The impact of obesity-induced inflammation on clonal hematopoiesis

Santhosh Kumar Pasupuleti[a] *and Reuben Kapur*[a,b]

Purpose of review
This review meticulously delves into existing literature and recent findings to elucidate the intricate link between obesity and clonal hematopoiesis of indeterminate potential (CHIP) associated clonal hematopoiesis. It aims to enhance our comprehension of this multifaceted association, offering insights into potential avenues for future research and therapeutic interventions.

Recent findings
Recent insights reveal that mutations in CHIP-associated genes are not limited to symptomatic patients but are also present in asymptomatic individuals. This section focuses on the impact of obesity-induced inflammation and fatty bone marrow (FBM) on the development of CHIP-associated diseases. Common comorbidities such as obesity, diabetes, and infection, fostering pro-inflammatory environments, play a pivotal role in the acceleration of these pathologies. Our research underscores a notable association between CHIP and an increased waist-to-hip ratio (WHR), emphasizing the link between obesity and myeloid leukemia. Recent studies highlight a strong correlation between obesity and myeloid leukemias in both children and adults, with increased risks and poorer survival outcomes in overweight individuals.

Summary
We discuss recent insights into how CHIP-associated pathologies respond to obesity-induced inflammation, offering implications for future studies in the intricate field of clonal hematopoiesis.

Keywords
clonal hematopoiesis, clonal hematopoiesis of indeterminate potential, inflammation, obesity

INTRODUCTION

Clonal hematopoiesis of indeterminate potential (CHIP) is linked to increased mortality risk and the development of hematologic malignancies [1,2]. CHIP affects 10–20% of adults over 70 years of age and is due to acquisition of somatic mutations accumulating in hematopoietic stem (HSCs) and progenitor cells (HSC/Ps) [3]. Commonly mutated genes in CHIP include *TET2*, *DNMT3A*, *ASXL1*, and *JAK2*. These mutations provide a competitive advantage to mutant HSCs and HSC/Ps in a process known as clonal hematopoiesis [2,4]. Unlike normal HSCs, CHIP-associated mutations in HSCs lead to skewed differentiation towards myeloid lineage [5]. While mutations in CHIP-associated genes are commonly found in patients with myeloproliferative neoplasms (MPNs) and acute myeloid leukemia (AML), these mutations can also be detected in individuals without any symptoms [6]. It is noteworthy that not all individuals with CHIP-associated mutations develop hematologic malignancies, indicating the presence of predisposing factors that might promote clonal expansion and disease development. To this end, inflammatory conditions, such as obesity, diabetes, infection, smoking, and pulmonary inflammation, may contribute to CHIP-associated diseases [7–12], suggesting that environmental and additional cell nonautonomous factors likely contribute to clonal hematopoiesis. The exact mechanism(s) are however not yet fully understood. Gaining a better understanding of these mechanism(s) will be crucial in identifying individuals at risk for developing CHIP-associated diseases and stratifying patients for appropriate treatment. Obesity and overweight

[a]Herman B Wells Center for Pediatric Research, Department of Pediatrics and [b]Department of Microbiology & Immunology, Indiana University School of Medicine, Indianapolis, Indiana, USA

Correspondence to Santhosh Kumar Pasupuleti, PhD, Assistant Research Professor of Pediatrics, Herman B Wells Center for Pediatric Research, Indiana University School of Medicine, 1044 W. Walnut Street, R4-169, Indianapolis, IN 46202, USA. Tel: +1 317 274 0303; e-mail: skpasupu@iu.edu

Curr Opin Hematol 2024, 31:193–198
DOI:10.1097/MOH.0000000000000819

KEY POINTS

- Obesity is associated with preleukemic CHIP mutations and exacerbates clonal hematopoiesis and risk factor for leukemia development.
- Obesity increases accumulation of bone marrow adipocytes, forming FBM. FBM negatively impacts bone mass by impeding osteoblast differentiation, thereby altering hematopoiesis.
- Accumulation of bone marrow adipocytes secrete abnormal amount of pro-inflammatory cytokines such as *IL-6*, *IL-1β*, and *TNF-α*, contributing to leukemia development.
- CHIP-associated mutations in obese individuals may reprogram adipocytes into cancer associated adipocytes, which subsequently secrete growth, inflammatory, fibrotic and angiogenic factors and lymphokines, contributing to leukemia development.

have been suggested as a risk factor for cancer development [13,14]. However, it is unclear if obesity is also a risk factor for clonal hematopoiesis and for transforming preleukemic stem cells (pre-LSCs) into full-blown leukemia such as AML or severe form of MPN. To this end, we analyzed exome sequencing and clinical data from 47 466 individuals with validated CHIP showed that CHIP is present in number of the study population and is associated with a significant increase in WHR. Importantly, we observed that obesity is associated with myeloid leukemia [15▪▪]. Furthermore, recent studies, alongside our own findings, reveal a strong association between obesity and myeloid leukemias in both children and adults with increased risk and worse survival outcomes in obese and/or overweight individuals [16–20]. Furthermore, our studies in mice have been confirmed in patients, demonstrating that obesity-induced changes can promote the expansion of preleukemic CHIP and lead to a severe MPN-like phenotype [15▪▪]. Given the shared pathogenetic mechanisms between obesity and CHIP, this review endeavors to investigate both preclinical and clinical evidence. Our focus is directed towards unraveling the intricate association between CHIP and obesity. Additionally, we delve into the consequential implications of this interaction on the pathophysiology of leukemia development.

OBESITY

Obesity, a prevalent global health concern, is associated with various conditions such as type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension, insulin resistance, and cardiovascular diseases (CVDs) [21,22]. The primary contributor to T2DM is obesity-induced insulin resistance, compounded by insufficient insulin secretion from pancreatic β-cells [21,22]. While adipose tissue serves as a crucial energy reservoir, its excessive accumulation fosters obesity by creating a pro-inflammatory, hyperlipidemic, and insulin-resistant milieu which is characterized by several metabolic abnormalities, including impaired glucose uptake by cells, elevated blood sugar levels, dyslipidemia (abnormal levels of fats in the blood), and often leads to the development of T2DM, obesity, and other metabolic disorders. This condition can increase the risk of CVD [21,23]. The BMI is a commonly utilized metric to assess overall body fat, determined by dividing an individual's weight in kilograms (kg) by the square of their height in meters. Typically, the conventional BMI range spans from 18.5 to 24.9 kg/m^2. Those with a BMI of 25 kg/m^2 or higher are classified as overweight, while individuals with a BMI of 30 kg/m^2 or higher are categorized as obese [24]. Additionally, to assess obesity comprehensively, factors like body fat distribution are crucial, prompting the utilization of tools such as WHR and computed tomography (CT) scanning [23]. Leptin, a peptide hormone exclusively secreted by adipocytes, plays a pivotal role in regulating body weight. Lack of leptin (Lep) or its receptor (Lepr) in both mice and humans leads to obesity, hyperglycemia, and insulin resistance [25]. In individuals with obesity, as well as in *Ob/Ob* mice, there is an increased accumulation of marrow adipocytes, forming fatty bone marrow (FBM). FBM negatively impacts bone mass by impeding osteoblast differentiation, thereby altering hematopoiesis [26,27]. Furthermore, bone marrow adipocytes secrete pro-inflammatory cytokines such as *IL-6*, *IL-1β*, and *TNF-α*, contributing to the complex interplay between obesity and its associated health complications [28,29].

OBESITY, CHIP, AND LEUKEMIA-CURRENT EVIDENCE

CHIP emerges as a noteworthy risk factor for hematologic malignancies, yet the factors influencing clonal expansion and disease progression remain elusive [1,2]. Exploring the association between obesity and CHIP-associated diseases, in our recent study, we investigated individuals with CHIP-associated mutations. Analyzing a cohort of 47 466 participants from the UK Biobank, we found a correlation between CHIP mutations and a higher WHR, along with an elevated prevalence of coronary artery disease (CAD), hypertension, and hypercholesterolemia compared to those with lower WHR [15▪▪]. Notably, our research revealed a significant association between obesity, measured by both BMI

($n = 46\,460$) and WHR ($n = 47\,405$), and myeloid leukemia [15▪▪]. This observation aligns with recent studies demonstrating a compelling link between obesity and various types of leukemia, encompassing myeloid and lymphoid subtypes [13,14,16,30–35]. Numerous publications, including works by Larsson and Wolk [14], Kasim [35], and Castillo *et al.* [30], have consistently shown an elevated risk and incidence of AML and chronic myeloid leukemia (CML) in individuals classified as obese or overweight. Furthermore, MacInnis *et al.* [36] established an association between increased BMI and myeloid leukemia risk, emphasizing the multifaceted impact of adiposity.

A distinct subset of AML, acute promyelocytic leukemia (APL), also demonstrates a correlation with higher BMIs, leading to complications such as thrombohemorrhagic early death and increased treatment-related mortality. Importantly, pediatric AML patients with obesity exhibit inferior survival rates, as revealed in the CCG-2961 clinical trial. The intricate relationship extends beyond clinical outcomes, as individuals with de novo APL showcase elevated median BMIs and a higher incidence of obesity, reinforcing the potential link between obesity and myeloid leukemias [34,37–39]. In a recent investigation involving adolescents and young adults (AYAs) receiving treatment with Dana-Farber Cancer Institute (DFCI) consortium protocols for acute lymphocytic leukemia (ALL), heigh BMI was identified as being associated with increased toxicity, elevated nonrelapse mortality (NRM), and compromised overall survival [40▪]. Moreover, a separate study emphasized the pivotal role of inflammatory signals from FBM in promoting *DNMT3A*-driven clonal hematopoiesis, with the inhibition of this process achievable through the disruption of the IL-6 pathway [41▪▪]. Notably, obesity and an elevated BMI are recognized as risk factors for the development of multiple myeloma [42,43▪▪]. For instance, individuals with obesity face a 20% higher risk of multiple myeloma compared to their lean counterparts [44]. Collectively, these studies strongly indicate a potential correlation between obesity and the occurrence and fatality rates of various forms of leukemia. Notably, evidence points towards associations with AML, CML, chronic lymphocytic leukemia (CLL), ALL, multiple myeloma, and preleukemic conditions like myelodysplastic syndromes (MDS) [13,14,30, 45,46].

In light of the co-occurrence of CHIP-associated mutations in both myeloid and lymphoid malignancies, our findings align with existing literature showcasing a correlation between obesity and leukemia. These collective insights emphasize the clinical significance of obesity in leukemia patient populations and underscore the need for further research to unravel the intricate mechanisms linking adiposity, clonal hematopoiesis, and hematologic malignancies.

Our experimental investigations in murine models validate the clinical observations within the patient cohort, establishing a proof of concept that alterations induced by obesity can instigate the expansion of preleukemic CHIP into a pronounced MPN-like phenotype. Utilizing several CHIP-associated genes, including *Tet2*, *Dnmt3a*, *Asxl1*, and *Jak2*, our studies consistently demonstrated heightened clonal expansion and the manifestation of an MPN-like phenotype [15▪▪]. This universal effect across various mutation types suggests that obesity might universally catalyze or exacerbate CHIP-associated diseases (Fig. 1) [15▪▪]. Similarly, recent studies revealed that obesity induced by a high-fat diet (HFD) and the transplantation of bone marrow cells from mice lacking one copy of *Dnmt3a* (referred to as HET, for $Dnmt3a^{+/-}$, heterozygous) resulted in increased spleen size, leukemia development, and reduced lifespan in HET recipients on HFD compared to control groups [47▪▪]. Moreover, HET recipients on a HFD exhibit elevates levels of pro-inflammatory cytokines, including IL-6, both in plasma and within immune cells [47▪▪]. Concurrently, an elevation in pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, along with increased intracellular Ca^{2+} levels, was observed [15▪▪].

The intricate link between intracellular Ca^{2+} levels and adipocyte lipid metabolism are noteworthy. The regulation of lipid metabolism and triglyceride storage in adipocytes heavily relies on intracellular Ca^{2+} levels [48]. Elevated intracellular Ca^{2+} stimulates the expression of lipogenic genes while concurrently suppressing lipolysis, ultimately leading to increased adiposity [48]. We hypothesized that elevated intracellular Ca^{2+} levels might instigate aberrant signaling, potentially accelerating the onset of severe MPN. To explore therapeutic avenues, we treated *Ob/Ob* mice harboring $Tet2^{-/-}$ preleukemic HSC/Ps with various agents, including metformin, pioglitazone, nifedipine, SKF-96365, MCC950, and anakinra, either individually or in combination [15▪▪]. Notably, the combination therapy outperformed individual treatments, indicating that a multipronged approach targeting multiple signaling pathways or environmental stimuli may be crucial for suppressing clonal hematopoiesis, particularly in the context of obesity. This combination therapy not only reduced the frequency of leukemic blasts, undifferentiated stem cells, HSCs, and granulocyte-macrophage progenitors but also mitigated arterial fatty deposits in *Ob/Ob* recipients

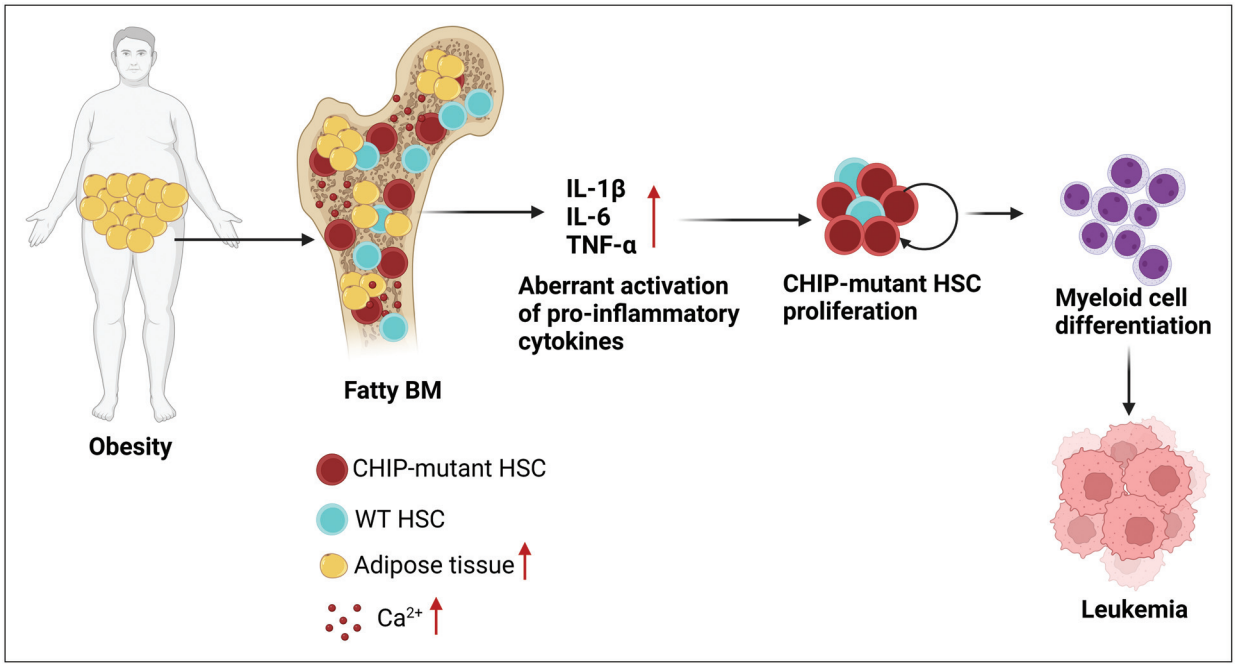

FIGURE 1. Illustration of the influence of obesity-induced inflammation on clonal hematopoiesis and leukemia development. In the obese bone marrow, inflammatory cytokines (IL-1β, IL-6, and TNF-α) and heightened Ca^{2+} levels activate CHIP-mutant (HSCs). This activation leads to the proliferation of CHIP-mutant HSCs and their subsequent differentiation into myeloid cells, ultimately contributing to the development of leukemia. CHIP, clonal hematopoiesis of indeterminate potential; HSC, hematopoietic stem cells.

with CHIP, demonstrating the potential of inhibiting Ca^{2+} signaling in ameliorating CHIP-associated diseases [15▪▪]. Conducting follow-up studies involving the transplantation of specific myeloid populations in HFD-induced obese models [47▪▪], similar to our previous investigations utilizing *Tet2* cells on *Ob/Ob* mice [15▪▪], promises to be an intriguing avenue for further research.

Supported by clinical evidence, CHIP emerges as a high-risk factor for the development of hematologic malignancies, and its association with poorer prognosis extends even to individuals with solid tumors [23–29]. Our analysis of cancer genome atlas (TCGA) data further underscores the intricate connection between CHIP and obesity. Specifically, the mutation rate of CHIP-associated genes was markedly higher in patients with a BMI exceeding 30 kg/m^2 compared to those with a BMI of 25 kg/m^2 or lower across seven distinct cancer types, including breast (BRCA), lung (LUAD), ovarian, stomach (STAD), colon (COAD), low-grade glioma (LGG), and liver (LIHC) cancer. Concomitantly, obesity itself is implicated in an escalated risk across various tumor types. A large cohort of study reported that a substantial proportion (40%) of cancer diagnoses in the United States, were attributed to being overweight or obese [49]. Cancer stem cells in obese individuals may reprogram adipocytes (highly accumulated in obese individuals BM) into cancer associated adipocytes, which subsequently secrete growth, inflammatory, fibrotic and angiogenic factors, and lymphokines [such as tumor necrosis factor (TNF-α), adiponectin, interleukin-6 (IL-6), IL-1β, and vascular endothelial growth factor (VEGF)] that may promote tumor growth [50] or alter anticancer effects of chemotherapy [51]. IL-6, for instance, plays a role in sustaining proliferative signaling, mutation, tumor-promoting inflammation, invasion, metastasis, genome instability, and resistance to cell death [52▪,53]. Similarly, IL-1β is associated with invasion activation, metastasis, genome instability, mutation, tumor-promoting inflammation, and immune evasion [52▪,54]. TNF-α is linked to proliferative signaling sustenance, evasion of growth suppressors, induction of angiogenesis, activation of invasion and metastasis, tumor-promoting inflammation, and immune evasion [52▪,55]. VEGF stands out as the paramount regulator in vascular system development, and obesity significantly accelerates tumor growth through mechanisms entailing the heightened activation of VEGF pathways [56].

Crucially, these proinflammatory cytokines, which are elevated in both obese individuals and those with CHIP, suggest a potential synergistic effect between these conditions in promoting cancer

development [52▪,57–59]. The intersection of obesity and CHIP unveils a complex interplay that may significantly contribute to the pathophysiology of cancer, shedding light on the need for comprehensive investigations into these multifaceted relationships.

In summary, while emerging research has initiated the exploration of connections among obesity, CHIP, and the development of leukemia, the intricacies of the underlying pathophysiological mechanisms remain speculative and warrant further investigation. Insightful studies delving into inflammation within FBM have revealed intriguing overlaps in biomarker profiles with those observed in CHIP. These findings underscore the need for comprehensive investigations to unravel the intricate interplay between obesity, CHIP, and leukemia, aiming to elucidate the mechanistic links and potential therapeutic targets in this complex disease.

FUTURE PERSPECTIVES AND CONCLUSION

Obesity is associated with heightened risks of CVD, diabetes, insulin resistance, leukemia, and increased mortality compared to those with normal weight [1,2,21,22]. The connection between obesity and leukemia holds critical implications for prevention and treatment. Obesity emerges as a modifiable risk factor for leukemia, potentially offering a path for prevention. While current leukemia research often concentrates on expensive treatments, prioritizing prevention could prevent numerous cases. Robust studies are necessary to investigate whether obesity predisposes individuals to leukemia. Further research is essential to pinpoint the precise magnitude of the increased vulnerability to developing CVD, T2DM, leukemia, and ultimately, mortality in obese individuals with CHIP. This information is pivotal for deciding whether active CHIP screening is necessary in the obese population, considering the potential significant rise in risk. Adopting a healthier lifestyle, encompassing weight loss, balanced nutrition, and regular exercise, may diminish cancer risk. The exploration of pharmacological interventions, repurposing drugs, and contemplating bariatric surgery could provide valuable strategies for preventing leukemia and other obesity-related cancers.

In conclusion, epidemiological findings indicate an association between obesity and leukemia. Furthermore, individuals with leukemia who are obese tend to experience poorer outcomes and higher mortality rates. Conversely, the shared pro-inflammatory characteristics associated with both CHIP and obesity set off a chain of events, consequently heightening the risk of leukemia development (Fig. 1).

Acknowledgements

The authors thank our colleagues for technical support, critically reading our manuscript, and suggestions to improve the manuscript.

Financial support and sponsorship

This work was supported by NIH grants R01CA173852, R01CA134777, R01HL146137, and R01HL140961, and Riley Children's Foundation (to R.K.). Indiana University Melvin and Bren Simon Comprehensive Cancer Center (IUSCCC), Hematopoiesis and Hematologic malignancies (HHM) Program Basic Science Pilot grant EPAR4061 to (S.K.P and R.K).

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Jaiswal S, Fontanillas P, Flannick J, *et al.* Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med 2014; 371:2488–2498.
2. Jaiswal S, Natarajan P, Silver AJ, *et al.* Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. N Engl J Med 2017; 377:111–121.
3. Fuster JJ, Walsh K. Somatic mutations and clonal hematopoiesis: unexpected potential new drivers of age-related cardiovascular disease. Circ Res 2018; 122:523–532.
4. Köhnke T, Majeti R. Clonal hematopoiesis: from mechanisms to clinical intervention. Cancer Discov 2021; 11:2987–2997.
5. Beerman I, Bhattacharya D, Zandi S, *et al.* Functionally distinct hematopoietic stem cells modulate hematopoietic lineage potential during aging by a mechanism of clonal expansion. Proc Natl Acad Sci U S A 2010; 107: 5465–5470.
6. Coombs CC, Zehir A, Devlin SM, *et al.* Therapy-related clonal hematopoiesis in patients with nonhematologic cancers is common and associated with adverse clinical outcomes. Cell Stem Cell 2017; 21:374–382.
7. Genovese G, Kähler AK, Handsaker RE, *et al.* Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med 2014; 37:2477–2487.
8. Hormaechea-Agulla D, Matatall KA, Le DT, *et al.* Chronic infection drives Dnmt3a-loss-of-function clonal hematopoiesis via IFNγ signaling. Cell Stem Cell 2021; 28:1428–1442.
9. Wong TN, Miller CA, Jotte MRM, *et al.* Cellular stressors contribute to the expansion of hematopoietic clones of varying leukemic potential. Nat Commun 2018; 9:455.
10. Cai Z, Lu X, Zhang C, Nelanuthala S, *et al.* Hyperglycemia cooperates with Tet2 heterozygosity to induce leukemia driven by proinflammatory cytokine-induced lncRNA Morrbid. J Clin Invest 2021; 131:e140707.
11. Miller PG, Qiao D, Rojas-Quintero J, *et al.* Association of clonal hematopoiesis with chronic obstructive pulmonary disease. Blood 2022; 139:357–368.
12. Cai Z, Kotzin JJ, Ramdas B, *et al.* Inhibition of inflammatory signaling in Tet2 mutant preleukemic cells mitigates stress-induced abnormalities and clonal hematopoiesis. Cell Stem Cell 2018; 23:833–849.
13. Lichtman MA. Obesity and the risk for a hematological malignancy: leukemia, lymphoma, or myeloma. Oncologist 2010; 15:1083–1101.
14. Larsson SC, Wolk A. Overweight and obesity and incidence of leukemia: a meta-analysis of cohort studies. Int J Cancer 2008; 122:1418–1421.
15. Pasupuleti SK, Ramdas B, Burns SS, *et al.* Obesity-induced inflammation ▪▪ exacerbates clonal hematopoiesis. J Clin Invest 2023; 133:e163968.

This study extensively investigated the link between inflammation induced by obesity and clonal hematopoiesis. The findings indicate a strong association between obesity and CHIP. Moreover, the study suggests that a proinflammatory state has the potential to enhance the progression of CHIP towards more pronounced hematologic neoplasia.

16. Söderberg KC, Kaprio J, Verkasalo PK, *et al.* Overweight, obesity and risk of haematological malignancies: a cohort study of Swedish and Finnish twins. Eur J Cancer 2009; 45:1232–1238.

17. Dhakal P, Lyden E, Lee A, *et al.* Effects of obesity on overall survival of adults with acute myeloid leukemia. Clin Lymphoma Myeloma Leuk 2020; 20:e131–e136.
18. Crysandt M, Kramer M, Ehninger G, *et al.* A high BMI is a risk factor in younger patients with de novo acute myelogenous leukemia. Eur J Haematol 2016; 97:17–24.
19. Inaba H, Surprise HC, Pounds S, *et al.* Effect of body mass index on the outcome of children with acute myeloid leukemia. Cancer 2012; 118:5989–5996.
20. Lange BJ, Gerbing RB, Feusner J, *et al.* Mortality in overweight and underweight children with acute myeloid leukemia. JAMA 2005; 293:203–211.
21. Kusminski CM, Bickel PE, Scherer PE. Targeting adipose tissue in the treatment of obesity-associated diabetes. Nat Rev Drug Discov 2016; 15:639–660.
22. Nagareddy PR, Kraakman M, Masters SL, *et al.* Adipose tissue macrophages promote myelopoiesis and monocytosis in obesity. Cell Metab 2014; 19:821–835.
23. Chait A, den Hartigh LJ. Adipose tissue distribution, inflammation and its metabolic consequences, including diabetes and cardiovascular disease. Front Cardiovasc Med 2020; 7:22.
24. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004; 363:157–163.
25. Farooqi IS, O'Rahilly S. 20 years of leptin: human disorders of leptin action. J Endocrinol 2014; 223:T63–70.
26. Fazeli PK, Horowitz MC, MacDougald OA, *et al.* Marrow fat and bone-new perspectives. J Clin Endocrinol Metab 2013; 98:935–945.
27. Lindenmaier LB, Philbrick KA, Branscum AJ, *et al.* Hypothalamic leptin gene therapy reduces bone marrow adiposity in ob/ob mice fed regular and high-fat diets. Front Endocrinol (Lausanne) 2016; 7:110.
28. Zatterale F, Longo M, Naderi J, *et al.* Chronic adipose tissue inflammation linking obesity to insulin resistance and Type 2 diabetes. Front Physiol 2020; 10:1607.
29. Miggitsch C, Meryk A, Naismith E, *et al.* Human bone marrow adipocytes display distinct immune regulatory properties. EBioMedicine 2019; 46:387–398.
30. Castillo JJ, Reagan JL, Ingham RR, *et al.* Obesity but not overweight increases the incidence and mortality of leukemia in adults: a meta-analysis of prospective cohort studies. Leuk Res 2012; 36:868–875.
31. Mazzarella L, Botteri E, Matthews A, *et al.* Obesity is a risk factor for acute promyelocytic leukemia: evidence from population and cross-sectional studies and correlation with FLT3 mutations and polyunsaturated fatty acid metabolism. Haematologica 2020; 105:1559–1566.
32. Abar L, Sobiecki JG, Cariolou M, *et al.* Body size and obesity during adulthood, and risk of lympho-haematopoietic cancers: an update of the WCRF-AICR systematic review of published prospective studies. Ann Oncol 2019; 30:528–541.
33. Psaltopoulou T, Sergentanis TN, Ntanasis-Stathopoulos I, *et al.* Anthropometric characteristics, physical activity and risk of hematological malignancies: a systematic review and meta-analysis of cohort studies. Int J Cancer 2019; 145:347–359.
34. Orgel E, Genkinger JM, Aggarwal D, *et al.* Association of body mass index and survival in pediatric leukemia: a meta-analysis. Am J Clin Nutr 2016; 103:808–817.
35. Kasim K, Levallois P, Abdous B, *et al.* Lifestyle factors and the risk of adult leukemia in Canada. Cancer Causes Control 2005; 16:489–500.
36. MacInnis RJ, English DR, Hopper JL, Giles GG. Body size and composition and the risk of lymphohematopoietic malignancies. J Natl Cancer Inst 2005; 97:1154–1157.
37. Estey E, Thall P, Kantarjian H, *et al.* Association between increased body mass index and a diagnosis of acute promyelocytic leukemia in patients with acute myeloid leukemia. Leukemia 1997; 11:1661–1664.
38. Lange BJ, Smith FO, Feusner J, *et al.* Outcomes in CCG-2961, a Children's Oncology Group Phase 3 Trial for untreated pediatric acute myeloid leukemia: a report from the Children's Oncology Group. Blood 2008; 111:1044–1053.
39. Elliott MA, Letendre L, Tefferi A, *et al.* Therapy-related acute promyelocytic leukemia: observations relating to APL pathogenesis and therapy. Eur J Haematol 2012; 88:237–243.
40. ▪ Shimony S, Flamand Y, Valtis YK, *et al.* Effect of BMI on toxicities and survival among adolescents and young adults treated on DFCI Consortium ALL trials. Blood Adv 2023; 7:5234–5245.

This study showed that adolescents and young adults undergoing treatment for acute lymphoblastic leukemia with DFCI Consortium regimens, higher BMI was linked to elevated toxicity and poor overall survival.

41. ▪▪ Zioni N, Bercovich AA, Chapal-Ilani N, *et al.* Inflammatory signals from fatty bone marrow support DNMT3A driven clonal hematopoiesis. Nat Commun 2023; 14:2070.

This study revealed that inflammatory signals originating from fatty bone marrow contribute to *DNMT3A*-driven clonal hematopoiesis, and such a process can be effectively restrained by blocking the IL-6 pathway.

42. Marinac CR, Birmann BM, Lee IM, *et al.* Body mass index throughout adulthood, physical activity, and risk of multiple myeloma: a prospective analysis in three large cohorts. Br J Cancer 2018; 118:1013–1019.
43. ▪▪ Choa R, Panaroni C, Bhatia R, Raje N. It is worth the weight: obesity and the transition from monoclonal gammopathy of undetermined significance to multiple myeloma. Blood Adv 2023; 7:5510–5523.

This is an interesting review provides a comprehensive summary of the epidemiological evidence elucidating the role of obesity in multiple myeloma and monoclonal gammopathy of undetermined significance (MGUS).

44. Lauby-Secretan B, Scoccianti C, Loomis D, *et al.* Body fatness and cancer–viewpoint of the IARC Working Group. N Engl J Med 2016; 375:794–798.
45. Teras LR, Patel AV, Carter BD, *et al.* Anthropometric factors and risk of myeloid leukaemias and myelodysplastic syndromes: a prospective study and meta-analysis. Br J Haematol 2019; 186:243–254.
46. Poynter JN, Richardson M, Blair CK, *et al.* Obesity over the life course and risk of acute myeloid leukemia and myelodysplastic syndromes. Cancer Epidemiol 2016; 40:134–140.
47. ▪▪ Reyes JM, Tovy A, Zhang L, *et al.* Hematologic DNMT3A reduction and high-fat diet synergize to promote weight gain and tissue inflammation. iScience 2024; 27:109122.

This study thoroughly examined the connection between obesity induced by a HFD and clonal hematopoiesis. The results suggest a significant link between DNMT3A-mutations and clonal hematopoiesis in mice exposed to HFD. Additionally, HFD was found to increase the presence of DNMT3A-mutant macrophages in adipose and pancreas tissues.

48. Zemel MB. Regulation of adiposity and obesity risk by dietary calcium: mechanisms and implications. J Am Coll Nutr 2002; 21:146S–151S.
49. Steele CB, Thomas CC, Henley SJ, *et al.* Vital signs: trends in incidence of cancers associated with overweight and obesity - United States, 2005-2014. MMWR Morb Mortal Wkly Rep 2017; 66:1052–1058.
50. Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. Nat Rev Cancer 2011; 11:886–895.
51. Butturini AM, Dorey FJ, Lange BJ, *et al.* Obesity and outcome in pediatric acute lymphoblastic leukemia. J Clin Oncol 2007; 25:2063–2069.
52. ▪ Harris BHL, Macaulay VM, Harris DA, *et al.* Obesity: a perfect storm for carcinogenesis. Cancer Metastasis Rev 2022; 41:491–515.

This comprehensive review focus on how the hallmarks is affected by obesity may lead to novel prevention and treatment strategies for the increasingly obese population.

53. Vendrell J, Broch M, Vilarrasa N, *et al.* Resistin, adiponectin, ghrelin, leptin, and proinflammatory cytokines: relationships in obesity. Obes Res 2004; 12:962–971.
54. Moschen AR, Molnar C, Enrich B, *et al.* Adipose and liver expression of interleukin (IL)-1 family members in morbid obesity and effects of weight loss. Mol Med 2011; 17:840–845.
55. Olszanecka-Glinianowicz M, Zahorska-Markiewicz B, Janowska J, Zurakowski A. Serum concentrations of nitric oxide, tumor necrosis factor (TNF)-alpha and TNF soluble receptors in women with overweight and obesity. Metabolism 2004; 53:1268–1273.
56. Brandon EL, Gu JW, Cantwell L, *et al.* Obesity promotes melanoma tumor growth: role of leptin. Cancer Biol Ther 2009; 8:1871–1879.
57. Henning RJ. Obesity and obesity-induced inflammatory disease contribute to atherosclerosis: a review of the pathophysiology and treatment of obesity. Am J Cardiovasc Dis 2021; 11:504–529.
58. Van de Voorde J, Pauwels B, Boydens C, Decaluwé K. Adipocytokines in relation to cardiovascular disease. Metabolism 2013; 62:1513–1521.
59. Tercan H, Van Deuren R, Schraa K, *et al.* Clonal hematopoiesis and inflammation in obesity. Atherosclerosis 2021; 331:e113.