ISSN 2618-1584 Vol. 6, Issue 2: 43-48, DOI: 10.25236/FMSR.2024.060208

Association between Triglyceride-glucose Index and Osteoporosis: A Cross-sectional Study Based on the National Health and Nutrition Examination Survey

Xiao Zhou[1,*], Yan Zhu[2]

[1]*Department of Endocrinology, Zhuji People's Hospital, Shaoxing, 311800, China*
[2]*Department of Spine Surgery, Zhuji People's Hospital, Shaoxing, 311800, China*
**Corresponding author: 470054985@qq.com*

Abstract: *Triglyceride-glucose (TyG) index is a substitute index for insulin resistance, and has been reported to be associated with many diseases, such as myocardial infarction, stroke, hypertension, and depression, while its association with osteoporosis has not been reported. Therefore, this study aims to explore the association between TyG index and osteoporosis. This was a cross-sectional study, and data were extracted from the National Health and Nutrition Examination Survey (NHANES). The association between TyG index and osteoporosis was assessed using logistic regression analysis, and results were shown as odds ratio (OR) and 95% confidence intervals (95%CI). Subgroup analysis was also performed based on age, BMI, and diabetes. A total of 4,351 participants were finally included, with 2,149 female and 2,202 male. After adjusting potential confounders, we found that higher level of TyG index was significantly associated with higher odds of osteoporosis in female with BMI > 30 kg/m^2 (OR = 1.88, 95%CI: 1.10-3.19). Moreover, TyG index was associated with osteoporosis in male with age < 65 years (OR = 2.16, 95%CI: 1.13-4.13), with BMI < 25 kg/m^2 (OR = 1.86, 95%CI: 1.01-3.42), or without diabetes (OR = 2.24, 95%CI: 1.26-3.97). High TyG index was associated with the high odds of osteoporosis in male with age < 65 years, with BMI < 25 kg/m^2, or without diabetes, and in female with BMI > 30 kg/m^2. Future studies are needed to verify our findings.*

Keywords: *triglyceride-glucose index, osteoporosis, body mass index, gender*

1. Introduction

Osteoporosis is a bone metabolic disease characterized by low bone mineral density (BMD) and decreased bone strength, which leads to an increased risk of fracture [1]. With the aging of population, the prevalence of osteoporosis is gradually increasing, especially in the population over 50 years old [2]. The prevalence is different between man and women, with 13% higher in women than that of men [2].

Insulin resistance has been reported to be associated with osteoporosis [3]. In insulin resistant states, insulin signaling in vivo leads to expansion of bone marrow adipose tissue, decreases trabecular BMD, and decreases cortical thickness [4]. Hyperinsulinemic normoglycemic clamp (HIEC) is considered as the gold standard to evaluate insulin resistance because it measures the sensitivity of peripheral tissue to insulin [5]. However, due to its complexity and cost, this technique has not been widely applied in the clinic [6]. Alternatively, homeostasis model assessment of insulin resistance (HOMA-IR) is a common method used to assess insulin resistance in clinical practice and has a good correlation with HIEC [7]. However, when calculating HOMA-IR, it is necessary to measure fasting insulin, which may be difficult to obtain in some primary medical institutions [6]. In 2008, triglyceride-glucose (TyG) index is firstly reported as a substitute index for insulin resistance, and is not dependent on fasting insulin levels [8]. TyG index has been proven to be comparable to the accuracy of HIEC and HOMA-IR for insulin resistance [9, 10]. Previous studies have reported that TyG index was associated with myocardial infarction, stroke, hypertension, and depression [11-14], while the association between TyG index and osteoporosis has not been reported.

Evidence has shown that the association between insulin resistance and osteoporosis may be affected by age, gender, body mass index (BMI), and diabetes [4, 15-17]. Studies have showed that insulin resistance is related to the decrease of BMD in middle-aged women and people without diabetes, and the effect of insulin resistance on BMD is differential according to gender and BMI [4, 15]. In patients with type 2 diabetes mellitus (T2DM), high degree of insulin resistance is significantly associated with an

ISSN 2618-1584 Vol. 6, Issue 2: 43-48, DOI: 10.25236/FMSR.2024.060208

increased risk of osteoporosis in female, but not in male [16]. A community study on nondiabetic older adults shows that the increase of insulin resistance is associated with high total hip BMD, but this association is no longer significant after adjusting BMI [17].

Therefore, this study aims to explore the association between TyG index and osteoporosis in female and male. Subgroup analysis was also performed based on age, BMI, and diabetes.

2. Methods

2.1 Study design and data source

This was a cross-sectional study based on the data extracting from the National Health and Nutrition Examination Survey (NHANES). NHANES aimed to assess American adults' and children's health and nutritional status, and used a complex, multistage, probability sampling design to examine a nationally representative sample of about 5,000 persons each year. The survey combined interviews and physical examinations, and conducted in a repeated 2-year cycle. The National Center for Health Statistics Research Ethics Review Board approved NHANES procedures and protocols annually, and all participants have provided written informed consent at the time of survey [18]. We used 2005-2018 data, of these, BMD measurement was not recorded in NHANES in 2011-2012 and 2015-2016; therefore, five cycles data (2005-2006, 2007-2008, 2009-2010, 2013-2014, and 2017-2018) were used for analysis [19]. Due to NHANES data were publicly available and de-identifiable, this study was exempt from ethical review from Institutional Review Board of Zhuji People's Hospital.

2.2 Study population

Participants who aged ≥ 50 years old were included in this study, and those who with incomplete data on BMD measurement and missing data on triglycerides (TG) and fasting blood glucose (FBG) were excluded.

2.3 Data extraction

We used data based on demographic characteristics [gender, age, race, marital status, educational level, drinking status, smoking status, hip fracture, poverty-to-income ratio (PIR)], physical examination (BMI), laboratory values [TG, FBG, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (TC)], physical activity, comorbidities [diabetes, hypertension, and cardiovascular diseases (CVD)], drug use (lipid-lowering drugs, osteoporosis drugs, and glucocorticoid), dietary intake (vitamin D, total energy, calcium), BMD measurement (Total femur BMD and femoral neck BMD), and menopause status.

BMI was not self-reported, and calculated as body weight (kg)/height $(m)^2$ [20]. Diabetes was determined by self-reported diagnosis, self-reported use of insulin or other diabetes medication, and laboratory examination [FBG ≥ 7.0 mmol/L or glycated hemoglobin (HbA1c) ≥ 6.5%] [21]. Hypertension was determined by self-reported diagnosis, systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg, and receiving antihypertensive treatment [22]. CVD was a composite of 5 self-reported CVD outcomes, which included coronary heart disease, congestive heart failure, stroke, angina, and heart attack [23]. Women were categorized as postmenopausal if they answered "menopause" to "What is the reason that you have not had a period in the past 12 months?"

2.4 Osteoporosis and TyG index

BMD was measured using dual-energy X-ray absorptiometry (DXA). BMD at the femur neck and total femur was utilized to calculate the T-score (respondent's BMD-reference group mean BMD)/reference group standard deviation (SD). Non-Hispanic White women aged 20-29 years from NHANES III was regarded as the reference group [24]. Osteoporosis was diagnosed as T-score ≤ -2.5 in the femur neck or total femur or trochanter or intertrochanter.

TyG index was calculated as ln [fasting TG (mg/dL) × FBG (mg/dL)/2] [25].

2.5 Statistical analysis

Data in this study were weighted using appropriate sample weights provided by NHANES to account

ISSN 2618-1584 Vol. 6, Issue 2: 43-48, DOI: 10.25236/FMSR.2024.060208

for complex sampling design of NHANES. Continuous data were represented as mean (standard error) (S.E), and intergroup differences were compared using t test. Counting data were represented as number and percentage [n (%)], and intergroup differences were compared using chi-squared test. Missing data were processed using multiple imputation. Univariate and multivariate logistic regression analysis was used to assess the association between TyG index and osteoporosis, with results shown as odds ratio (OR) and 95% confidence intervals (95%CI). Model 1 was unadjusted model; Model 2 adjusted age, BMI, osteoporosis drugs; Model 3 adjusted age, BMI, osteoporosis drugs, education level, marital status, hip fracture, PIR, hypertension, CVD, glucocorticoid, energy, postmenopausal status for female and adjusted age, BMI, osteoporosis drugs, race, marital status, drinking for male. Subgroup analysis based on age, BMI, and diabetes was also performed to explore the association between TyG index and osteoporosis. The results were visualized using "visreg" package in R (version 4.2.0, R Foundation for Statistical Computing, Vienna, Austria). Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.2.0. $P < 0.05$ was considered to be statistical significance.

3. Results

3.1 Selection and characteristics of participants

A total of 11,952 participants aged ≥ 50 years were extracted from the NHANES. Of these, 2,585 participants with incomplete data on BMD measurement and 5,016 participants missing data on TG and FBG were excluded. In the remaining 4,351 participants, there were 2,149 female (451 participants with osteoporosis and 1698 participants with non-osteoporosis) and 2,202 male (139 participants with osteoporosis and 2063 with non-osteoporosis). It shows that age, race, marital status, education level, hip fracture, BMI, TG, FBG, physical activity, diabetes, CVD, glucocorticoid, calcium, total femur BMD, femoral neck BMD, and postmenopausal status were statistically different between osteoporosis group and non-osteoporosis group in female. Age, race, education level, drinking, BMI, total energy, total femur BMD, and femoral neck BMD were statistically different between osteoporosis group and non-osteoporosis group in male.

3.2 Association between TyG index and osteoporosis

It shows that age, marital status, education level, hip fracture, PIR, BMI, hypertension, CVD, osteoporosis drugs, glucocorticoid, total energy, and postmenopausal status were significant covariates in female, and age, race, marital status, drinking, and BMI were significant covariates in male. In the unadjusted model, we found that there was no statistical difference in the association between TyG index and osteoporosis in female and male (both $P > 0.05$). After adjusting age, BMI, and osteoporosis drugs, the results were similar (both $P > 0.05$). Further adjusting education level, marital status, hip fracture, PIR, hypertension, CVD, glucocorticoid, energy, and postmenopausal status, we found higher TyG index was associated with higher odds of osteoporosis despite no statistical difference in female (OR = 1.13, 95%CI: 0.84-1.53, $P = 0.401$) and male (OR = 1.21, 95%CI: 0.72-2.04, $P = 0.456$).

3.3 Subgroup analysis based on age, BMI, and diabetes for the association between TyG index and osteoporosis

It shows that the association between TyG index and osteoporosis may be affected by age, BMI, and diabetes. In female, we found that higher degree of TyG index was significantly associated with higher odds of osteoporosis in participants with BMI > 30 kg/m^2 (OR = 1.88, 95%CI: 1.10-3.19) in Model 3. In male, we found the positive association between TyG index and osteoporosis in participants with age < 65 years (OR = 2.16, 95%CI: 1.13-4.13), with BMI < 25 kg/m^2 (OR = 1.86, 95%CI: 1.01-3.42), or without diabetes (OR = 2.24, 95%CI: 1.26-3.97) in Model 3.

4. Discussion

In this national representative cross-sectional study, the association between TyG index and osteoporosis was assessed. The main finding of this study is that high level of TyG was associated with high odds of osteoporosis in male with age < 65 years, with BMI < 25 kg/m^2, or without diabetes. The similar result was found in female with BMI > 30 kg/m^2. To our best knowledge, this study is the first of the relationship of TyG index to the osteoporosis.

ISSN 2618-1584 Vol. 6, Issue 2: 43-48, DOI: 10.25236/FMSR.2024.060208

A previous study has reported that insulin resistance was associated with age, and it increased with the increase of age [26]. In addition, age is the main determinants for the risk of osteoporosis and related fragile fractures [27]. A nationwide and multicenter study in China showed that the prevalence of osteoporosis significantly increases as age increases in both male and female after 55 years old [28]. Our results showed that TyG index was significantly associated with the higher odds of osteoporosis in male with age < 65 years, indicating that insulin resistance may affect the osteoporosis. There are several mechanisms may account for this. First, levels of proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α), are increased in insulin-resistant subjects and may induce bone loss by stimulating osteoclast activity [29-31]. Second, considering that various blood lipid levels have been proven to be related to BMD, changes in lipid levels in insulin-resistant subjects may also affect bone health [32, 33]. In addition to the possible indirect mechanisms mentioned above, insulin resistance may also directly affect bone mass [34]. Insulin resistance may impair osteoblastic insulin signaling, leading to a decrease in osteoblast proliferation and resulting in osteoporosis [34]. In participants with age ≥ 65 years, we found no significance between TyG index and osteoporosis. This may be explained by that subjects over 65 years old are more likely to suffer from osteoporosis [35], which may weaken the relationship between insulin resistance and osteoporosis.

Low BMI has been reported as an indicator for osteoporosis and its related fractures [36]. Alay et al. have reported that BMI level was significantly lower in the osteoporosis patients [37]. Patients with high BMI may experience a significant increase in insulin resistance [38]. Chen et al. found that the risk of insulin resistance increased with increasing BMI, indicating that high BMI was a risk factor for insulin resistance [39]. In this study, we found the association between TyG index and osteoporosis in male with BMI < 25 kg/m^2. This finding indicated that clinicians should pay more attention to insulin resistance in male with BMI < 25 kg/m^2. We also found the similar association in female with BMI > 30 kg/m^2. This may be explained by that the increase in fat mass in insulin-resistant subjects may affect BMD because it is well known that fat mass affect bone as a main weight-bearing component and as a metabolic active organ [40].

Diabetes has been recognized to be independently associated with the risk of fragile fractures [41]. Hyperglycemia plays an important role during the bone metabolism damage in diabetes patients, resulting in a decrease in bone strength [42]. A study showed that the risk of osteoporosis increased with increasing glycosylated hemoglobin (HbA1c) level in newly diagnosed diabetes, which implied that increase of glucose level could impair bone metabolism even in the early stage of diabetes [43]. Hyperglycemia and its associated hyperosmolarity could also inhibit the expression of osteoblast maturation-related genes [44]. Hyperglycemia led to calcium homeostasis imbalance via suppressing the bone formation and accelerating bone resorption, and it was also demonstrated that high glucose may induce increased osteoblast apoptosis [43]. Our results showed that there was no significant difference in the association between TyG index and osteoporosis in diabetes. This may be explained by that the level of insulin resistance was high in diabetes patients that effect of changes in insulin resistance level on osteoporosis may be relatively small [45]. Yoon et al. have found the association between TyG index and reduced BMD [15]. In this study, the results demonstrated that the TyG index was an influencing factor of osteoporosis in patients without diabetes. Monitoring this index in patients without diabetes may help reduce the odds of osteoporosis and resultant healthcare burdens.

Our study showcases the initial evidence of an association between TyG index and osteoporosis, which may provide several guidance for the management of osteoporosis. However, there are some limitations in this study. This is a cross-sectional study, which is difficult to infer causal relationships. Second, some possible confounders, such as drug use and comorbidities, have been adjusted; however, factors such as disease course and drug dose are difficult to obtain due to the limitation of the database. Third, due to DXA examination sites are different in every NHANES survey years, this study selected BMD of total femur and femur neck to diagnose the osteoporosis, which may underestimate the prevalence rate.

5. Conclusion

In conclusion, high TyG index was associated with the high odds of osteoporosis in male with age < 65 years, with BMI < 25 kg/m^2, or without diabetes, and in female with BMI > 30 kg/m^2. Those population with a higher TyG index should be aware of the following odds of osteoporosis, so as to take intervention measures in time. Future studies are needed to verify our findings and elucidate the exact mechanisms underlying the association between TyG index and osteoporosis.

ISSN 2618-1584 Vol. 6, Issue 2: 43-48, DOI: 10.25236/FMSR.2024.060208

Acknowledgements

A novel slow-release bionic bone scaffold loaded with ursolic acid in promoting bone tissue regeneration and functional reconstruction, Zhejiang Provincial Administration of Traditional Chinese Medicine, Project number: 2024ZL1170.

Authors' contributions

Xiao Zhou and Yan Zhu designed the study. Xiao Zhou wrote the manuscript. Xiao Zhou and Yan Zhu collected, analyzed and interpreted the data. Yan Zhu critically reviewed, and edited the manuscript. All authors read and approved the final manuscript.

References

[1] Khandelwal, S. and N.E. Lane, Osteoporosis: Review of Etiology, Mechanisms, and Approach to Management in the Aging Population. Endocrinol Metab Clin North Am, 2023. 52(2): p. 259-275.
[2] Zou, Z., et al., Advances in the occurrence and biotherapy of osteoporosis. Biochem Soc Trans, 2020. 48(4): p. 1623-1636.
[3] Fu, Y.H., et al., Associations of insulin resistance and insulin secretion with bone mineral density and osteoporosis in a general population. Front Endocrinol (Lausanne), 2022. 13: p. 971960.
[4] Shieh, A., et al., Longitudinal associations of insulin resistance with change in bone mineral density in midlife women. JCI Insight, 2022. 7(20).
[5] DeFronzo, R.A., J.D. Tobin, and R. Andres, Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol, 1979. 237(3): p. E214-223.
[6] Zhou, Y., et al., The U-Shape Relationship between Triglyceride-Glucose Index and the Risk of Diabetic Retinopathy among the US Population. J Pers Med, 2023. 13(3).
[7] Matthews, D.R., et al., Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia, 1985. 28(7): p. 412-419.
[8] Simental-Mendía, L.E., M. Rodríguez-Morán, and F. Guerrero-Romero, The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. Metab Syndr Relat Disord, 2008. 6(4): p. 299-304.
[9] Guerrero-Romero, F., et al., The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. J Clin Endocrinol Metab, 2010. 95(7): p. 3347-3351.
[10] Wang, S., et al., Stronger association of triglyceride glucose index than the HOMA-IR with arterial stiffness in patients with type 2 diabetes: a real-world single-centre study. Cardiovasc Diabetol, 2021. 20(1): p. 82.
[11] Tian, X., et al., Triglyceride-glucose index is associated with the risk of myocardial infarction: an 11-year prospective study in the Kailuan cohort. Cardiovasc Diabetol, 2021. 20(1): p. 19.
[12] Wang, A., et al., Triglyceride-glucose index and the risk of stroke and its subtypes in the general population: an 11-year follow-up. Cardiovasc Diabetol, 2021. 20(1): p. 46.
[13] Wang, Y., W. Yang, and X. Jiang, Association Between Triglyceride-Glucose Index and Hypertension: A Meta-Analysis. Front Cardiovasc Med, 2021. 8: p. 644035.
[14] Shi, Y.Y., et al., The association between triglyceride glucose index and depression: data from NHANES 2005-2018. BMC Psychiatry, 2021. 21(1): p. 267.
[15] Yoon, J.H., et al., Association of Triglyceride-Glucose Index with Bone Mineral Density in Non-diabetic Koreans: KNHANES 2008-2011. Calcif Tissue Int, 2021. 108(2): p. 176-187.
[16] Wang, X., L. Jiang, and X. Shao, Association Analysis of Insulin Resistance and Osteoporosis Risk in Chinese Patients with T2DM. Ther Clin Risk Manag, 2021. 17: p. 909-916.
[17] Napoli, N., et al., Effect of Insulin Resistance on BMD and Fracture Risk in Older Adults. J Clin Endocrinol Metab, 2019. 104(8): p. 3303-3310.
[18] Paulose-Ram, R., et al., Overview of Asian American Data Collection, Release, and Analysis: National Health and Nutrition Examination Survey 2011-2018. Am J Public Health, 2017. 107(6): p. 916-921.
[19] Liu, B., et al., The association of diabetes status and bone mineral density among US adults: evidence from NHANES 2005-2018. BMC Endocr Disord, 2023. 23(1): p. 27.
[20] MacGregor, K.A., I.J. Gallagher, and C.N. Moran, Relationship Between Insulin Sensitivity and Menstrual Cycle Is Modified by BMI, Fitness, and Physical Activity in NHANES. J Clin Endocrinol Metab, 2021. 106(10): p. 2979-2990.

ISSN 2618-1584 Vol. 6, Issue 2: 43-48, DOI: 10.25236/FMSR.2024.060208

[21] McClure, S.T., et al., Dietary intake of adults with and without diabetes: results from NHANES 2013-2016. BMJ Open Diabetes Res Care, 2020. 8(1).
[22] Zhou, C., et al., Inverse Association Between Variety of Proteins With Appropriate Quantity From Different Food Sources and New-Onset Hypertension. Hypertension, 2022. 79(5): p. 1017-1027.
[23] Shi, Z., et al., The Circadian Syndrome Is a Significant and Stronger Predictor for Cardiovascular Disease than the Metabolic Syndrome-The NHANES Survey during 2005-2016. Nutrients, 2022. 14(24).
[24] Looker, A.C., et al., Prevalence of low femoral bone density in older U.S. adults from NHANES III. J Bone Miner Res, 1997. 12(11): p. 761-768.
[25] Li, T., et al., Elevated triglyceride-glucose index predicts mortality following endovascular abdominal aortic aneurysm repair. Front Nutr, 2023. 10: p. 1116425.
[26] Sakurai, T., et al., Age-associated increase in abdominal obesity and insulin resistance, and usefulness of AHA/NHLBI definition of metabolic syndrome for predicting cardiovascular disease in Japanese elderly with type 2 diabetes mellitus. Gerontology, 2010. 56(2): p. 141-149.
[27] Yong, E.L. and S. Logan, Menopausal osteoporosis: screening, prevention and treatment. Singapore Med J, 2021. 62(4): p. 159-166.
[28] Zeng, Q., et al., The Prevalence of Osteoporosis in China, a Nationwide, Multicenter DXA Survey. J Bone Miner Res, 2019. 34(10): p. 1789-1797.
[29] Akash, M.S.H., K. Rehman, and A. Liaqat, Tumor Necrosis Factor-Alpha: Role in Development of Insulin Resistance and Pathogenesis of Type 2 Diabetes Mellitus. J Cell Biochem, 2018. 119(1): p. 105-110.
[30] Rehman, K., et al., Role of Interleukin-6 in Development of Insulin Resistance and Type 2 Diabetes Mellitus. Crit Rev Eukaryot Gene Expr, 2017. 27(3): p. 229-236.
[31] Wang, T. and C. He, TNF-α and IL-6: The Link between Immune and Bone System. Curr Drug Targets, 2020. 21(3): p. 213-227.
[32] Zhang, Q., et al., Association Between Bone Mineral Density and Lipid Profile in Chinese Women. Clin Interv Aging, 2020. 15: p. 1649-1664.
[33] Tang, X., et al., Associations of insulin resistance and beta-cell function with abnormal lipid profile in newly diagnosed diabetes. Chin Med J (Engl), 2022. 135(21): p. 2554-2562.
[34] Conte, C., S. Epstein, and N. Napoli, Insulin resistance and bone: a biological partnership. Acta Diabetol, 2018. 55(4): p. 305-314.
[35] Gopinath, V., Osteoporosis. Med Clin North Am, 2023. 107(2): p. 213-225.
[36] Jiang, X., et al., Osteoporosis screening in postmenopausal women aged 50-64 years: BMI alone compared with current screening tools. Maturitas, 2016. 83: p. 59-64.
[37] Alay, I., et al., The relation of body mass index, menopausal symptoms, and lipid profile with bone mineral density in postmenopausal women. Taiwan J Obstet Gynecol, 2020. 59(1): p. 61-66.
[38] Li, Q., et al., The effects of body mass index on insulin resistance in patients undergoing total hip arthroplasty: a pilot study. Int Orthop, 2022. 46(8): p. 1775-1782.
[39] Chen, M., et al., Non-linear associations of body mass index with impaired fasting glucose, β-cell dysfunction, and insulin resistance in nondiabetic Chinese individuals: a cross-sectional study. Endokrynol Pol, 2021. 72(6): p. 618-624.
[40] Ahmed, B., R. Sultana, and M.W. Greene, Adipose tissue and insulin resistance in obese. Biomed Pharmacother, 2021. 137: p. 111315.
[41] Rathinavelu, S., C. Guidry-Elizondo, and J. Banu, Molecular Modulation of Osteoblasts and Osteoclasts in Type 2 Diabetes. J Diabetes Res, 2018. 2018: p. 6354787.
[42] Napoli, N., et al., Mechanisms of diabetes mellitus-induced bone fragility. Nat Rev Endocrinol, 2017. 13(4): p. 208-219.
[43] Wen, Y., et al., Correlation of Osteoporosis in Patients With Newly Diagnosed Type 2 Diabetes: A Retrospective Study in Chinese Population. Front Endocrinol (Lausanne), 2021. 12: p. 531904.
[44] Botolin, S., et al., Increased bone adiposity and peroxisomal proliferator-activated receptor-gamma2 expression in type I diabetic mice. Endocrinology, 2005. 146(8): p. 3622-3631.
[45] Lebovitz, H.E., Insulin resistance--a common link between type 2 diabetes and cardiovascular disease. Diabetes Obes Metab, 2006. 8(3): p. 237-249.