry. 2014;23(3):264–9. [PubMed: 24844386]
403. Hay DL, Chen S, Lutz TA, Parkes DG, Roth JD. Amylin: Pharmacology, Physiology, and Clinical Potential. Pharmacological reviews. 2015;67(3):564–600. [PubMed: 26071095]
404. Ratner RE, Dickey R, Fineman M, Maggs DG, Shen L, Strobel SA, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus: a 1-year, randomized controlled trial. Diabetic medicine : a journal of the British Diabetic Association. 2004;21(11):1204–12. [PubMed: 15498087]
405. Hollander PA, Levy P, Fineman MS, Maggs DG, Shen LZ, Strobel SA, et al. Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. Diabetes care. 2003;26(3):784–90. [PubMed: 12610038]
406. Younk LM, Mikeladze M, Davis SN. Pramlintide and the treatment of diabetes: a review of the data since its introduction. Expert opinion on pharmacotherapy. 2011;12(9):1439–51. [PubMed: 21564002]
407. Pittner RA, Albrandt K, Beaumont K, Gaeta LS, Koda JE, Moore CX, et al. Molecular physiology of amylin. Journal of cellular biochemistry. 1994;55 Suppl:19–28. [PubMed: 7929615]
408. Gingell JJ, Burns ER, Hay DL. Activity of pramlintide, rat and human amylin but not Abeta1–42 at human amylin receptors. Endocrinology. 2014;155(1):21–6. [PubMed: 24169554]
409. Cornish J, Naot D. Amylin and adrenomedullin: novel regulators of bone growth. Current pharmaceutical design. 2002;8(23):2009–21. [PubMed: 12171515]
410. Cornish J, Callon KE, Lin CQ, Xiao CL, Mulvey TB, Coy DH, et al. Dissociation of the effects of amylin on osteoblast proliferation and bone resorption. The American journal of physiology. 1998;274(5 Pt 1):E827–33. [PubMed: 9612240]
411. Villa I, Rubinacci A, Ravasi F, Ferrara AF, Guidobono F. Effects of amylin on human osteoblast-like cells. Peptides. 1997;18(4):537–40. [PubMed: 9210172]
412. Cornish J, Reid IR. Effects of amylin and adrenomedullin on the skeleton. Journal of musculoskeletal & neuronal interactions. 2001;2(1):15–24. [PubMed: 15758473]
413. Cornish J, Callon KE, Gasser JA, Bava U, Gardiner EM, Coy DH, et al. Systemic administration of a novel octapeptide, amylin-(1-−−8), increases bone volume in male mice. American journal of physiology Endocrinology and metabolism. 2000;279(4):E730–5. [PubMed: 11001752]
414. Cornish J, Callon KE, King AR, Cooper GJ, Reid IR. Systemic administration of amylin increases bone mass, linear growth, and adiposity in adult male mice. The American journal of physiology. 1998;275(4 Pt 1):E694–9. [PubMed: 9755090]
415. Gutierrez-Rojas I, Lozano D, Nuche-Berenguer B, Moreno P, Acitores A, Ramos-Alvarez I, et al. Amylin exerts osteogenic actions with different efficacy depending on the diabetic status. Molecular and cellular endocrinology. 2013;365(2):309–15. [PubMed: 23178165]

416. Cornish J, Callon KE, Cooper GJ, Reid IR. Amylin stimulates osteoblast proliferation and increases mineralized bone volume in adult mice. Biochemical and biophysical research communications. 1995;207(1):133–9. [PubMed: 7857256]

417. Datta HK, Zaidi M, Wimalawansa SJ, Ghatei MA, Beacham JL, Bloom SR, et al. In vivo and in vitro effects of amylin and amylin-amide on calcium metabolism in the rat and rabbit. Biochemical and biophysical research communications. 1989;162(2):876–81. [PubMed: 2787991]

418. Pietschmann P, Farsoudi KH, Hoffmann O, Klaushofer K, Horandner H, Peterlik M. Inhibitory effect of amylin on basal and parathyroid hormone-stimulated bone resorption in cultured neonatal mouse calvaria. Bone. 1993;14(2):167–72. [PubMed: 8334035]

419. Gilbey SG, Ghatei MA, Bretherton-Watt D, Zaidi M, Jones PM, Perera T, et al. Islet amyloid polypeptide: production by an osteoblast cell line and possible role as a paracrine regulator of osteoclast function in man. Clinical science. 1991;81(6):803–8. [PubMed: 1722443]

420. Zaidi M, Datta HK, Bevis PJ, Wimalawansa SJ, MacIntyre I. Amylin-amide: a new bone-conserving peptide from the pancreas. Experimental physiology. 1990;75(4):529–36. [PubMed: 2223054]

421. Dacquin R, Davey RA, Laplace C, Levasseur R, Morris HA, Goldring SR, et al. Amylin inhibits bone resorption while the calcitonin receptor controls bone formation in vivo. The Journal of cell biology. 2004;164(4):509–14. [PubMed: 14970190]

422. Lerner UH. Deletions of genes encoding calcitonin/alpha-CGRP, amylin and calcitonin receptor have given new and unexpected insights into the function of calcitonin receptors and calcitonin receptor-like receptors in bone. Journal of musculoskeletal & neuronal interactions. 2006;6(1): 87–95. [PubMed: 16675892]

423. Horcajada-Molteni MN, Davicco MJ, Lebecque P, Coxam V, Young AA, Barlet JP. Amylin inhibits ovariectomy-induced bone loss in rats. The Journal of endocrinology. 2000;165(3):663–8. [PubMed: 10828850]

424. Horcajada-Molteni MN, Chanteranne B, Lebecque P, Davicco MJ, Coxam V, Young A, et al. Amylin and bone metabolism in streptozotocin-induced diabetic rats. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2001;16(5):958–65.

425. Romero DF, Bryer HP, Rucinski B, Isserow JA, Buchinsky FJ, Cvetkovic M, et al. Amylin increases bone volume but cannot ameliorate diabetic osteopenia. Calcified tissue international. 1995;56(1):54–61. [PubMed: 7796348]

426. Borm AK, Klevesath MS, Borcea V, Kasperk C, Seibel MJ, Wahl P, et al. The effect of pramlintide (amylin analogue) treatment on bone metabolism and bone density in patients with type 1 diabetes mellitus. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 1999;31(8):472–5. [PubMed: 10494873]

427. Pedersen M, Bruunsgaard H, Weis N, Hendel HW, Andreassen BU, Eldrup E, et al. Circulating levels of TNF-alpha and IL-6-relation to truncal fat mass and muscle mass in healthy elderly individuals and in patients with type-2 diabetes. Mechanisms of ageing and development. 2003;124(4):495–502. [PubMed: 12714258]

428. D'Souza DM, Al-Sajee D, Hawke TJ. Diabetic myopathy: impact of diabetes mellitus on skeletal muscle progenitor cells. Frontiers in physiology. 2013;4:379. [PubMed: 24391596]

429. Krause MP, Riddell MC, Hawke TJ. Effects of type 1 diabetes mellitus on skeletal muscle: clinical observations and physiological mechanisms. Pediatric diabetes. 2011;12(4 Pt 1):345–64. [PubMed: 20860561]

430. Wang T, Feng X, Zhou J, Gong H, Xia S, Wei Q, et al. Type 2 diabetes mellitus is associated with increased risks of sarcopenia and pre-sarcopenia in Chinese elderly. Scientific reports. 2016;6:38937. [PubMed: 27958337]

431. Park SW, Goodpaster BH, Lee JS, Kuller LH, Boudreau R, de Rekeneire N, et al. Excessive loss of skeletal muscle mass in older adults with type 2 diabetes. Diabetes care. 2009;32(11):1993–7. [PubMed: 19549734]

432. Sala D, Zorzano A. Differential control of muscle mass in type 1 and type 2 diabetes mellitus. Cellular and molecular life sciences : CMLS. 2015;72(20):3803–17. [PubMed: 26091746]

433. Workeneh B, Bajaj M. The regulation of muscle protein turnover in diabetes. The international journal of biochemistry & cell biology. 2013;45(10):2239–44. [PubMed: 23838169]

434. Andersen H, Schmitz O, Nielsen S. Decreased isometric muscle strength after acute hyperglycaemia in Type 1 diabetic patients. Diabetic medicine : a journal of the British Diabetic Association. 2005;22(10):1401–7. [PubMed: 16176203]

435. Jakobsen J, Reske-Nielsen E. Diffuse muscle fiber atrophy in newly diagnosed diabetes. Clinical neuropathology. 1986;5(2):73–7. [PubMed: 3708956]

436. Komatsu WR, Gabbay MA, Castro ML, Saraiva GL, Chacra AR, de Barros Neto TL, et al. Aerobic exercise capacity in normal adolescents and those with type 1 diabetes mellitus. Pediatric diabetes. 2005;6(3):145–9. [PubMed: 16109070]

437. Monaco CMF, Hughes MC, Ramos SV, Varah NE, Lamberz C, Rahman FA, et al. Altered mitochondrial bioenergetics and ultrastructure in the skeletal muscle of young adults with type 1 diabetes. Diabetologia. 2018;61(6):1411–23. [PubMed: 29666899]

438. Fritzsche K, Bluher M, Schering S, Buchwalow IB, Kern M, Linke A, et al. Metabolic profile and nitric oxide synthase expression of skeletal muscle fibers are altered in patients with type 1 diabetes. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association. 2008;116(10):606–13.

439. Krentz AJ, Viljoen A, Sinclair A. Insulin resistance: a risk marker for disease and disability in the older person. Diabetic medicine : a journal of the British Diabetic Association. 2013;30(5):535–48. [PubMed: 23173973]

440. Shen WH, Boyle DW, Wisniowski P, Bade A, Liechty EA. Insulin and IGF-I stimulate the formation of the eukaryotic initiation factor 4F complex and protein synthesis in C2C12 myotubes independent of availability of external amino acids. The Journal of endocrinology. 2005;185(2):275–89. [PubMed: 15845920]

441. Abdulla H, Smith K, Atherton PJ, Idris I. Role of insulin in the regulation of human skeletal muscle protein synthesis and breakdown: a systematic review and meta-analysis. Diabetologia. 2016;59(1):44–55. [PubMed: 26404065]

442. Abdulla H, Phillips B, Smith K, Wilkinson D, Atherton PJ, Idris I. Physiological mechanisms of action of incretin and insulin in regulating skeletal muscle metabolism. Current diabetes reviews. 2014;10(5):327–35. [PubMed: 25323297]

443. Chow LS, Albright RC, Bigelow ML, Toffolo G, Cobelli C, Nair KS. Mechanism of insulin's anabolic effect on muscle: measurements of muscle protein synthesis and breakdown using aminoacyl-tRNA and other surrogate measures. American journal of physiology Endocrinology and metabolism. 2006;291(4):E729–36. [PubMed: 16705065]

444. Stump CS, Short KR, Bigelow ML, Schimke JM, Nair KS. Effect of insulin on human skeletal muscle mitochondrial ATP production, protein synthesis, and mRNA transcripts. Proceedings of the National Academy of Sciences of the United States of America. 2003;100(13):7996–8001. [PubMed: 12808136]

445. Wang X, Hu Z, Hu J, Du J, Mitch WE. Insulin resistance accelerates muscle protein degradation: Activation of the ubiquitin-proteasome pathway by defects in muscle cell signaling. Endocrinology. 2006;147(9):4160–8. [PubMed: 16777975]

446. Charlton M, Nair KS. Protein metabolism in insulin-dependent diabetes mellitus. The Journal of nutrition. 1998;128(2 Suppl):323S–7S. [PubMed: 9478016]

447. Gordon CS, Serino AS, Krause MP, Campbell JE, Cafarelli E, Adegoke OA, et al. Impaired growth and force production in skeletal muscles of young partially pancreatectomized rats: a model of adolescent type 1 diabetic myopathy? PloS one. 2010;5(11):e14032. [PubMed: 21103335]

448. Pain VM, Albertse EC, Garlick PJ. Protein metabolism in skeletal muscle, diaphragm, and heart of diabetic rats. The American journal of physiology. 1983;245(6):E604–10. [PubMed: 6362429]

449. Price SR, Bailey JL, Wang X, Jurkovitz C, England BK, Ding X, et al. Muscle wasting in insulinopenic rats results from activation of the ATP-dependent, ubiquitin-proteasome proteolytic pathway by a mechanism including gene transcription. The Journal of clinical investigation. 1996;98(8):1703–8. [PubMed: 8878419]

450. Bennet WM, Connacher AA, Smith K, Jung RT, Rennie MJ. Inability to stimulate skeletal muscle or whole body protein synthesis in type 1 (insulin-dependent) diabetic patients by insulin-plus-glucose during amino acid infusion: studies of incorporation and turnover of tracer L-[1–13C]leucine. Diabetologia. 1990;33(1):43–51. [PubMed: 2406180]

451. Nair KS, Ford GC, Ekberg K, Fernqvist-Forbes E, Wahren J. Protein dynamics in whole body and in splanchnic and leg tissues in type I diabetic patients. The Journal of clinical investigation. 1995;95(6):2926–37. [PubMed: 7769135]

452. Tessari P, Nosadini R, Trevisan R, De Kreutzenberg SV, Inchiostro S, Duner E, et al. Defective suppression by insulin of leucine-carbon appearance and oxidation in type 1, insulin-dependent diabetes mellitus. Evidence for insulin resistance involving glucose and amino acid metabolism. The Journal of clinical investigation. 1986;77(6):1797–804. [PubMed: 3519679]

453. Cree-Green M, Newcomer BR, Brown MS, Baumgartner AD, Bergman B, Drew B, et al. Delayed skeletal muscle mitochondrial ADP recovery in youth with type 1 diabetes relates to muscle insulin resistance. Diabetes. 2015;64(2):383–92. [PubMed: 25157095]

454. Rosenfalck AM, Almdal T, Hilsted J, Madsbad S. Body composition in adults with Type 1 diabetes at onset and during the first year of insulin therapy. Diabetic medicine : a journal of the British Diabetic Association. 2002;19(5):417–23. [PubMed: 12027931]

455. Sinha A, Formica C, Tsalamandris C, Panagiotopoulos S, Hendrich E, DeLuise M, et al. Effects of insulin on body composition in patients with insulin-dependent and non-insulin-dependent diabetes. Diabetic medicine : a journal of the British Diabetic Association. 1996;13(1):40–6. [PubMed: 8741811]

456. Influence of intensive diabetes treatment on body weight and composition of adults with type 1 diabetes in the Diabetes Control and Complications Trial. Diabetes care. 2001;24(10):1711–21. [PubMed: 11574431]

457. Park SW, Goodpaster BH, Strotmeyer ES, de Rekeneire N, Harris TB, Schwartz AV, et al. Decreased muscle strength and quality in older adults with type 2 diabetes: the health, aging, and body composition study. Diabetes. 2006;55(6):1813–8. [PubMed: 16731847]

458. Ostler JE, Maurya SK, Dials J, Roof SR, Devor ST, Ziolo MT, et al. Effects of insulin resistance on skeletal muscle growth and exercise capacity in type 2 diabetic mouse models. American journal of physiology Endocrinology and metabolism. 2014;306(6):E592–605. [PubMed: 24425761]

459. Skovso S, Damgaard J, Fels JJ, Olsen GS, Wolf XA, Rolin B, et al. Effects of insulin therapy on weight gain and fat distribution in the HF/HS-STZ rat model of type 2 diabetes. International journal of obesity. 2015;39(10):1531–8. [PubMed: 26121961]

460. Boirie Y Insulin regulation of mitochondrial proteins and oxidative phosphorylation in human muscle. Trends in endocrinology and metabolism: TEM. 2003;14(9):393–4. [PubMed: 14580754]

461. Pereira S, Marliss EB, Morais JA, Chevalier S, Gougeon R. Insulin resistance of protein metabolism in type 2 diabetes. Diabetes. 2008;57(1):56–63. [PubMed: 17940118]

462. Denne SC, Brechtel G, Johnson A, Liechty EA, Baron AD. Skeletal muscle proteolysis is reduced in noninsulin-dependent diabetes mellitus and is unaltered by euglycemic hyperinsulinemia or intensive insulin therapy. The Journal of clinical endocrinology and metabolism. 1995;80(8):2371–7. [PubMed: 7629232]

463. Gin H, Rigalleau V, Perlemoine C. Insulin therapy and body weight, body composition and muscular strength in patients with type 2 diabetes mellitus. Journal of nutrition and metabolism. 2010;2010.

464. Shah PK, Mudaliar S, Chang AR, Aroda V, Andre M, Burke P, et al. Effects of intensive insulin therapy alone and in combination with pioglitazone on body weight, composition, distribution and liver fat content in patients with type 2 diabetes. Diabetes, obesity & metabolism. 2011;13(6):505–10.

465. Shishikura K, Tanimoto K, Sakai S, Tanimoto Y, Terasaki J, Hanafusa T. Association between skeletal muscle mass and insulin secretion in patients with type 2 diabetes mellitus. Endocrine journal. 2014;61(3):281–7. [PubMed: 24420336]

466. Gupta P, Bala M, Gupta S, Dua A, Dabur R, Injeti E, et al. Efficacy and risk profile of anti-diabetic therapies: Conventional vs traditional drugs-A mechanistic revisit to understand their mode of action. Pharmacological research. 2016;113(Pt A):636–74. [PubMed: 27697646]

467. Mounier R, Theret M, Lantier L, Foretz M, Viollet B. Expanding roles for AMPK in skeletal muscle plasticity. Trends in endocrinology and metabolism: TEM. 2015;26(6):275–86. [PubMed: 25818360]

468. Oliveira AG, Gomes-Marcondes MC. Metformin treatment modulates the tumour-induced wasting effects in muscle protein metabolism minimising the cachexia in tumour-bearing rats. BMC cancer. 2016;16:418. [PubMed: 27388367]

469. Li DJ, Huang F, Lu WJ, Jiang GJ, Deng YP, Shen FM. Metformin promotes irisin release from murine skeletal muscle independently of AMP-activated protein kinase activation. Acta physiologica. 2015;213(3):711–21. [PubMed: 25382002]

470. Lee CG, Boyko EJ, Barrett-Connor E, Miljkovic I, Hoffman AR, Everson-Rose SA, et al. Insulin sensitizers may attenuate lean mass loss in older men with diabetes. Diabetes care. 2011;34(11): 2381–6. [PubMed: 21926282]

471. Aghili R, Malek M, Valojerdi AE, Banazadeh Z, Najafi L, Khamseh ME. Body composition in adults with newly diagnosed type 2 diabetes: effects of metformin. Journal of diabetes and metabolic disorders. 2014;13(1):88. [PubMed: 25247153]

472. Mathieu-Costello O, Kong A, Ciaraldi TP, Cui L, Ju Y, Chu N, et al. Regulation of skeletal muscle morphology in type 2 diabetic subjects by troglitazone and metformin: relationship to glucose disposal. Metabolism: clinical and experimental. 2003;52(5):540–6. [PubMed: 12759881]

473. Laksmi PW, Setiati S, Tamin TZ, Soewondo P, Rochmah W, Nafrialdi N, et al. Effect of Metformin on Handgrip Strength, Gait Speed, Myostatin Serum Level, and Health-related Quality of Life: A Double Blind Randomized Controlled Trial among Non-diabetic Pre-frail Elderly Patients. Acta medica Indonesiana. 2017;49(2):118–27. [PubMed: 28790226]

474. Braun B, Eze P, Stephens BR, Hagobian TA, Sharoff CG, Chipkin SR, et al. Impact of metformin on peak aerobic capacity. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme. 2008;33(1):61–7.

475. Malin SK, Gerber R, Chipkin SR, Braun B. Independent and combined effects of exercise training and metformin on insulin sensitivity in individuals with prediabetes. Diabetes care. 2012;35(1): 131–6. [PubMed: 22040838]

476. Malin SK, Braun B. Impact of Metformin on Exercise-Induced Metabolic Adaptations to Lower Type 2 Diabetes Risk. Exercise and sport sciences reviews. 2016;44(1):4–11. [PubMed: 26583801]

477. Boule NG, Kenny GP, Larose J, Khandwala F, Kuzik N, Sigal RJ. Does metformin modify the effect on glycaemic control of aerobic exercise, resistance exercise or both? Diabetologia. 2013;56(11):2378–82. [PubMed: 23975325]

478. Hevener AL, He W, Barak Y, Le J, Bandyopadhyay G, Olson P, et al. Muscle-specific Pparg deletion causes insulin resistance. Nature medicine. 2003;9(12):1491–7.

479. Asp ML, Tian M, Wendel AA, Belury MA. Evidence for the contribution of insulin resistance to the development of cachexia in tumor-bearing mice. International journal of cancer. 2010;126(3): 756–63. [PubMed: 19634137]

480. Iida M, Katsuno M, Nakatsuji H, Adachi H, Kondo N, Miyazaki Y, et al. Pioglitazone suppresses neuronal and muscular degeneration caused by polyglutamine-expanded androgen receptors. Human molecular genetics. 2015;24(2):314–29. [PubMed: 25168383]

481. Bajpeyi S, Pasarica M, Conley KE, Newcomer BR, Jubrias SA, Gamboa C, et al. Pioglitazone-induced improvements in insulin sensitivity occur without concomitant changes in muscle mitochondrial function. Metabolism: clinical and experimental. 2017;69:24–32. [PubMed: 28285649]

482. Bajaj M, Baig R, Suraamornkul S, Hardies LJ, Coletta DK, Cline GW, et al. Effects of pioglitazone on intramyocellular fat metabolism in patients with type 2 diabetes mellitus. The Journal of clinical endocrinology and metabolism. 2010;95(4):1916–23. [PubMed: 20157197]

483. Rabol R, Boushel R, Almdal T, Hansen CN, Ploug T, Haugaard SB, et al. Opposite effects of pioglitazone and rosiglitazone on mitochondrial respiration in skeletal muscle of patients with type 2 diabetes. Diabetes, obesity & metabolism. 2010;12(9):806–14.

484. Ciaraldi TP, Aroda V, Mudaliar SR, Henry RR. Inflammatory cytokines and chemokines, skeletal muscle and polycystic ovary syndrome: effects of pioglitazone and metformin treatment. Metabolism: clinical and experimental. 2013;62(11):1587–96. [PubMed: 23958241]

485. Shea MK, Nicklas BJ, Marsh AP, Houston DK, Miller GD, Isom S, et al. The effect of pioglitazone and resistance training on body composition in older men and women undergoing hypocaloric weight loss. Obesity. 2011;19(8):1636–46. [PubMed: 21233810]

486. Rasouli N, Kern PA, Elbein SC, Sharma NK, Das SK. Improved insulin sensitivity after treatment with PPARgamma and PPARalpha ligands is mediated by genetically modulated transcripts. Pharmacogenetics and genomics. 2012;22(7):484–97. [PubMed: 22437669]

487. Slim R, Ben Salem C, Zamy M, Biour M. Pioglitazone-induced acute rhabdomyolysis. Diabetes care. 2009;32(7):e84. [PubMed: 19564463]

488. Kennie N, Antoniou T, Berger P. Elevated creatine kinase and myalgia in a patient taking rosiglitazone. The Annals of pharmacotherapy. 2007;41(3):521–4. [PubMed: 17327290]

489. Nyomba BL, Freymond D, Raz I, Stone K, Mott DM, Bogardus C. Skeletal muscle glycogen synthase activity in subjects with non-insulin-dependent diabetes mellitus after glyburide therapy. Metabolism: clinical and experimental. 1990;39(11):1204–10. [PubMed: 2122177]

490. Gorray KC, Maimon J, Schneider BS. Studies of antiproteolytic effects of glyburide on rat L6 myoblasts: comparisons with insulin. Metabolism: clinical and experimental. 1990;39(2):109–16. [PubMed: 2105434]

491. Montoya-Perez R, Saavedra-Molina A, Trujillo X, Huerta M, Andrade F, Sanchez-Pastor E, et al. Inhibition of oxygen consumption in skeletal muscle-derived mitochondria by pinacidil, diazoxide, and glibenclamide, but not by 5-hydroxydecanoate. Journal of bioenergetics and biomembranes. 2010;42(1):21–7. [PubMed: 20066482]

492. Skalska J, Debska G, Kunz WS, Szewczyk A. Antidiabetic sulphonylureas activate mitochondrial permeability transition in rat skeletal muscle. British journal of pharmacology. 2005;145(6):785–91. [PubMed: 15895111]

493. Wasada T, Yano T, Ohta M, Yui N, Iwamoto Y. ATP-Sensitive potassium channels modulate glucose transport in cultured human skeletal muscle cells. Endocrine journal. 2001;48(3):369–75. [PubMed: 11523909]

494. Vestergaard H, Weinreb JE, Rosen AS, Bjorbaek C, Hansen L, Pedersen O, et al. Sulfonylurea therapy improves glucose disposal without changing skeletal muscle GLUT4 levels in noninsulin-dependent diabetes mellitus subjects: a longitudinal study. The Journal of clinical endocrinology and metabolism. 1995;80(1):270–5. [PubMed: 7829624]

495. Tsiani E, Ramlal T, Leiter LA, Klip A, Fantus IG. Stimulation of glucose uptake and increased plasma membrane content of glucose transporters in L6 skeletal muscle cells by the sulfonylureas gliclazide and glyburide. Endocrinology. 1995;136(6):2505–12. [PubMed: 7750472]

496. Pulido N, Romero R, Suarez AI, Rodriguez E, Casanova B, Rovira A. Sulfonylureas stimulate glucose uptake through GLUT4 transporter translocation in rat skeletal muscle. Biochemical and biophysical research communications. 1996;228(2):499–504. [PubMed: 8920942]

497. Mele A, Calzolaro S, Cannone G, Cetrone M, Conte D, Tricarico D. Database search of spontaneous reports and pharmacological investigations on the sulfonylureas and glinides-induced atrophy in skeletal muscle. Pharmacology research & perspectives. 2014;2(1):e00028. [PubMed: 25505577]

498. Duty S, Allen DG. The effects of glibenclamide on tetanic force and intracellular calcium in normal and fatigued mouse skeletal muscle. Experimental physiology. 1995;80(4):529–41. [PubMed: 7576594]

499. Andrade F, Trujillo X, Sanchez-Pastor E, Montoya-Perez R, Saavedra-Molina A, Ortiz-Mesina M, et al. Glibenclamide increases post-fatigue tension in slow skeletal muscle fibers of the chicken. Journal of comparative physiology B, Biochemical, systemic, and environmental physiology. 2011;181(3):403–12.

500. Luque MA, Gonzalez N, Marquez L, Acitores A, Redondo A, Morales M, et al. Glucagon-like peptide-1 (GLP-1) and glucose metabolism in human myocytes. The Journal of endocrinology. 2002;173(3):465–73. [PubMed: 12065236]

501. Chai W, Dong Z, Wang N, Wang W, Tao L, Cao W, et al. Glucagon-like peptide 1 recruits microvasculature and increases glucose use in muscle via a nitric oxide-dependent mechanism. Diabetes. 2012;61(4):888–96. [PubMed: 22357961]

502. Arnes L, Gonzalez N, Tornero-Esteban P, Sancho V, Acitores A, Valverde I, et al. Characteristics of GLP-1 and exendins action upon glucose transport and metabolism in type 2 diabetic rat skeletal muscle. International journal of molecular medicine. 2008;22(1):127–32. [PubMed: 18575785]

503. Andreozzi F, Raciti GA, Nigro C, Mannino GC, Procopio T, Davalli AM, et al. The GLP-1 receptor agonists exenatide and liraglutide activate Glucose transport by an AMPK-dependent mechanism. Journal of translational medicine. 2016;14(1):229. [PubMed: 27473212]

504. Alcantara AI, Morales M, Delgado E, Lopez-Delgado MI, Clemente F, Luque MA, et al. Exendin-4 agonist and exendin(9–39)amide antagonist of the GLP-1(7–36)amide effects in liver and muscle. Archives of biochemistry and biophysics. 1997;341(1):1–7. [PubMed: 9143346]

505. Colin IM, Colin H, Dufour I, Gielen CE, Many MC, Saey J, et al. Extrapancreatic effects of incretin hormones: evidence for weight-independent changes in morphological aspects and oxidative status in insulin-sensitive organs of the obese nondiabetic Zucker rat (ZFR). Physiological reports. 2016;4(15).

506. Takada S, Masaki Y, Kinugawa S, Matsumoto J, Furihata T, Mizushima W, et al. Dipeptidyl peptidase-4 inhibitor improved exercise capacity and mitochondrial biogenesis in mice with heart failure via activation of glucagon-like peptide-1 receptor signalling. Cardiovascular research. 2016;111(4):338–47. [PubMed: 27450980]

507. Honors MA, Kinzig KP. Chronic exendin-4 treatment prevents the development of cancer cachexia symptoms in male rats bearing the Yoshida sarcoma. Hormones & cancer. 2014;5(1): 33–41. [PubMed: 24101584]

508. Chai W, Fu Z, Aylor KW, Barrett EJ, Liu Z. Liraglutide prevents microvascular insulin resistance and preserves muscle capillary density in high-fat diet-fed rats. American journal of physiology Endocrinology and metabolism. 2016;311(3):E640–8. [PubMed: 27436611]

509. Liu J, Hu Y, Zhang H, Xu Y, Wang G. Exenatide treatment increases serum irisin levels in patients with obesity and newly diagnosed type 2 diabetes. Journal of diabetes and its complications. 2016;30(8):1555–9. [PubMed: 27503404]

510. Perna S, Guido D, Bologna C, Solerte SB, Guerriero F, Isu A, et al. Liraglutide and obesity in elderly: efficacy in fat loss and safety in order to prevent sarcopenia. A perspective case series study. Aging clinical and experimental research. 2016;28(6):1251–7. [PubMed: 26749118]

511. Yajima T, Yajima K, Takahashi H, Yasuda K. The effect of dulaglutide on body composition in type 2 diabetes mellitus patients on hemodialysis. Journal of diabetes and its complications. 2018;32(8):759–63. [PubMed: 29937137]

512. Hu H, Xu M, Qi R, Wang Y, Wang C, Liu J, et al. Sitagliptin downregulates retinol-binding protein 4 and upregulates glucose transporter type 4 expression in a type 2 diabetes mellitus rat model. International journal of clinical and experimental medicine. 2015;8(10):17902–11. [PubMed: 26770384]

513. Giannocco G, Oliveira KC, Crajoinas RO, Venturini G, Salles TA, Fonseca-Alaniz MH, et al. Dipeptidyl peptidase IV inhibition upregulates GLUT4 translocation and expression in heart and skeletal muscle of spontaneously hypertensive rats. European journal of pharmacology. 2013;698(1–3):74–86. [PubMed: 23051671]

514. Hasegawa Y, Hayashi K, Takemoto Y, Cheng C, Takane K, Lin B, et al. DPP-4 inhibition with linagliptin ameliorates the progression of premature aging in klotho−/− mice. Cardiovascular diabetology. 2017;16(1):154. [PubMed: 29195509]

515. Richard KR, Shelburne JS, Kirk JK. Tolerability of dipeptidyl peptidase-4 inhibitors: a review. Clinical therapeutics. 2011;33(11):1609–29. [PubMed: 22071236]

516. Khan MW, Kurian S, Bishnoi R. Acute-onset rhabdomyolysis secondary to sitagliptin and atorvastatin interaction. International journal of general medicine. 2016;9:103–6. [PubMed: 27199569]

517. Kao DP, Kohrt HE, Kugler J. Renal failure and rhabdomyolysis associated with sitagliptin and simvastatin use. Diabetic medicine : a journal of the British Diabetic Association. 2008;25(10): 1229–30. [PubMed: 19046202]

518. DiGregorio RV, Pasikhova Y. Rhabdomyolysis caused by a potential sitagliptin-lovastatin interaction. Pharmacotherapy. 2009;29(3):352–6. [PubMed: 19249953]

519. Hoffmann P, Martin L, Keselica M, Gunson D, Skuba E, Lapadula D, et al. Acute Toxicity of Vildagliptin. Toxicologic pathology. 2017;45(1):76–83. [PubMed: 27753637]

520. O'Brien TP, Jenkins EC, Estes SK, Castaneda AV, Ueta K, Farmer TD, et al. Correcting Postprandial Hyperglycemia in Zucker Diabetic Fatty Rats With an SGLT2 Inhibitor Restores Glucose Effectiveness in the Liver and Reduces Insulin Resistance in Skeletal Muscle. Diabetes. 2017;66(5):1172–84. [PubMed: 28246292]

521. Joannides CN, Mangiafico SP, Waters MF, Lamont BJ, Andrikopoulos S. Dapagliflozin improves insulin resistance and glucose intolerance in a novel transgenic rat model of chronic glucose overproduction and glucose toxicity. Diabetes, obesity & metabolism. 2017;19(8):1135–46.

522. Naznin F, Sakoda H, Okada T, Tsubouchi H, Waise TM, Arakawa K, et al. Canagliflozin, a sodium glucose cotransporter 2 inhibitor, attenuates obesity-induced inflammation in the nodose ganglion, hypothalamus, and skeletal muscle of mice. European journal of pharmacology. 2017;794:37–44. [PubMed: 27876617]

523. Yamamoto C, Miyoshi H, Ono K, Sugawara H, Kameda R, Ichiyama M, et al. Ipragliflozin effectively reduced visceral fat in Japanese patients with type 2 diabetes under adequate diet therapy. Endocrine journal. 2016;63(6):589–96. [PubMed: 27052123]

524. Tsurutani Y, Nakai K, Inoue K, Azuma K, Mukai S, Maruyama S, 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, obesity & metabolism. 2018.

525. Sugiyama S, Jinnouchi H, Kurinami N, Hieshima K, Yoshida A, Jinnouchi K, et al. Dapagliflozin Reduces Fat Mass without Affecting Muscle Mass in Type 2 Diabetes. Journal of atherosclerosis and thrombosis. 2018;25(6):467–76. [PubMed: 29225209]

526. Amin NB, Wang X, Mitchell JR, Lee DS, Nucci G, Rusnak JM. Blood pressure-lowering effect of the sodium glucose co-transporter-2 inhibitor ertugliflozin, assessed via ambulatory blood pressure monitoring in patients with type 2 diabetes and hypertension. Diabetes, obesity & metabolism. 2015;17(8):805–8.

527. Ledwig D, Muller H, Bischoff H, Eckel J. Early acarbose treatment ameliorates resistance of insulin-regulated GLUT4 trafficking in obese Zucker rats. European journal of pharmacology. 2002;445(1–2):141–8. [PubMed: 12065205]

528. Taira S, Shimabukuro M, Higa M, Yabiku K, Kozuka C, Ueda R, et al. Lipid deposition in various sites of the skeletal muscles and liver exhibits a positive correlation with visceral fat accumulation in middle-aged Japanese men with metabolic syndrome. Internal medicine. 2013;52(14):1561–71. [PubMed: 23857087]

529. Nyholm B, Moller N, Gravholt CH, Orskov L, Mengel A, Bryan G, et al. Acute effects of the human amylin analog AC137 on basal and insulin-stimulated euglycemic and hypoglycemic fuel metabolism in patients with insulin-dependent diabetes mellitus. The Journal of clinical endocrinology and metabolism. 1996;81(3):1083–9. [PubMed: 8772580]

SEARCH STRATEGIES

Literature utilized in the compilation of this manuscript included articles identified through database searches of PubMed, Embase, Cochrane Library, and ClinicalTrials.gov , as available through the second quarter of 2018. Search strategies included each individual drug class, along with individual terms or a combination of terms, including bone, skeleton, osteoblast, osteoclast, osteoporosis, fracture, bone mineral density, calcium, phosphorus, muscle, musculoskeletal, muscle mass, muscle atrophy, myocyte, adverse event, and safety. Searches were conducted independently by each author, and results were compiled. Articles included for review and analysis included: 1) studies published in English; 2) *in vitro*, preclinical, or human-participant clinical outcome trials, when published in referred biomedical journals; 3) independently conducted post-marketing drug surveillance safety studies; 4) drug information sheets; and 5) efficacy and safety data results posted on NIH ClinicalTrials.gov. As such, this review is considered a comprehensive discussion of the literature, but is not intended as a clinical management guideline or recommendation; hence, a literature grading system was not employed. Finally, the authors have no financial or personal conflicts of interest regarding the drug classifications covered in this review.

Table 1:

Diabetes Pharmacotherapy: Mechanisms of Glucose Lowering

A list of all currently FDA-approved glucose lowering medications is provided, according to their drug classification. Drugs are listed alphabetically under each classification heading. Only mono-component drugs are listed; pre-mixed insulin products or drug class combination products are not included. Abbreviations: T1D, type 1 diabetes; T2D, type 2 diabetes; RpR, ryanodine receptors; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; GIP, gastric inhibitory polypeptide; SGLT2, sodium-dependent glucose co-transporter-2. *Expanded off-label use.

Drug Classification	FDA-Approved Agents	Cellular Mechanism(s) of Action	Physiological Mechanism(s) of Action	Active or Envisioned Clinical Indication(s)
Insulin Action • **Insulin analogs**	Rapid • Aspar, Glulisine, Inhaled, Lispro Short • Regular Intermediate • NPH Basal • Degludec, Detemir, Glargine	Activate insulin receptors; Mimic insulin action, with variability in onset and duration of effect	Increase glucose disposal; Suppress hepatic gluconeogenesis; Suppress ketogenesis	T1D + T2D
Insulin Sensitizers • **Biguanides**	Metformin	Activate AMP-kinase signaling pathways	Inhibit hepatic gluconeogenesis; Enhance peripheral insulin sensitivity	T2D
• **Thiazolidinediones**	Pioglitazone Rosiglitazone	Activate Peroxisome Proliferator-Activated Receptor gamma (PPARγ)	Enhance insulin sensitivity and adipogenesis; Increase glucose utilization	T2D
Insulin Secretagogues • **Sulfonylureas**	Glimepiride Glipizide Glyburide	Block K_{ATP} channels on β-cell membrane, causing membrane depolarization and exocytosis of insulin granules; Direct interaction with Epac2A, with activation of the Epac2A-RIP signaling pathways and stimulation of insulin secretion.	Increase β-cell insulin secretion; Reduce post-prandial glucose rise	T2D
• **Metglinitides**	Nateglinide Repaglinide	Block K_{ATP} channels on β-cell membrane, causing membrane depolarization and exocytosis of insulin granules; Activate sarcoplasmic reticulum RyRs and trigger intracellular $Ca2^{+}$ release, with stimulation of insulin secretion.	Increase β-cell insulin secretion; Reduce post-prandial glucose rise	T2D

Drug Classification	FDA-Approved Agents	Cellular Mechanism(s) of Action	Physiological Mechanism(s) of Action	Active or Envisioned Clinical Indication(s)
Incretins • **DPP-4 Inhibitors**	Alogliptin Linagliptin Saxagliptin Sitagliptin	Inhibit the incretin-deactivating enzyme, DPP-4, thereby increasing concentrations of incretins (GLP-1 and GIP)	Enhance glucose-stimulated insulin secretion; Suppress glucagon secretion	T2D
• **GLP-1R Agonists**	Albiglutide Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Activate GLP-1 receptors; Stimulate glucose-dependent insulin secretion; Resistance to degradation by DDP-4 prolongs their half-life.	Enhance glucose-stimulated insulin secretion; Suppress glucagon secretion; Promote satiety; Delay gastric emptying	T2D
Glucosurics • **SGLT2 Inhibitors**	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Selectively inhibit SGLT2 co-transporters; Inhibit renal glucose reabsorption	Increase glucosuria	T1D* + T2D
Glucose uptake inhibitors • **Alpha Glucosidase Inhibitors**	Acarbose Miglitol	Inhibit α-glucosidase in intestinal brush border	Inhibit breakdown of ingested carbohydrate; Delay intestinal glucose absorption	T2D
Amylin Mimetics	Pramlintide	Activate amylin receptors; Reproduce amylin action	Delay gastric emptying; Suppress postprandial glucagon secretion; Promote satiety	T1D + T2D

Table 2:

Diabetes Pharmacotherapy: Summary of Musculoskeletal Effects

Bone and muscle effects of each drug classification are summarized, and an overall impact statement is provided. Abbreviations: T1D, type 1 diabetes; T2D, type 2 diabetes; AE, adverse effect; BMD, bone mineral density; TZDs, thiazolidinediones; BMC, bone mineral content; Mg, magnesium; Phos, phosphorus. Symbols: ↑ = increased; ↓= decreased; ↔ = no change; ρ = delta (change).

Drug Classification	Bone Effects		Muscle Effects		Overall Impact
	Preclinical	Clinical	Preclinical	Clinical	
Insulin Action • **Insulin analogs**	↑ bone formation; ↑ bone regeneration; ↑ markers of bone formation; ↓ markers of bone resorption; ↑ bone strength	Insulin use in T2D is associated with ↑fracture risk. Insulin dose in T1D is associated with ↑ markers of bone formation.	↑ protein synthesis; ↓ protein degradation; ↑ (T1D/T2D) in muscle mass	↔ protein synthesis (T1D/T2D); ↓ (T1D) or ↔ (T2D) protein degradation; ↔ effect on mitochondrial function (T1D/T2D); ↑ (T1D) or no change (T2D) in muscle mass	Preclinical models demonstrate insulin to improve bone and muscle. Clinical models are inconclusive regarding muscle. Insulin may have negative effects on bone in T2D, yet positive effects in T1D.
Insulin Sensitizer • **Biguanides**	Induces shift from adipogenic to osteogenic mesenchymal cell differentiation; generally anabolic in preclinical models (particularly diabetes); mitigates detrimental effects of diabetes on bone; less effect on bone regeneration/repair	Neutral or modestly beneficial effect on bone health and fracture risk; ↓in bone turnover markers in T2D; bone effects perhaps attributable to glycemic improvement	↑ muscle strength; ↑ muscle mass; ↑ mitochondrial function	↑ muscle mass; ↑/↔ strength; ↓ muscle lipid content; but might attenuate exercise-induced muscle benefits; AE: myalgia, muscle weakness	Preclinical models generally support improvements in both bone and muscle. Clinical data indicate that fractures risk is not increased (neutral effect), and may be reduced slightly, with improved glucose control. Muscle function is often improved.
• **Thiazolidinediones**	Inhibits osteoblast differentiation and mineralization; ↓ bone formation; ↓ BMD; ↑osteoclastogenesis; ↑bone resorption (rosiglitazone/ pioglitazone)	Inconsistent results about bone turnover markers; ↓BMD; ↑risk of fracture (rosiglitazone/pioglitazone); ↔ in BMD (lobeglitazone)	↓ protein degradation; ↑muscle mass; ↓ oxidative stress	↓ muscle lipid content; ↔/↑/↓ mitochondrial function; ↔ muscle mass; AE: rhabdomyolysis-rare (pioglitazone)	There are negative effects on bone metabolism and an increase in fracture risk, possibly with an exception for newer agents. Positive or neutral effects on muscle are observed.
Insulin Secretagogues • **Sulfonylureas**	Might ameliorate estrogen-deficiency bone loss (limited data)	↑ Fracture risk in at-risk populations (elderly and post-menopausal women), but confounded by an increased risk of hypoglycemia	↓ muscle mass	↓ muscle mass	Preclinical data is very limited. Clinical data has not established this drug class as being harmful or beneficial in regards to fracture; however, hypoglycemia-associated, fall-related fractures are of concern.
• **Meglitinides**	No data	1 study: ↑ risk of fracture (repaglinide + TZDs) in older women	↓ muscle mass	No data	Data on bone or muscle effects are very limited: hence, the overall impact from meglitinides remains unclear, and the indications for use are for selective populations.
Incretins • **DPP-4 Inhibitors**	↔(MK 0626) or ↓ (saxagliptin) osteoblast differentiation; ↑ (vildagliptin, sitagliptin) or ↓	↔ in bone turnover markers (vildagliptin); ↔ in BMD (sitagliptin, vildagliptin); ↓ (alogliptin), ↓/↔	↑ muscle mass; ↑ mitochondrial function	↔ muscle mass (limited data); AE: rhabdomyolysis (saxagliptin with statin),	Clinical data on fracture risk is inconsistent (potentially increased with saxagliptin), but the overall impact on bone seems neutral at present.

Drug Classification	Bone Effects		Muscle Effects		Overall Impact
	Preclinical	Clinical	Preclinical	Clinical	
	BMD (saxagliptin); ↓osteoclastogenesis (sitagliptin)	(vildagliptin, sitagliptin) or ↑ (saxagliptin) risk of fracture		myalgia, muscle weakness	Preclinical studies of muscle demonstrate anabolic (or anti-catabolic) effects but clinical data is limited.
• **GLP-1R Agonists**	Promote proliferation and differentiation of osteoblasts; Anabolic effects in pre-clinical models, + possible inhibitory effects on bone resorption.	No effect on BMD or bone turnover markers; mostly neutral effect on fracture risk, however some studies have found ↑ (exenatide) or ↓ (exenatide, liraglutide) fracture risk	Beneficial effects on muscle metabolism and cachexia	Limited data: increase in skeletal muscle index (liraglutide); muscle loss (dulaglutide)	Preclinical models show a beneficial effect on bone. Clinical data shows mostly neutral effects, although a few studies have shown harmful or beneficial effects on risk for fracture.
Glucosurics • **SGLT2 Inhibitors**	Possible effects on bone mineral homeostasis/resorption; ↑ calciuria; ↔ BMC (T2D, rat)	Small ↑ in serum Mg and Phos levels (drug specific), ↑ risk of fracture in at-risk subgroups (canagliflozin) and ↑lower limb amputation (canagliflozin/ ± ertugliflozin)	↑muscle glucose uptake, ↑ muscle mass, ↑ muscle strength	Limited data: ↓ skeletal muscle index (T2D; ipragliflozin), ↔ muscle mass (T2D; dapagliflozin)	Preclinical models infer some effect on bone mineral homeostasis. Clinical data indicate concern for increased fracture risk and/or amputation, with specific agents, when used in specific at-risk populations. Data on muscle effects are limited.
Alpha Glucosidase Inhibitors	1 study (T2D, rat): did not mitigate detrimental effects of diabetes on bone	No data	No data	↔ muscle lipid metabolism (limited data)	Data on bone or muscle effects are very limited: hence, the overall impact from alpha glucosidase inhibitors remains unclear, and drugs are used primarily as add-on therapy.
Amylin Mimetics	No data on pramlintide. Data inferred from native amylin: ↑bone volume, ↑bone formation, ↑ bone strength, ↓ bone resorption	1 study (T1D): no Δ in BMD or bone biomarkers after 1 year	No data	↑ lactate with hypoglycemia (limited data)	Data on bone or muscle effects are very limited; hence, the overall impact from amylin mimetics remains unclear.