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Glucose-Lowering Drugs and Fracture Risk among Diabetics: Review Article

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ABSTRACT

Background: Diabetic patients have an increased risk of bone fractures. Patients with type 1 DM are seven times more likely to suffer a fracture than those without DM, whereas those with type 2 DM are 1.3 times more likely to do so. Patients with T2DM have an increased risk for fractures, despite having a normal to increased bone mineral density, suggesting that other factors besides bone quantity must account for increased bone fragility.

Objective: The aim of the current work was to assess fracture risk among diabetics who use glucose-lowering drugs.

Methods: Fracture Risk, Glucose-Lowering Drugs, and diabetics were all looked for in PubMed, Google scholar, and ScienceDirect. References from relevant literature were also evaluated by the authors, but only the most recent or complete study from February 2016 to August 2022 was included. Due to the lack of sources for translation, documents in languages other than English have been ruled out. Papers that did not fall under the purview of major scientific investigations, such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations, were omitted.

Conclusion: Some of the newer glucose-lowering therapies for type 2 diabetes have been shown to improve renal and cardiovascular outcomes. However, treatments aimed at reducing glucose levels may potentially influence fractures risks.

Keywords: Fracture Risk, Glucose-Lowering Drugs, Diabetics.

INTRODUCTION

Chronic hyperglycemia and abnormalities in carbohydrate, lipid, and protein metabolism define diabetes mellitus, a multifactorial metabolic illness. Caused by either a lack of insulin production (Type 1 Diabetes) or a failure of insulin action (Type 2 Diabetes), or often both, this disease affects a person's blood sugar levels**,** defined by high levels of sugar in the blood and urine, and weight loss [(1)].

According to the data, 43% of diabetic patients and most pre-diabetic patients in Egypt are undiagnosed. The significant rise in diabetes incidence in Egypt from 4.4 million cases in 2007 to 7.5 million in 2013 has occurred within a very short time frame. It is anticipated that by 2035, this figure would have increased to 13.1 million [(1)].

The incidence of type 2 diabetes has nearly tripled in Egypt over the past two decades. This dramatic increase may be attributable to an upward trend in the prevalence of traditional risk factors, such as obesity, inactivity, and dietary shifts, or to risk factors unique to Egypt, such as the country's heavy reliance on pesticides and its endemic hepatitis C virus [(1)].

The probability of breaking a bone increases with the presence of diabetes mellitus. Patients with type 1 DM have a risk of fracture that is seven times higher than that of persons without DM, while patients with type 2 DM have an elevated risk of fracture that is only 1.3 times that of people without DM. People with type 2 diabetes (T2D) are often said to have higher bone mineral density (BMD) than those without the disease; however, BMD alone cannot account for the elevated risk of fracture in T2D patients [(1)].

It has been shown that micro-fractures caused by inadequate bone turnover, which can occur despite a healthy bone mineral density (BMD), are responsible for the degeneration of bone in DM. This includes an increase in cortical porosity and modifications to the bone collagen. The diabetes symptoms and severity have also been studied. Even in the absence of other medical conditions, those with diabetes are at a higher risk of fractures. Studies have linked the duration of diabetes to an increased risk of fracture; however, research designed to investigate T2D specifically have not found this association, possible inclusion of some individuals with type 1 diabetes. Underreporting and information bias contribute to a lack of research on falls and hypoglycemia in DM. However, the high prevalence of fractures in people with type 1 and type 2 diabetes cannot be explained solely by falls and hypoglycemia [(2)].

Loss of bone mineral, mostly calcium, and the natural architecture of the skeleton bring to osteoporosis. Bone mineral density loss refers to the gradual depletion of bone tissue's mineral content. Two hundred million people all over the world suffer from osteoporosis, making it the most prevalent metabolic bone ailment. It's becoming more common, yet doctors still miss most cases and offer inadequate care. Part of the reason for this is that the illness shows no signs of existence until it causes a fracture. This can lead to higher morbidity and mortality as well as severe pain and deformity [(2)].

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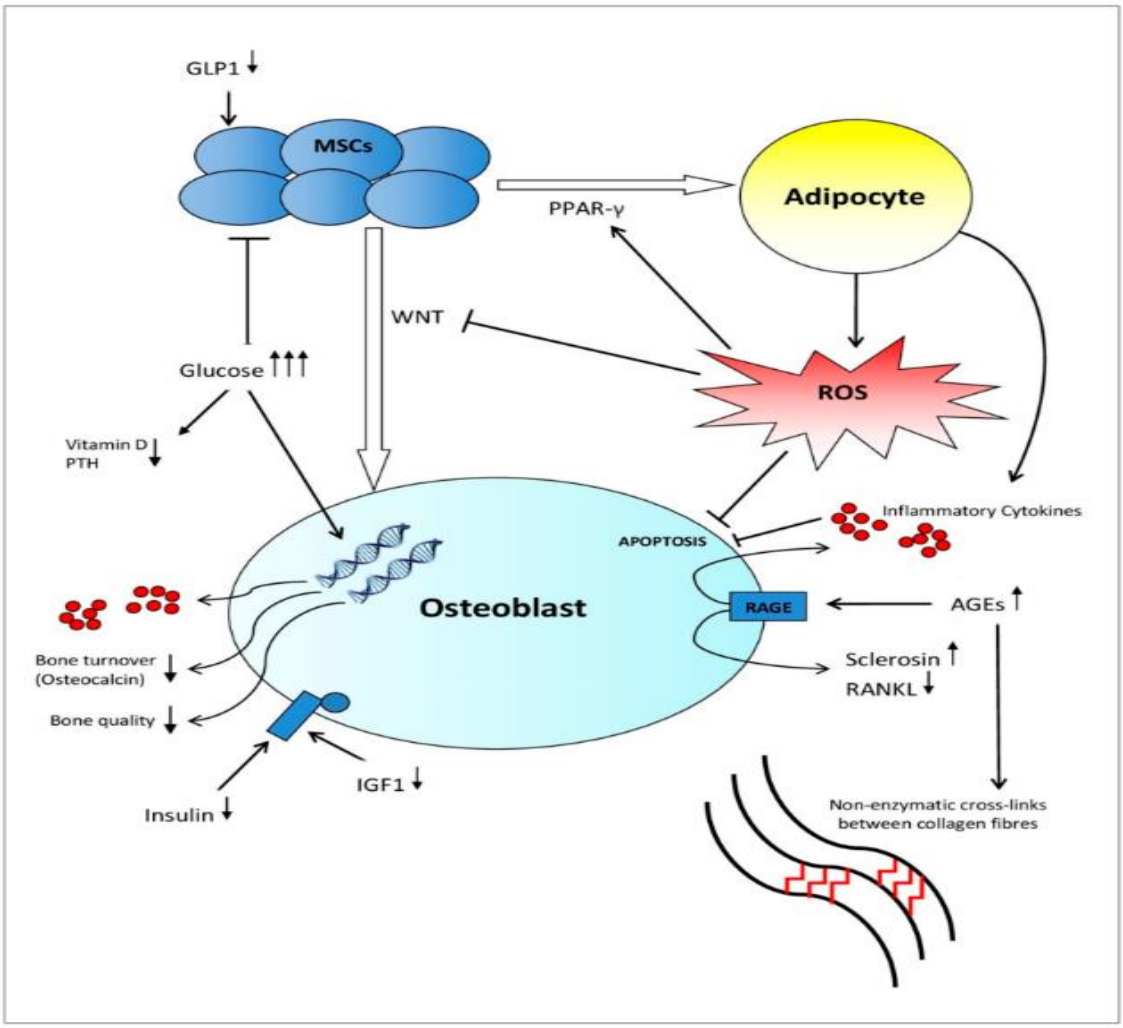

Figure (1): Alteration of bone marrow environment in diabetes mellitus [(2)].

Consequently, there may be many factors playing in the increased risk of fracture. Some of the most recent medications for type 2 diabetes reduce glucose levels, which has improved renal and cardiovascular results. Contrarily, treatments that try to reduce glucose levels may affect fracture chances. Metformin is the first line treatment for type 2 diabetes. Examples of secondary treatments include insulin, sulphonylureas, glitazones, dipeptidyl peptidase-IV inhibitors, and glucagon-like peptide-1 receptor agonists. As of late, it has been recommended that SGLT2-is and GLP-1 RAs be used to treat type 2 diabetes and cardiovascular disease, and to prevent the worsening of chronic renal disease in patients with an eGFR (estimated glomerular filtration rate) of 30-60 ml/min. This study aims to examine the effects of glucose-lowering medications on fracture risk in people with type 2 diabetes by using previously collected data [(3)].

METHODS

Methods: Fracture Risk, Glucose-Lowering Drugs, and diabetics were all looked for in PubMed, Google scholar, and ScienceDirect. References from relevant literature were also evaluated by the authors, but only the most recent or complete study from February 2016 to August 2022 was included. Due to the lack of sources for translation, documents in languages other than English have been ruled out. Papers that did not fall under the purview of major scientific investigations, such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations, were omitted.

What follows is a discussion and presentation of results for each of the medication categories:

Metformin:

Observational studies were the most common type of research done on metformin's effects. One randomized controlled trial with a 4-year follow-up, however, found that metformin users had a lower incidence of fractures than rosiglitazone users. A higher rate of fracture was observed in people taking metformin alone compared to those in the non-diabetic and type 2 diabetes (T2D) groups who did not take glucose-lowering drugs. Metformin, in contrast to other glucose-lowering drugs, was mostly associated with either no change in result or a reduced risk of fracture. It appears that the interpretation of metformin in relation to fracture risk is affected by the choice of comparator. It appears that metformin does not increase fracture risk, but there is not enough information to establish a firm judgement [(4)].

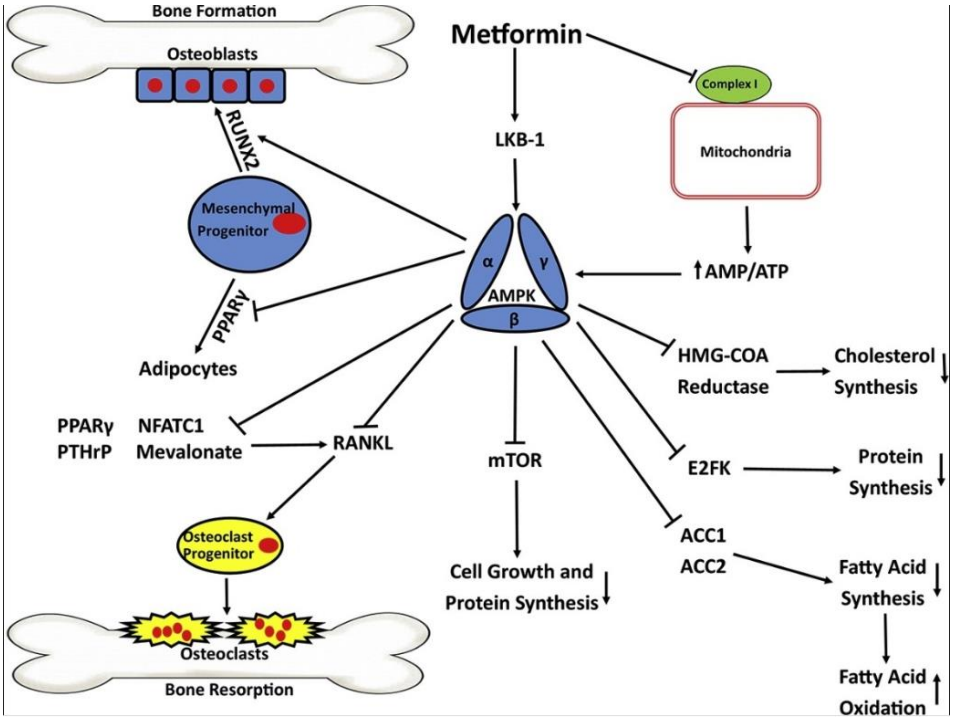

Figure (2): Metformin actions on bone resorbtion[4].

Sulphonylureas:

Glyburide users had a lower risk than rosiglitazone users, the results of a randomized controlled experiment with a median treatment duration of four years. Users of metformin and glyburide had comparable fracture rates; however this was not directly compared in the trial (RCT), which also compared rosiglitazone with metformin. These results appear to emphasize the significance of the benchmark. However, observational studies have found conflicting results when it comes to the effects of sulphonylureas. Different studies have shown conflicting results on the impact of sulphonylureas on fracture risk when compared to other glucose-lowering medicines, with some showing an increased risk and others showing no difference [5].

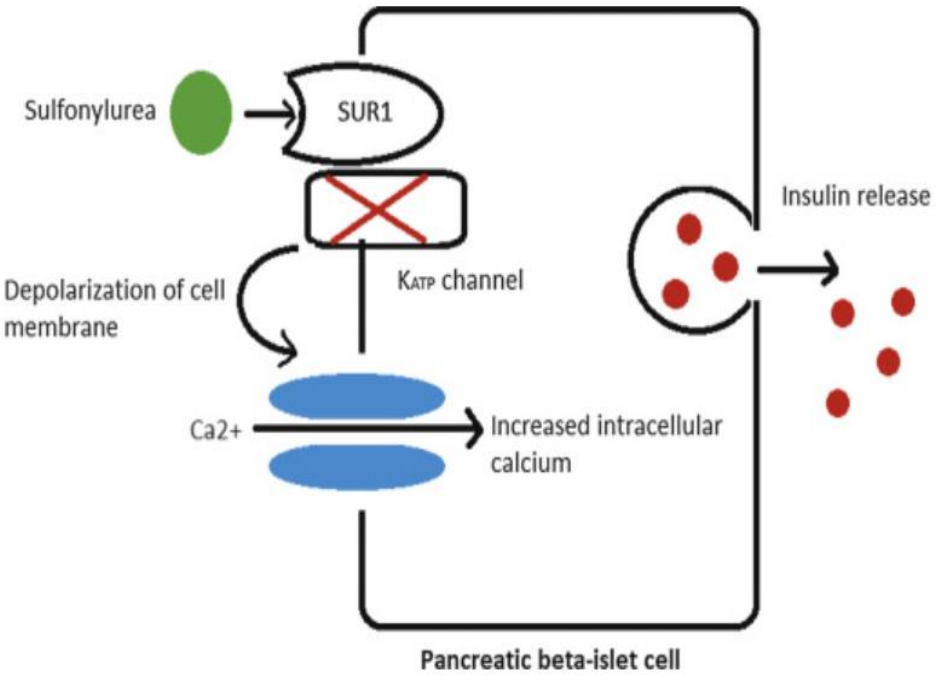

Figure (3): Sulphonylureas Mechanism of Action [5].

Sulphonylureas reduced the risk of bone fracture in two clinical trials. For men with a HbA1c of 6.5%, taking sulphonylureas was associated with a higher risk of fracture than not taking the drug.: patients in a study were treated with a wider variety of medications.; and Sulphonylurea users have a 14% higher risk of fracture than T2D patients who are treated with alternate ways, according to a new meta-analysis. The results of research on sulphonylureas, then, are still inconclusive [6].

Glitazones:

Ten separate randomized controlled studies all came to the same conclusion: women who took glitazone had a higher risk of fracture than those who took a placebo or an active comparator. This finding was statistically significant only in females and not in males. Metformin monotherapy improved glycemic control more than glitazone monotherapy in persons with type 2 diabete., those who took other glucose-lowering medicines, or those who did not have diabetes, glitazone users had a higher incidence of fractures in observational studies; The higher risk of fracture was shown only in women, however, in trials that stratified participants by gender. Additionally, a study looking into the effects of stopping glitazones found that doing so significantly reduced fracture risk [7].

Insulin:

Those with type 2 diabetes had an increased risk of fracture, and this increased risk was observed in both women using insulin and those not taking insulin. In a propensity score-matched research, those with type 2 diabetes who transitioned from oral glucose-lowering drugs to insulin had a higher risk of fracture than those who remained on oral glucose-lowering medicines [8].

Some studies compare findings to a control group of people without diabetes, while others look at how people with diabetes fare in comparison to one another. Hypoglycemia is a potential side effect of insulin treatment just as it is with sulphonylureas. Diabetic individuals on insulin are more likely to sustain injuries from low-impact falls, which could result in fractures if the premise of brittle bones is correct. Men with a HbA1c of 6.5% are at a higher risk of fracture when using insulin, and the use of insulin in conjunction with sulphonylureas doubles the risk of hip fracture. Using insulin was correlated with a lower incidence of fracture in one study. Therefore, medical professionals should be aware of the potential link between insulin-induced hypoglycemia and bone fractures [9, 10].

GLP-1 Receptor Agonists:

In cohort studies, there was no statistically significant difference between GLP-1 RA treatment users and non-users in terms of fracture outcomes. GLP-1 RA therapy was related with a decreased incidence of fractures in one meta-analysis of RCTs with follow-up periods, but other RCT meta-analyses revealed conflicting findings. These meta-analyses include limitations, such as the relatively short follow-up periods (12-104 weeks). Therefore, the evidence we have so far indicates that T2D patients' fracture risk is unaffected [10].

Sodium-Glucose Co transporter 2 Inhibitors:

Small sample numbers and brief follow-up periods have hampered the current body of data from observational research and randomized controlled trials. In two cohort studies, there was no significant difference in fracture risk between new SGLT2-is users and new GLP-1 RA users. A greater incidence of fracture was seen in new SGLT2-i users compared to new DPP-IVi users in a propensity score-matched cohort trial; however, this impact was attenuated with extended treatment duration for both groups [8].

A case-control study found no association between fracture and combination therapy with metformin and SGLT2-is compared to metformin and DPP-IVi. The onset of fractures in this research cohort may have been due to an early bout of hypoglycemia. We think this was an outlier case because insulin users were not included in the study and SGLT2-is are generally thought to be hypoglycemia-safe. In addition, a pooled study of 13 RCTs [11, 12].

Metformin with SGLT2-is was not linked with an increased risk of fracture compared to metformin plus DPP-IVi, according to a case-control study. Early episodes of hypoglycemia may have contributed to the development of fractures in the study population. Because of the low risk of hypoglycemia associated with SGLT2-is and the exclusion of insulin users from the trial [12, 13].

DISCUSSION

Low bone mass, micro-architectural degeneration of bone tissue that causes bone fragility, and an elevated risk of fractures are all symptoms of osteoporosis, a systemic skeletal condition. According to research by **Hopham *et al.*** [14], the pathogenic process causing bone fragility in T2DM is complicated and not entirely understood. Bone fracture may be caused by both reduced bone mass and abnormal bone microstructure.

Li *et al.* [15] also made it evident that T2DM may have an impact on bone quality and quantity, changing the structural characteristics of bone mass. Because T2DM interferes with bone homeostasis, associated fractures are regarded as T2DM-related. Numerous studies have already revealed that T2DM patients have a higher fracture risk.

According to **Xu and Wu** [16], the prevalence of osteoporosis among those with type 2 diabetes rose from 3.13 percent to 6.10 percent after adjusting for several factors. During this time, there was no change in the adjusted prevalence of osteoporosis among non-diabetics. Adjusted rates of osteopenia have been rising steadily among both those with type 2 diabetes and the general population.

Multiple linear regression analysis revealed that gender, age, race, history of fracture, body mass index (BMI), smoking status, and level of physical activity

were substantial predictors of outcomes for people with type 2 diabetes. Therefore, it is possible that the declining trend in mean BMD is due in part to these linked risk factors [17].

According to research by **Xu *et al.*** [18], osteoporosis and osteopenia are more common in women than men. After accounting for potential confounders, the results revealed that overweight individuals with type 2 diabetes were at a reduced risk for osteoporosis and osteopenia.

Men often had a greater mean BMD than women among T2DM patients. Despite these findings, **Napoli *et al.*** [19] suggested that males should receive special care because their research showed that men with diabetes were more likely to have fractures.

When it comes to anti-diabetic medicine and insulin treatment, normal and osteoporosis patients do not differ much from one another. In elderly diabetic patients, Thiazolidinedione usage and bone loss were investigated by **Sundararaghavan *et al.*** [20]. They discovered throughout their research that the observed tendency may be influenced by the anti-diabetic medicine taken by T2DM patients.

Numerous research that looked at how TZD affected bone metabolism discovered that it was linked to increased adiposity and decreased osteoblast genesis, which may result in defective bone production and eventually fractures. Other research revealed that the use of the drugs eventide, a glucagonlike peptide 1 receptor agonist, and dapagliflozin, an inhibitor of sodium glucose cotransporter-2, increased the risk of bone fractures, whereas the use of dipeptidyl peptidase-4 inhibitors was linked to a reduced risk of fracture [21].

According to **Xu *et al.*** [18] findings, poor glycemic control was shown to be linked to an increased risk of osteoporosis and osteopenia in men, whereas metformin therapy was linked to a lower risk in women.

Patients with type 2 diabetes mellitus have higher bone mineral density (BMD) than healthy individuals, according to research by **Sellmeyer *et al.*** [22]. Additionally, they demonstrated that type 2 diabetes has high bone mineral density and a higher risk of fractures due to poor glucose management.

CONCLUSION

It could be concluded that some of the newer glucose-lowering therapies for type 2 diabetes have been shown to improve renal and cardiovascular outcomes. However, treatments aimed at reducing glucose levels may potentially influence fractures risks. The link between antidiabetic therapy and osteoporosis deserves more investigation, perhaps in the form of long-term trials.

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