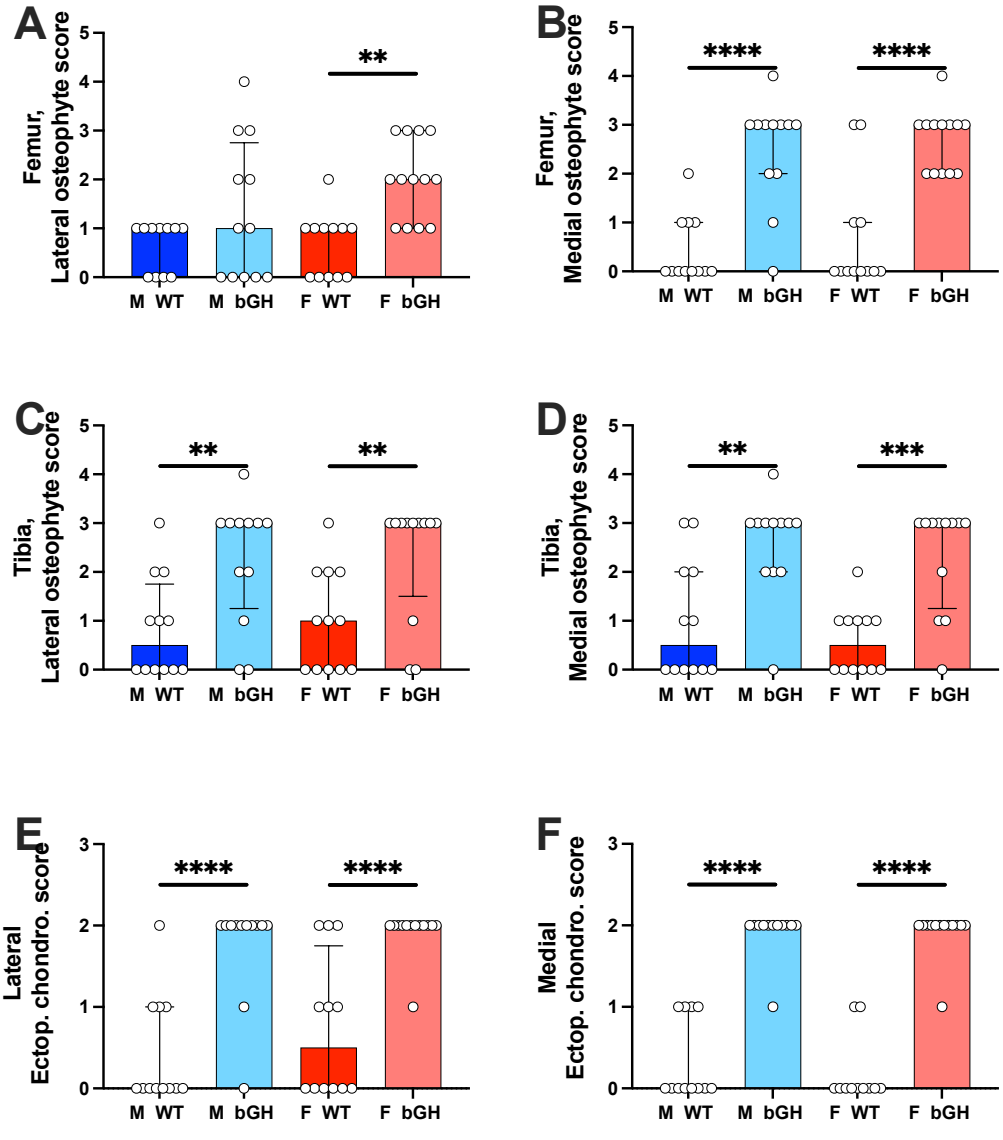Supplement figure 4