How Does Long-Term Obesity Affect the Immune System and Bone?
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Introduction:
Obesity, a serious condition leading to diseases such as Type II diabetes (T2D), is known to impair immune response, yet their impacts on the bone marrow niche and bone quality are still unclear. In this study, a murine model of diet-induced obesity (DIO) was used to investigate the relationship between an increasing adipose burden on phenotypic and dysfunctional changes in bone marrow immune cells (B and T cells), bone quality and the overall health (e.g., glucose tolerance) of the animal. Additionally, DIO-related changes in circulating immune cells and soluble factors such as tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and macrophage inflammatory protein 1-beta (MIP-1β) were evaluated.

Method:
To investigate the effects of DIO on bone quality, twenty 7w male C57BL/6J mice were randomly assigned to either a high fat (HF) diet (45% kcal) or a regular chow diet group (RD) (n=10) for ~6 months. The trabecular bone in the proximal metaphyseal compartment of tibia was evaluated at 12µm isotropic resolution using micro-computed tomography (µCT). Furthermore, to assess characteristics of T2D and any downstream effects resulting from obesity, 1) abdominal adipose tissue volume (lumbar region L1 to L5) was evaluated at 76µm isotropic resolution with µCT, 2) glucose tolerance test (GTT) was performed following overnight fasting (~16 hours) and intraperitoneal glucose injection (1g/kg), blood glucose levels were monitored for 2 hours (at 15, 30, 45, 60, 90 and 120 minutes post-injection) and glucose tolerance was established by comparing area under curves (GTT-AUC) showing the change of blood glucose over time post-injection, 3) levels of fasting insulin, TNFα, IFNγ and MIP-1β in blood were measured and 4) changes in the cell populations from myeloid and lymphoid lineages within the bone marrow extracted from tibia and femur, and the blood (subgroup, n=4) were evaluated using flow cytometry and fluorescent dye conjugated antibodies (B cells: B220, T cells: CD4 and CD8, and myeloid cells: GR1 and MAC1).

Result:
The long term HF diet treatment leads to significant increases in body mass (42%, p≤.001), adipose tissue volume (56%, p≤.001) and fasting insulin (354%, p=.03). Accompanying the increasing adipose burden and insulin resistance is the significant changes in the trabecular bone compartment in the HF group: As compared to the RD group, the HF group has 11% higher trabecular thickness Tb.Th (p=.026), but 24% lower trabecular number Tb.N (p=.023) and 39% larger trabecular separation Tb.Sp (p=.05). While body mass is positively correlated to the Tb.Th (r=.63, p=.009) and negatively correlated to the Tb.N (r=-.54, p=.032), glucose intolerance as shown by GTT-AUC is also negatively correlated to Tb.N (r=-.61, p=.012) and positively correlated to Tb.Sp (r=.60, p=.014). Interestingly, amongst cells from myeloid and lymphoid lineages, the HF group shows a significant reduction in the B cell proportion both in bone marrow (66.9%, p≤.011) and blood (36.5%, p=.045). While the level of circulating TNFα is not significantly different between the two diet groups, levels of circulating IFNγ and MIP-1β are significantly lower (p≤.01) in the HF group compared to the RD group.

Discussion:
Not only does the long-term high fat diet treatment induce significantly increases in adipose burden and T2D symptom, but it also impacts the immune system and bone. The DIO-related glucose intolerance could contribute to the changes in immune cells both in blood and in bone marrow, and compromise the immune system as well as the ability of the bone to adapt to the increased load bearing challenges. The significant reduction of the B cell proportion both in bone marrow and blood due to DIO indicates an impairment of hematopoiesis in the bone marrow. Given that bone marrow space is a loosely compartmentalized, it will be interesting to further explore whether immune cells and bone cells interact differently within the increased bone marrow spacing in the DIO subjects. Besides, the significant reduction of circulating levels of IFNγ and MIP-1β leads us to wonder about the effects of various immunoregulatory cytokines on the bone remodeling process. The understanding of the interplay between the immune system and bone remodeling could potentially leads to better treatment of bone diseases.