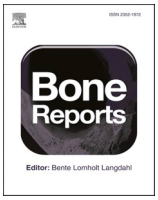
Bone Reports 25 (2025) 101836

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr



Chronic heavy alcohol consumption impairs the ability of demineralized allogenic bone matrix to support osteoinduction in alcohol-naïve rats

Russell T. Turner [a,c], Amida F. Kuah [a], Cynthia H. Trevisiol [a], Kathy S. Howe [a], Adam J. Branscum [b], Urszula T. Iwaniec [a,c,*]

[a] Skeletal Biology Laboratory, School of Nutrition and Public Health, Oregon State University, Corvallis, OR 97331, USA
[b] Biostatistics Program, School of Nutrition and Public Health, Oregon State University, Corvallis, OR 97331, USA
[c] Center for Healthy Aging Research, Oregon State University, Corvallis, OR 97331, USA

ARTICLE INFO

Keywords:
Bone graft
Ethanol
Critical size defect
Microcomputed tomography

ABSTRACT

Allografts play an important role in treatment of complex bone fractures and deformities. The purpose of this study was to test the hypothesis that alcohol consumption impairs graft incorporation and bone healing by two mechanisms: (1) by lowering osteoinductive capacity and (2) by suppressing bone formation. We performed experiments using a demineralized allogeneic bone matrix (DBM) model in which DBM harvested from donor rats fed control or ethanol diet was implanted subcutaneously into recipient rats fed control or ethanol diet. We also evaluated the efficacy of intermittent parathyroid hormone (PTH) on bone graft incorporation (DBM from donor rats fed alcohol or control diet) using a critical size defect model. Bone formed during osteoinduction was measured by micro-computed tomography. Experiment 1: Bone volume was lower in DBM harvested from ethanol-consuming donors 6 weeks following implantation into recipients fed control diet, indicating that exposure of the donor rats to ethanol lowered osteoinductive capacity. Experiment 2: Bone volume was lower in DBM harvested 3 weeks following implantation from ethanol-consuming donors into ethanol-consuming recipients compared to DBM harvested from control donors implanted into control recipients or DBM harvested from control donors implanted into ethanol-consuming recipients. Experiment 3: Ethanol consumption by donors resulted in a tendency for lower DBM bone volume ($p = 0.085$) whereas PTH treatment resulted in higher DBM bone volume in the critical size defect model. Our results suggest that chronic heavy alcohol consumption by allograft donors may impair osteoinduction and this negative outcome may be worsened by alcohol intake during bone healing. Additionally, PTH has the potential to increase osteoinduction in DBM harvested from both abstinent and alcohol-consuming donors.

1. Introduction

Worldwide, there were an estimated 178 million new bone fractures in 2019 (Wu et al., 2021). While most fractures heal without incident, delayed unions and non-unions make up 2–10 % of fractures and greatly increase the likelihood for death or long-term disability (Ekegren et al., 2018; Volpin and Shtarker, 2014). Fracture healing is a complex process. Osteoinduction at the site of injury initiates osteogenesis and plays a critical role in supporting early bone repair. Under suboptimal conditions (e.g., complex fractures, critical size defects) fracture healing can be supported with use of allogenic and/or autologous bone grafts (Sohn and Oh, 2019). Specifically, these grafts promote osteoinduction as well as osteoconduction (migration of bone cells into the graft) and osteointegration (fusion of newly formed bone with the graft).

Nearly 2.2 million procedures involving bone grafts are performed worldwide each year (Zhao et al., 2021). While grafts play an important role in treatment of patients with complex bone fractures or deformities, graft failures, predominantly of unknown cause, are common (Flierl et al., 2013; Sohn and Oh, 2019). Previous studies have focused on intrinsic factors (e.g., age of donor) influencing the graft's osteoinductive potential. Few studies have investigated the impact of extrinsic factors (e.g., alcohol consumption, smoking, or physical activity of donor) on graft incorporation. Because osteoinduction by bone grafts is predicated on the release of biologically active growth factors present in the graft (Hauschka et al., 1988), it is possible that extrinsic factors such as heavy drinking could reduce the concentration of skeletal growth

* Corresponding author at: Skeletal Biology Laboratory, School of Nutrition and Public Health, Oregon State University, Corvallis, OR 97331, USA.
E-mail address: urszula.iwaniec@oregonstate.edu (U.T. Iwaniec).

https://doi.org/10.1016/j.bonr.2025.101836
Received 17 February 2025; Accepted 11 March 2025
Available online 12 March 2025

factors deposited into bone matrix, compromizing osteoinductive potential of a bone graft.

There is compelling evidence that chronic heavy alcohol intake leads to increased fracture rates (Yuan et al., 2023; Cherpitel, 2013; Riuttanen et al., 2020). Contributing to this increase are reduced bone mass and quality, alcohol-associated comorbidities (e.g., diabetes, pancreatitis, liver disease), increased fall frequency, and increased rates of traumatic injuries (Santori et al., 2008; Berg et al., 2008). Once a fracture occurs, chronic heavy alcohol consumers are more likely to suffer a delayed union or non-union fracture (Nyquist et al., 1997; Campenfeldt et al., 2018; Stavrou et al., 2016; Zura et al., 2017). Although it is well established that alcohol abuse impairs post-fracture bone healing, few studies have specifically considered alcohol-induced changes in bone matrix as a risk factor contributing to impaired fracture healing or bone graft failures.

Osteoinduction is mediated, in part, by signaling factors (e.g., TGF-β, IGF-1) activated and released from bone matrix during resorption. We have shown that heavy alcohol consumption in rodents, in addition to suppressing bone formation, suppresses IGF-1 gene expression in bone and lowers IGF-1 levels in blood (Maddalozzo et al., 2009; Turner et al., 1998). While there is evidence that alcohol consumption inhibits the generation of skeletal coupling factors by osteoblasts, particularly IGF-1, remarkably little work has been performed to establish if this alcohol-induced response reduces future osteoinductive capacity.

Osteoinduction can be modeled using demineralized allogeneic bone matrix (DBM), a complex of collagen, non-colagenous protein, and growth factors which remain after mature bone is demineralized and defatted (Cornell, 2004). DBM implanted intramuscularly or subcutaneously in rodents forms a mature ossicle between 3 and 6 weeks post-implantation (Urist and Strates, 1970). The purpose of the current studies was to test the hypothesis that alcohol consumption, a risk factor for fracture repair, can impair DBM-mediated osteoinduction and DBM-facilitated bone healing by two non-mutually exclusive mechanisms: (1) by lowering osteoinductive capacity, potentially by reducing deposition of growth factors into bone matrix, and (2) by suppressing bone accrual. In addition, we evaluated the effects of intermittent parathyroid hormone (PTH) as an adjuvant therapy on bone graft incorporation using grafts from alcohol-consuming donors. We chose intermittent PTH as a countermeasure because we have shown that the bone anabolic effects of PTH are not dependent on growth hormone/IGF-1 signaling (Schmidt et al., 1995) and that suppression of bone formation in growing rats by alcohol can be prevented by treatment with therapeutic levels of PTH (Howe et al., 2011).

2. Materials and methods

We performed 3 experiments using 2 osteoinduction models: (1) a DBM model in which DBM was harvested from donor rats fed a control or ethanol diet and then implanted into recipient rats fed control or ethanol diets (Experiments 1 and 2), and (2) a critical size bone defect model where DBM was harvested from donor rats fed a control or ethanol diet and used to close a critical size defect in fibula of recipient rats fed a control diet (Experiment 3) (Fig. 1).

2.1. Experiment 1

The purpose of Experiment 1 was to test the hypothesis that heavy alcohol consumption by the donor will reduce the osteoinductive capacity of DBM. The experimental design is depicted graphically in Fig. 1A. Femora were harvested from male Sprague-Dawley rats fed (1) liquid ethanol diet (Lieber-DeCarli, BioServ, #F1258SP) or (2) control isocaloric diet in which ethanol was replaced with maltose-dextran (BioServ, #F1259SP) for 3 months (from 1 to 4 months of age). The rats in the ethanol group consumed 35 % of their caloric intake as ethanol. Control rats were pair fed to ethanol rats. Alcohol consumption during rapid growth (1–4 months of age) ensured that a large majority of cortical bone matrix harvested for DBM preparation would have formed while the rats consumed alcohol. For graft preparation, the femora were cleaned of soft tissue and soaked in deionized cold water. The diaphyses were separated from the metaphyses and the marrow flushed out using deionized cold water. The resulting diaphyseal shafts were demineralized overnight in 0.6 N HCl at 4 °C with gentle stirring. After rinsing in deionized water, the demineralized bone shafts were extracted at 4 °C with 70 % ethanol for 1 h, 100 % ethanol for 1 h and then overnight in chloroform/methanol (1:1). The femoral shafts were then cut into cylinders approximately 5 mm in length.

Complete demineralization was ensured by analyzing 2 randomly selected samples by micro-computed tomography (μCT). In addition, bone matrix IGF-1, an important osteoinductive factor, was measured in 5 randomly selected DBM cylinders/group using an enzyme-linked immunosorbent assay (American Lab Products Company, Windham, NH).

The DBM cylinders were weighed, dried at room temperature, stored at −20 °C and transferred to a sterile saline solution prior to implantation. The cylinders were implanted subcutaneously into 3-month-old male recipient Sprague-Dawley rats ($n = 12$). All grafts were placed ventrally with each rat receiving 4 grafts: 2 thoracic (from control and ethanol diet donors) and 2 abdominal (from control and ethanol diet donors). The recipient rats were fed control diet (rodent chow) for 6 weeks. We have shown that maximum mineralization of DBM matrix occurs by 6 weeks post-implantation (Vandersteenhoven et al., 1988).

Bone formed during osteoinduction was measured ex vivo by μCT; recovered implants (2/rat/treatment; 1 thoracic and 1 abdominal) were scanned using a Scanco μCT 40 scanner (Scanco Medical AG, Basserdorf, Switzerland) at a voxel size of 12 × 12 × 12 μm (55 kVp x-ray voltage, 145 μA intensity, and 200 ms integration time). Filtering parameters sigma and support were set to 0.8 and 1, respectively. Bone segmentation was conducted at a threshold of 265 (scale, 0–1000) determined empirically. Bone volume/mass (mm^3/mg) for 2 DBM implants/rat/treatment was averaged to obtain a mean endpoint value.

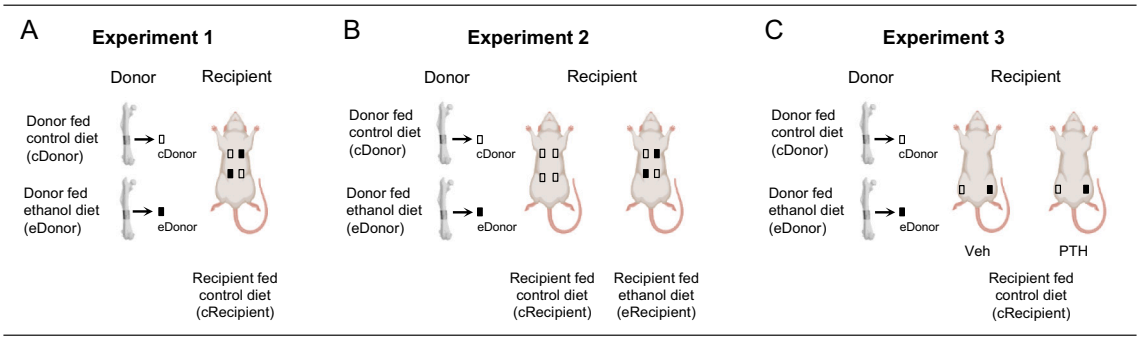


Fig. 1. Schematic representation of the experimental protocols for Experiment 1 (A), Experiment 2 (B), and Experiment 3 (C). The rat icon was adapted from "Rat (supine, curved tail)", by BioRender.com (2025). Retrieved from https://app.biorender.com/biorender-templates.

2.2. Experiment 2

The purpose of Experiment 2 was to test the hypothesis that heavy alcohol consumption following graft implantation will antagonize osteoinduction by DBM prepared from donor rats fed control or ethanol diet. This experiment was performed in female rats as our previous studies were conducted exclusively in male rats (Trevisiol et al., 2007; Iwaniec et al., 2008). The experimental design is depicted graphically in Fig. 1B. Donor grafts were prepared from rats fed control or ethanol diets and implanted, as described in Experiment 1, into 3-month-old female recipient Sprague-Dawley rats, with the exception that recipient rats fed control diet received 4 implants from donor rats fed control diet. The recipient rats were fed a control diet ($n = 8$) or ethanol diet ($n = 9$) for 4 weeks prior to DBM implantation and for 3 weeks following implantation. We have shown that 3 weeks post-implantation is an excellent time interval to detect treatment-mediated defects in bone matrix used to support osteoinduction (Vandersteenhoven et al., 1988). Bone formed during osteoinduction was measured via μCT as in Experiment 1 with the exception that bone segmentation was conducted at a threshold of 245.

2.3. Experiment 3

The purpose of Experiment 3 was to evaluate effects of treatment with a clinically relevant dose of PTH on healing of a critical size defect in which DBM grafts were prepared from rats fed a control or ethanol diet. The experimental design is depicted graphically in Fig. 1C. Bilateral ~2-mm long critical size defects were created in the fibula mid-diaphysis of 2-month-old male Sprague-Dawley rats fed control diet. DBM grafts from rats fed control or ethanol diets for 3 months were used to repair the defect in the recipient rats. Grafts were prepared as in Experiment 1. Each recipient rat was engrafted with an implant from a control diet-fed rat and an ethanol diet-fed rat. The recipient rats were injected subcutaneously with low dose PTH (5 μg/kg/d; $n = 12$) or vehicle (carrier) ($n = 12$) immediately following surgery and 5×/week thereafter and sacrificed following 6 weeks of treatment. Bone formed during osteoinduction was measured via μCT. The fibula was scanned at a voxel size of 16 × 16 × 16 μm (55 kVp x-ray voltage, 145 μA intensity, 200 ms integration time, filtering parameters sigma set to 0.8 and support set to 1). Bone volume was assessed in 100 slices (1.6 mm) of implant at a threshold of 245. Examples of a critical size defect and a defect 6 weeks following implantation of DBM in fibula are shown in Fig. 2A and B, respectively.

2.4. Statistical analysis

Mean responses on bone volume and IGF-1 were compared using independent two-sample *t*-tests (Experiment 1). Analysis of bone volume was performed using the Kruskal-Wallis distribution-free test followed by Wilcoxon-Mann-Whitney tests for pairwise comparisons because normality was violated (Experiment 2), and bone volume data from the 2 × 2 factorial design of Experiment 3 were analyzed using two-way analysis of variance. Model diagnostics included use of Levene's test for homogeneity of variance, plots of residuals versus fitted values, normal quantile plots, and the Anderson-Darling test of normality. The Benjamini and Hochberg (Benjamini and Hochberg, 1995) method for maintaining the false discovery rate at a maximum of 5 % was used to adjust for multiple comparisons. Data analysis was performed using R version 4.12.

3. Results

3.1. Experiment 1: DBM harvested from donor rats fed control or ethanol diet and implanted for 6 weeks into recipient rats fed control diet

IGF-1 was 45 % lower in bone matrix harvested from ethanol-fed rats compared to that harvested from control rats (Fig. 3A). DBM bone volume was 23 % lower in DBM from ethanol-fed donor rats following implantation into recipient rats fed control diet (eDonor → cRecipient) (Fig. 3B), indicating that exposure of the donor rats to ethanol lowered osteoinductive capacity of their bone matrix. The effects can be readily appreciated in μCT reconstructions of representative implants (Fig. 3C).

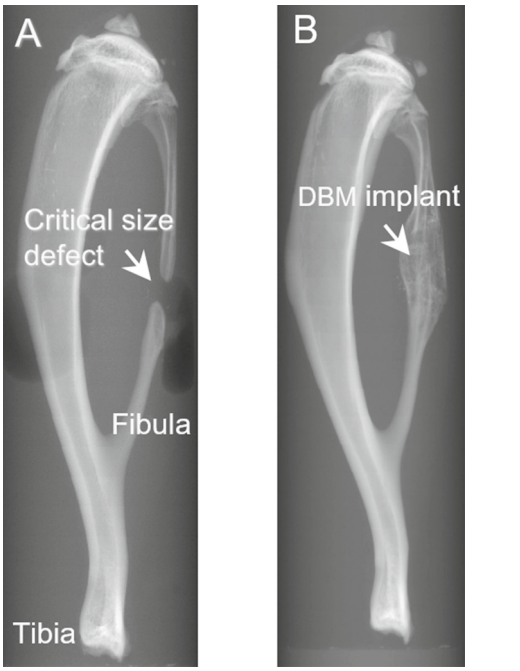


Fig. 2. Representative images of a critical size defect in fibula without (A) and with DBM implant (B) 6 weeks following implantation.

3.2. Experiment 2: DBM harvested from donor rats fed control or ethanol diet and implanted for 3 weeks into recipient rats fed control or ethanol diet

Bone volume was lower in DBM harvested from ethanol-consuming donors implanted into ethanol-consuming recipients (eDonor → eRecipient) compared to DBM harvested from control diet-consuming donors implanted into control diet-consuming recipients (cDonor → cRecipient) or ethanol-consuming recipients (cDonor → eRecipient) (Fig. 4A). Significant differences in bone volume were not detected between DBM harvested from control diet-consuming donors implanted into control diet-consuming recipients (cDonor → cRecipient) and control diet-consuming donors implanted into ethanol-consuming recipients (cDonor → eRecipient). The effects can be appreciated in μCT reconstructions of representative implants (Fig. 4B).

3.3. Experiment 3: DBM grafts from donor rats fed control or ethanol diet engrafted in fibula (critical size defect) of recipient rats fed control diet and treated with vehicle or PTH for 6 weeks

Ethanol consumption by donor rats resulted in a tendency ($p = 0.085$) for lower DBM bone volume whereas PTH treatment resulted in higher DBM mineralized volume in the critical size defect model (Fig. 5). There was no significant interaction between diet consumed by DBM donor rats and intermittent PTH treatment in recipient rats.

4. Discussion

We investigated the effects of chronic heavy alcohol consumption by

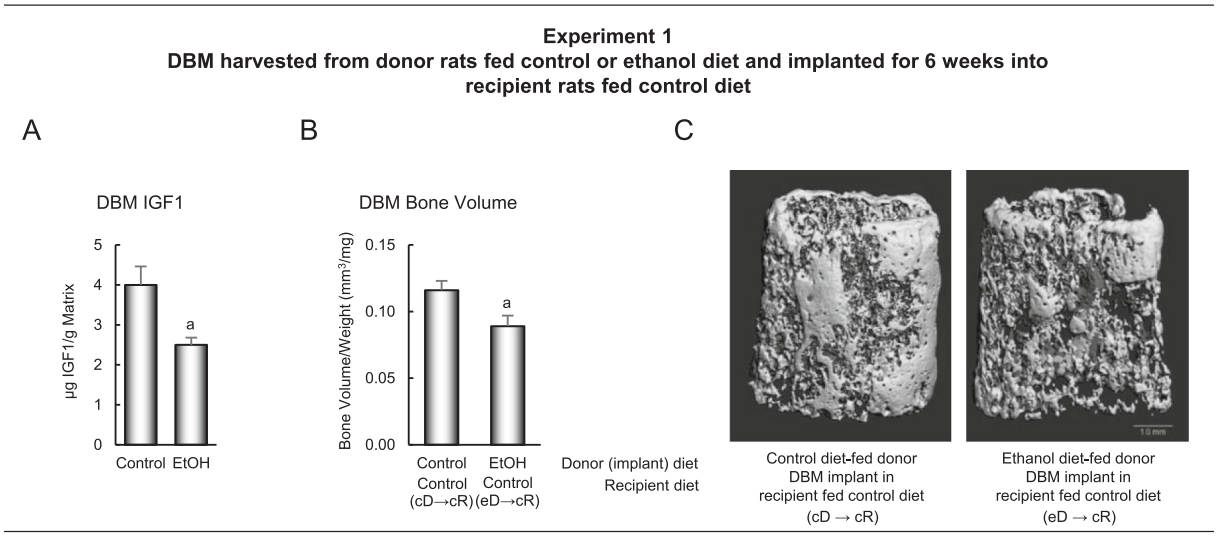


Fig. 3. Effect of donor diet (control or ethanol) on implant IGF-1 levels prior to implantation (A) and DBM bone volume 6 weeks following implantation into male recipient rats fed control diet (B). μCT reconstructions of representative implants are shown in panel C. Data are mean ± SE. $N = 12$/group. [a]Different from control, $P \leq 0.05$.

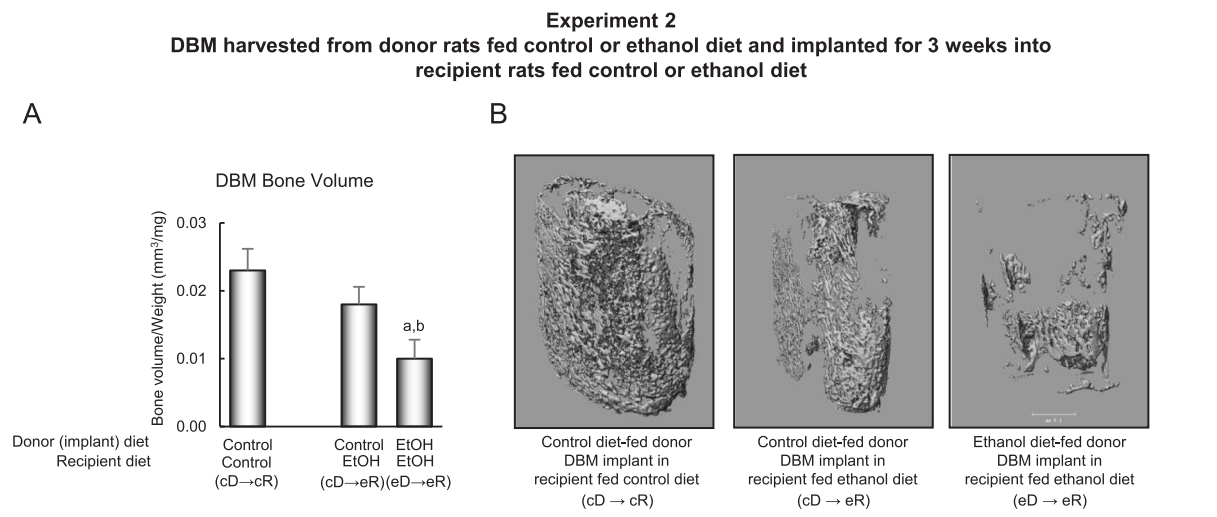


Fig. 4. Effect of donor diet (control or ethanol) on DBM bone volume 3 weeks following implantation into female recipient rats fed control or ethanol diet (A). μCT reconstructions of representative implants are shown in panel B. Data are mean ± SE. $N = 8$–9/group. [a]Different from control diet-consuming donors implanted into control diet-consuming recipients, $P \leq 0.05$. [b]Different from control diet-consuming donors implanted into ethanol diet-consuming recipients, $P \leq 0.05$.

graft donors on graft osteoinductive capacity using two models: 1) ectopic bone formation in subcutaneously-implanted DBM grafts, and 2) DBM graft-facilitated healing of a critical size bone defect. Chronic heavy alcohol consumption by the graft donor impaired ectopic-inducted osteoinduction and the impairment was exacerbated by current alcohol consumption by the graft recipient. The defect in osteoinduction by DBM from chronic alcohol consumers was associated with a decrease in bone matrix IGF-1 level. Chronic heavy alcohol consumption by graft donors tended to impair DBM-facilitated healing of a critical size defect in the graft recipient. Treatment with intermittent PTH ameliorated any negative effects of prior alcohol consumption by donors on DBM-facilitated critical size defect healing.

Alcohol consumption by male graft recipients was previously shown to decrease osteoinduction by subcutaneously implanted DBM from alcohol-naïve donor rats (Trevisiol et al., 2007; Iwaniec et al., 2008). This finding was not surprising because high blood levels of alcohol are known to inhibit endochondral ossification, intramembranous ossification, and bone remodeling (Roper et al., 2016; Pandini et al., 2022; Turner et al., 2001). We now extend this prior research by showing that osteoinduction induced by subcutaneously-implanted DBM bone grafts is impaired in alcohol-naïve rats when the bone matrix is acquired from rats that consumed alcohol. These data strongly support the conclusion that alcohol consumption alters the properties of bone matrix, reducing its osteoinductive capacity. Because osteoinduction plays an important role in fracture healing, it is plausible that a reduction in osteoinductive capacity of bone matrix contributes to impaired fracture healing often noted in chronic alcohol abusers (Albrektsson and Johansson, 2001). This possibility will require additional investigation but is suggested by our finding of a tendency ($p = 0.085$) for reduced DBM-facilitated critical size defect healing when DBM was acquired from alcohol-consuming donors.

While the goal of this investigation focused on assessment of osteoinduction during injury repair, it is important to appreciate that osteoinduction plays a key role in bone remodeling balance (Daponte

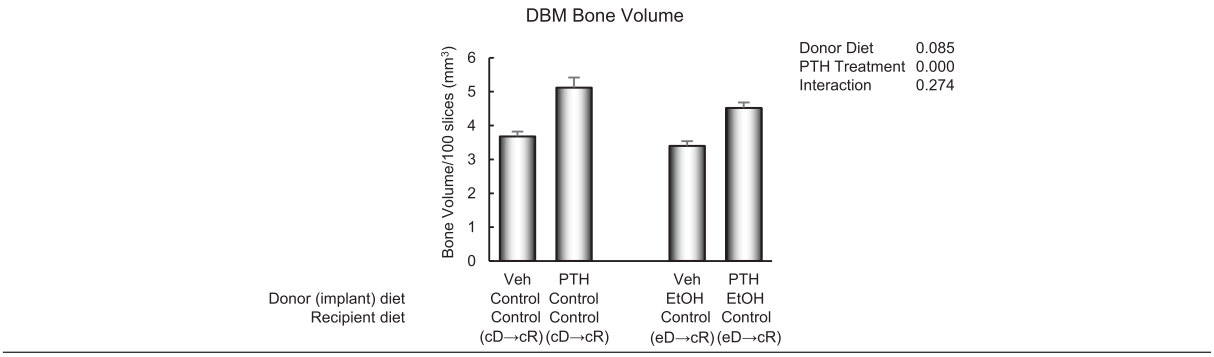


Fig. 5. Effect of donor diet (control or ethanol) and intermittent PTH administration on DBM bone volume 6 weeks following engraftment in fibula (critical size defect) in male recipient rats fed control diet. Data are mean ± SE. $N = 10–12$/group.

et al., 2024). Specifically, factors present in bone matrix released during bone resorption are critical to coupling bone formation to resorption. We and others have noted that cessation of drinking in skeletally mature rats prevents further bone loss but does not restore lost bone (Sibonga et al., 2007). Restoration of bone loss requires a positive bone remodeling balance which might be difficult to achieve if prior alcohol consumption had lowered the concentration of critical skeletal coupling factors in bone matrix. If this interpretation is correct, the negative impact of chronic alcohol consumption on fracture repair may persist during abstinence.

In previous studies, the bone that was formed from alcohol-fed DBM donor rats, although lower in quantity, was shown to mineralize normally; no changes were detected in the concentration of Ca, P, Mg, Mn, Fe or Cu (Trevisiol et al., 2007; Turner et al., 2012). The presence of normal mineral concentrations implies that the alcohol-induced impairment of osteoinduction does not involve changes in the extracellular skeletal ground substance required for mineralization. As mentioned, the osteoinductive capacity of DBM is believed to be mediated by skeletal growth factors that are deposited into bone matrix prior to its mineralization. These proteins are also believed to play an initiating role in bone repair following fracture as well as coupling bone formation to bone resorption during bone remodeling (Bolander, 1992; Cornell, 2004). We hypothesize that the reduced osteoinductive capacity of bone matrix may contribute to alcohol-induced skeletal pathologies and may delay the ability of bone to recover following alcohol withdrawal. We have performed whole genome and candidate gene expression evaluation in distal femur of rats fed alcohol for 1 h to 7 days and have shown that acute and chronic exposure to alcohol decreases mRNA levels for IGF-1 but not for TGF-β_1, TGF-β_2, TGF-β_3, IGF-2, IGFBP4, IGF-BP5, BMP1, BMP2, BMP3, BMP6, BMP7, or LTβ (Turner et al., 1998). In the current study, chronic alcohol consumption was shown to decrease the concentration of IGF-1 in bone matrix.

Growth hormone is an important physiological regulator of bone metabolism (Bouillon, 1991). IGF-1, levels of which are largely determined by growth hormone status, mediates most of the skeletal actions of growth hormone (Carrascosa and Audi, 1993; Locatelli and Bianchi, 2014). Heavy alcohol consumption reduces IGF-1 levels in rat serum (Sibonga et al., 2007). Similar findings have been reported in non-human primates and humans (Ilias et al., 2011; de la Monte et al., 2008; Sattgast et al., 2022; Sibonga et al., 2007). Additionally, alcohol was shown to antagonize the skeletal response of hypophysectomized rats to growth hormone and disturb the positive relationship between plasma IGF-1 and osteocalcin, a marker of global bone formation, in non-human primates (Sattgast et al., 2022; Turner et al., 2010). Thus, alcohol may reduce IGF-1 levels as well as impair its function.

Intermittent PTH is under preclinical and clinical investigation as adjunctive therapy to promote fracture healing. To date, clinical studies have shown that PTH may be valuable to reduce risk for delayed unions and non-unions but much work remains to determine the specific indications (Orbeanu et al., 2022; Wagner et al., 2019; Johansson, 2016; Peichl et al., 2011). Intermittent PTH enhances fracture healing in animal models (Ellegaard et al., 2010). However, these data must be interpreted with care because the dose-dependent effects of PTH on bone are bone-compartment specific and many preclinical studies were performed at dose rates (e.g., ≥40 μg/kg/d) that are unlikely to be clinically relevant (Komatsu et al., 2009). Intermittent PTH increased cancellous bone formation at a dose rate of 1 μg/kg/d but had no effect on cortical bone formation or on DBM mineralization (Trevisiol et al., 2007; Iwaniec et al., 2008). Dose response studies suggest that a higher dose (≥3 μg/kg/d) may be required to enhance fracture repair (Komatsu et al., 2009). In the present study, treatment with intermittent PTH at a dose rate of 5 μg/kg/d was effective in enhancing DBM-mediated (DBM sourced from alcohol-naïve or alcohol consuming donors) healing of a critical size bone defect.

This study has several limitations. The research specifically focused on chronic heavy alcohol consumption, but it is possible that other lifestyle factors (e.g. smoking, physical activity) influence osteoinduction. The critical size defect study was only performed in male rats and we cannot rule out the possibility that sex hormones influence the skeletal response to DBM during fracture healing. Based on the similar response of males and females to subcutaneously-implanted DBM grafts this is unlikely but should be investigated in future studies. While evidence to date supports decreased matrix IGF-1 as a strong candidate for alcohol-impaired bone healing, we acknowledge that additional undefined factors in bone matrix or in circulation are likely to be important mediators of alcohol's bioactivity. Because multiple classes of systemic factors influence bone, including hormones, chemokines and cytokines (Johnson et al., 2022; Gonzalez-Reimers et al., 2014; Maurel et al., 2012; Mercer et al., 2015), understanding the precise mechanisms will require additional research.

In summary, our findings demonstrate that lifestyle factors may influence fracture healing and graft incorporation by altering the osteoinductive capacity of bone matrix. Specifically, our results suggest that (1) a history of heavy alcohol consumption by a donor may impair osteoinduction in allografts and (2) this negative outcome may be worsened by alcohol intake during graft incorporation and bone healing in the recipient. Mechanistically, our results suggest that decreased IGF-1 levels in bone matrix contribute to the reduction of osteoinduction by DBM harvested from alcohol consumers. Additionally, intermittent PTH, a bone anabolic agent, has the potential to increase osteoinduction in

DBM harvested from both alcohol-naïve and alcohol-consuming donors.

CRediT authorship contribution statement

Russell T. Turner: Conceptualization, Funding acquisition, Project administration, Writing – original draft, Writing – review & editing. **Amida F. Kuah:** Writing – review & editing. **Cynthia H. Trevisiol:** Investigation, Writing – review & editing. **Kathy S. Howe:** Investigation, Writing – review & editing. **Adam J. Branscum:** Formal analysis, Funding acquisition, Writing – review & editing. **Urszula T. Iwaniec:** Conceptualization, Funding acquisition, Investigation, Visualization, Writing – original draft, Writing – review & editing.

Funding

This work was supported the by NIAAA (R01 AA026289 and R01 AA011140) and DOD (PR043181) as well as the National Institute of Food and Agriculture - Agricultural Experimental Station Multi-state (W5002) and Oregon Agricultural Experiment Station (OR00735).

Declaration of competing interest

The authors have nothing to declare.

Data availability

Data will be made available on request.

References

Albrektsson, T., Johansson, C., 2001. Osteoinduction, osteoconduction and osseointegration. Eur. Spine J. 10 (Suppl. 2), S96–101.
Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate - a practical and powerful approach to multiple testing. J. R. Stat. Soc. Ser. B Stat. Methodol. 57, 289–300.
Berg, K.M., Kunins, H.V., Jackson, J.L., Nahvi, S., Chaudhry, A., Harris JR., K.A., Malik, R., Arnsten, J.H., 2008. Association between alcohol consumption and both osteoporotic fracture and bone density. Am. J. Med. 121, 406–418.
Bolander, M.E., 1992. Regulation of fracture repair by growth factors. Proc. Soc. Exp. Biol. Med. 200, 165–170.
Bouillon, R., 1991. Growth hormone and bone. Horm. Res. 36 (Suppl. 1), 49–55.
Campenfeldt, P., Al-Ani, A., Hedstrom, M., Ekstrom, W., 2018. Low BMD and high alcohol consumption predict a major re-operation in patients younger than 70 years of age with a displaced femoral neck fracture-A two -year follow up study in 120 patients. Injury 49, 2042–2046.
Carrascosa, A., Audi, L., 1993. Human studies on the biological actions of IGF-1. Evidence suggesting that human fetal and postnatal epiphyseal cartilage is a target tissue for IGF-1 action. J. Pediatr. Endocrinol. 6, 257–261.
Cherpitel, C.J., 2013. Focus on: the burden of alcohol use–trauma and emergency outcomes. Alcohol Res. 35, 150–154.
Cornell, C.N., 2004. Osteobiologics. Bull. Hosp. Jt Dis. 62, 13–17.
Daponte, V., Henke, K., Drissi, H., 2024. Current perspectives on the multiple roles of osteoclasts: mechanisms of osteoclast-osteoblast communication and potential clinical implications. Elife 13.
De La Monte, S.M., Tong, M., Cohen, A.C., Sheedy, D., Harper, C., Wands, J.R., 2008. Insulin and insulin-like growth factor resistance in alcoholic neurodegeneration. Alcohol. Clin. Exp. Res. 32, 1630–1644.
Ekegren, C.L., Edwards, E.R., De Steiger, R., Gabbe, B.J., 2018. Incidence, Costs and Predictors of Non-Union, Delayed Union and Mal-Union Following Long Bone Fracture. Int. J. Environ. Res. Public Health 15.
Ellegaard, M., Jorgensen, N.R., Schwarz, P., 2010. Parathyroid hormone and bone healing. Calcif. Tissue Int. 87, 1–13.
Flierl, M.A., Smith, W.R., Mauffrey, C., Irgit, K., Williams, A.E., Ross, E., Peacher, G., Hak, D.J., Stahel, P.F., 2013. Outcomes and complication rates of different bone grafting modalities in long bone fracture nonunions: a retrospective cohort study in 182 patients. J. Orthop. Surg. Res. 8, 33.
Gonzalez-Reimers, E., Santolaria-Fernandez, F., Martin-Gonzalez, M.C., Fernandez-Rodriguez, C.M., Quintero-Platt, G., 2014. Alcoholism: a systemic proinflammatory condition. World J. Gastroenterol. 20, 14660–14671.
Hauschka, P.V., Chen, T.L., Mavrakos, A.E., 1988. Polypeptide growth factors in bone matrix. CIBA Found. Symp. 136, 207–225.
Howe, K.S., Iwaniec, U.T., Turner, R.T., 2011. The effects of low dose parathyroid hormone on lumbar vertebrae in a rat model for chronic alcohol abuse. Osteoporos. Int. 22, 1175–1181.
Ilias, I., Paparrigopoulos, T., Tzavellas, E., Karaiskos, D., Kontoleon, P., Liappas, I., 2011. IGF-I and IGFBP-3 before and after inpatient alcohol detoxification in alcohol-dependent subjects. Med. Sci. Monit. 17, CR547–51.
Iwaniec, U.T., Trevisiol, C.H., Maddalozzo, G.F., Rosen, C.J., Turner, R.T., 2008. Effects of low-dose parathyroid hormone on bone mass, turnover, and ectopic osteoinduction in a rat model for chronic alcohol abuse. Bone 42, 695–701.
Johansson, T., 2016. PTH 1-34 (teriparatide) may not improve healing in proximal humerus fractures. A randomized, controlled study of 40 patients. Acta Orthop. 87, 79–82.
Johnson, J.T., Hussain, M.A., Cherian, K.E., Kapoor, N., Paul, T.V., 2022. Chronic alcohol consumption and its impact on bone and metabolic health - A narrative review. Indian J. Endocrinol. Metab. 26, 206–212.
Komatsu, D.E., Brune, K.A., Liu, H., Schmidt, A.L., Han, B., Zeng, Q.Q., Yang, X., Nunes, J.S., Lu, Y., Geiser, A.G., Ma, Y.L., Wolos, J.A., Westmore, M.S., Sato, M., 2009. Longitudinal in vivo analysis of the region-specific efficacy of parathyroid hormone in a rat cortical defect model. Endocrinology 150, 1570–1579.
Locatelli, V., Bianchi, V.E., 2014. Effect of GH/IGF-1 on bone metabolism and Osteoporsosis. Int. J. Endocrinol. 2014, 235060.
Maddalozzo, G.F., Turner, R.T., Edwards, C.H., Howe, K.S., Widrick, J.J., Rosen, C.J., Iwaniec, U.T., 2009. Alcohol alters whole body composition, inhibits bone formation, and increases bone marrow adiposity in rats. Osteoporos. Int. 20, 1529–1538.
Maurel, D.B., Boisseau, N., Benhamou, C.L., Jaffre, C., 2012. Alcohol and bone: review of dose effects and mechanisms. Osteoporos. Int. 23, 1–16.
Mercer, K.E., Hennings, L., Ronis, M.J., 2015. Alcohol consumption, Wnt/beta-catenin signaling, and hepatocarcinogenesis. Adv. Exp. Med. Biol. 815, 185–195.
Nyquist, F., Berglund, M., Nilsson, B.E., Obrant, K.J., 1997. Nature and healing of tibial shaft fractures in alcohol abusers. Alcohol Alcohol. 32, 91–95.
Orbeanu, V., Haragus, H., Crisan, D., Cirstoiu, C., Ristic, B., Jamieson, V., 2022. Novel parathyroid hormone-based bone graft, KUR-113, in treatment of acute open Tibial shaft fracture: A Phase-2 randomized controlled trial. J. Bone Joint Surg. Am. 104, 441–450.
Pandini, F.E., Kubo, F.M.M., Plepis, A.M.G., Martins, V., Da CUnha, M.R., Silva, V.R., Hirota, V.B., Lopes, E., Menezes, M.A., Pelegrine, A.A., Andrade, T.N., Iatecola, A., Britto, B.D.C., Fernandes, V.A.R., Gameiro, L.F.O., Correia, R.R., Teixeira, M.L., Duarte Junior, G., Reis, C.H.B., Pereira, E., Buchaim, D.V., Pomini, K.T., Teixeira, D. B., Buchaim, R.L., Lourenco, E.A., 2022. In Vivo Study of Nasal Bone Reconstruction with Collagen, Elastin and Chitosan Membranes in Abstainer and Alcoholic Rats. Polymers (Basel) 14.
Peichl, P., Holzer, L.A., Maier, R., Holzer, G., 2011. Parathyroid hormone 1-84 accelerates fracture-healing in pubic bones of elderly osteoporotic women. J. Bone Joint Surg. Am. 93, 1583–1587.
Riuttanen, A., Jantti, S.J., Mattila, V.M., 2020. Alcohol use in severely injured trauma patients. Sci. Rep. 10, 17891.
Roper, P.M., Abbasnia, P., Vuchkovska, A., Natoli, R.M., Callaci, J.J., 2016. Alcohol-related deficient fracture healing is associated with activation of FoxO transcription factors in mice. J. Orthop. Res. 34, 2106–2115.
Santori, C., Ceccanti, M., Diacinti, D., Attilia, M.L., Toppo, L., D'erasmo, E., Romagnoli, E., Mascia, M.L., Cipriani, C., Prastaro, A., Carnevale, V., Minisola, S., 2008. Skeletal turnover, bone mineral density, and fractures in male chronic abusers of alcohol. J. Endocrinol. Investig. 31, 321–326.
Sattgast, L.H., Branscum, A.J., Newman, N., Gonzales, S.W., Benton, M.L., Baker, E.J., Grant, K.A., Turner, R.T., Iwaniec, U.T., 2022. Ethanol alters the relationship between IGF-1 and bone turnover in male macaques. J. Endocrinol. 255, 131–141.
Schmidt, I.U., Dobnig, H., Turner, R.T., 1995. Intermittent parathyroid hormone treatment increases osteoblast number, steady state messenger ribonucleic acid levels for osteocalcin, and bone formation in tibial metaphysis of hypophysectomized female rats. Endocrinology 136, 5127–5134.
Sibonga, J.D., Iwaniec, U.T., Shogren, K.L., Rosen, C.J., Turner, R.T., 2007. Effects of parathyroid hormone (1-34) on tibia in an adult rat model for chronic alcohol abuse. Bone 40, 1013–1020.
Sohn, H.S., Oh, J.K., 2019. Review of bone graft and bone substitutes with an emphasis on fracture surgeries. Biomater. Res. 23, 9.
Stavrou, P.Z., Ciriello, V., Theocharakis, S., Gudipati, S., Tosounidis, T.H., Kanakaris, N. K., Giannoudis, P.V., 2016. Prevalence and risk factors for re-interventions following reamed intramedullary tibia nailing. Injury 47 (Suppl. 7), S49–S52.
Trevisiol, C.H., Turner, R.T., Pfaff, J.E., Hunter, J.C., Menagh, P.J., Hardin, K., Ho, E., Iwaniec, U.T., 2007. Impaired osteoinduction in a rat model for chronic alcohol abuse. Bone 41, 175–180.
Turner, R.T., Wronski, T.J., Zhang, M., Kidder, L.S., Bloomfield, S.A., SIBONGA, J. D., 1998. Effects of ethanol on gene expression in rat bone: transient dose-dependent changes in mRNA levels for matrix proteins, skeletal growth factors, and cytokines are followed by reductions in bone formation. Alcohol. Clin. Exp. Res. 22, 1591–1599.
Turner, R.T., Kidder, L.S., Kennedy, A., Evans, G.L., Sibonga, J.D., 2001. Moderate alcohol consumption suppresses bone turnover in adult female rats. J. Bone Miner. Res. 16, 589–594.
Turner, R.T., Rosen, C.J., Iwaniec, U.T., 2010. Effects of alcohol on skeletal response to growth hormone in hypophysectomized rats. Bone 46, 806–812.
Turner, R.T., Doran, E., Iwaniec, U.T., Yunfeng, L., 2012. Detrimental effects of alcohol on bone growth. In: Osteogenesis. IntechOpen, Rijeka.
Urist, M.R., Strates, B.S., 1970. Bone formation in implants of partially and wholly demineralized bone matrix. Including observations on acetone-fixed intra and extracellular proteins. Clin. Orthop. Relat. Res. 71, 271–278.
VAndersteenhoven, J.J., Delustro, F.A., Bell, N.H., Turner, R.T., 1988. Osteoinduction by implants of demineralized allogeneic bone matrix is diminished in vitamin D-deficient rats. Calcif. Tissue Int. 42, 39–45.
Volpin, G9., Shtarker, H., 2014. Management of Delayed Union, Non-Union and Mal-Union of Long Bone Fractures. In: Bentley, G. (Ed.), European Surgical Orthopaedics

and Traumatology: The EFORT Textbook. Springer Berlin Heidelberg, Berlin, Heidelberg.
Wagner, F., Vach, W., Augat, P., Varady, P.A., Panzer, S., Keiser, S., Eckardt, H., 2019. Daily subcutaneous Teriparatide injection increased bone mineral density of newly formed bone after tibia distraction osteogenesis, a randomized study. Injury 50, 1478–1482.
Wu, A.-M., Bisignano, C., James, S.L., Abady, G.G., Abedi, A., Abu-Gharbieh, E., Alhassan, R.K., Alipour, V., Arabloo, J., Asaad, M., Asmare, W.N., Awedew, A.F., Banach, M., Banerjee, S.K., Bijani, A., Birhanu, T.T.M., Bolla, S.R., Cámera, L.A., Chang, J.-C., Cho, D.Y., Chung, M.T., Couto, R.A.S., Dai, X., Dandona, L., Dandona, R., Farzadfar, F., Filip, I., Fischer, F., Fomenkov, A.A., Gill, T.K., Gupta, B., Haagsma, J.A., Haj-Mirzaian, A., Hamidi, S., Hay, S.I., Ilic, I.M., Ilic, M.D., Ivers, R. Q., Jürisson, M., Kalhor, R., Kanchan, T., Kavetskyy, T., Khalilov, R., Khan, E.A., Khan, M., Kneib, C.J., Krishnamoorthy, V., Kumar, G.A., Kumar, N., Lalloo, R., Lasrado, S., Lim, S.S., Liu, Z., Manafi, A., Manafi, N., Menezes, R.G., Meretoja, T.J., Miazgowski, B., Miller, T.R., Mohammad, Y., Mohammadian-Hafshejani, A., Mokdad, A.H., Murray, C.J.L., Naderi, M., Naimzada, M.D., Nayak, V.C., Nguyen, C. T., Nikbakhsh, R., Olagunju, A.T., Otstavnov, N., Otstavnov, S.S., Padubidri, J.R., Pereira, J., Pham, H.Q., Pinheiro, M., Polinder, S., Pourchamani, H., Rabiee, N., Radfar, A., Rahman, M.H.U., Rawaf, D.L., Rawaf, S., Saeb, M.R., Samy, A.M., Sanchez Riera, L., Schwebel, D.C., Shahabi, S., Shaikh, M.A., Soheili, A., Tabarés-Seisdedos, R., Tovani-Palone, M.R., Tran, B.X., Travillian, R.S., Valdez, P.R., Vasankari, T.J., Velazquez, D.Z., Venketasubramanian, N., Vu, G.T., Zhang, Z.-J., Vos, T., 2021. Global, regional, and national burden of bone fractures in 204 countries and territories, 1990–2019: a systematic analysis from the global burden of disease study 2019. Lancet Healthy Longev. 2, e580–e592.
Yuan, K., Haddad, Y., Law, R., Shakya, I., Haileyesus, T., Navon, L., Zhang, L., Liu, Y., Bergen, G., 2023. Emergency department visits for alcohol-associated falls among older adults in the United States, 2011 to 2020. Ann. Emerg. Med. 82, 666–677.
Zhao, R., Yang, R., Cooper, P.R., Khurshid, Z., Shavandi, A., Ratnayake, J., 2021. Bone grafts and substitutes in dentistry: A review of current trends and developments. Molecules 26.
Zura, R., Braid-Forbes, M.J., Jeray, K., Mehta, S., Einhorn, T.A., Watson, J.T., Della Rocca, G.J., Forbes, K., Steen, R.G., 2017. Bone fracture nonunion rate decreases with increasing age: A prospective inception cohort study. Bone 95, 26–32.