THE SYSTEMATIC REVIEW OF ADIPOCYTES IN ACUTE LEUKEMIA

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ABSTRACT

Background: Adipose tissue, a major cell type in the bone marrow microenvironment, plays a crucial role in the development and progression of cancer. Adipocytes, which make up the majority of cells in adipose tissue, exhibit distinct metabolic roles, replication and development abilities, cytokine production, and reactions to external stimuli. Adipocytes are abundant in bone marrow, a key site of metastasis for solid tumors and a crucial microenvironment for hematological malignancies.

The aim: This study aims to determine the association of adipocytes in acute leukemia.

Methods: By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like PubMed and ScienceDirect, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.

Results: In the PubMed database, the results of our search brought up 27 articles, whereas the results of our search on ScienceDirect brought up 281 articles. The results of the search conducted by title screening yielded a total 14 articles for PubMed and 3 articles for ScienceDirect. We compiled a total of 12 papers, 10 of which came from PubMed and 2 of which came from ScienceDirect. We excluded 4 review articles, 2 articles having ineligible subjects, and 1 article having insufficient outcomes. In the end, we included five research that met the criteria.

Conclusion: Acute leukemia cells have various effects on adipocytes which alter adipogenic differentiation capacities or adipocyte lipolysis and promote bone marrow adipocyte remodeling. Adipocytes play a crucial role in acute leukemia cell survival and their treatment.

Keywords: Adipocytes, role, acute leukemia
INTRODUCTION
Acute leukemia is the most common type of cancer in the pediatric population. Acute lymphoblastic leukaemia (ALL) is a cancerous proliferation of lymphoid cells that can spread to bone marrow, blood, and extramedullary locations. In kids between the ages of two and five, ALL accounts for 61% to 87.5% of cases, making it the most prevalent variety. Its incidence in the United States was predicted to be 1.57 per 100,000 persons in 2014. In 2018, there were about 5960 new cases identified and 1470 deaths. Acute myeloid leukaemia (AML) is a bone marrow disease characterised by abnormalities in hematopoietic stem cells caused by genetic changes in blood cell precursors that lead to an excess of clonal myeloid stem cells that are malignant. Age-adjusted AML incidence was first estimated to be 3.43 per 100,000 per year by Surveillance, Epidemiology, and End Results (SEER). However, over time, incidence rates have risen, persistently exceeding 4.2 per 100,000 per year starting in 2010.

The BM adipocyte is a major cell type within the bone marrow microenvironment (BMM) that has long been overlooked and has just recently come to the fore. The secretory cells known as adipocytes are quite active. Adipocytes make up the majority of the cells in adipose tissue, but it also comprises stromal vascular fraction, which is made up of pluripotent stem cells, monocytes, macrophages, endothelial cells, and pericytes. Fascinatingly, distinct metabolic roles, ability for replication and development, cytokine production, and reactions to external stimuli are all exhibited by adipocytes from various adipose tissue regions. The BM microenvironment, or niche, provides cues to the closely regulated process of hematopoiesis, which in turn controls self-renewal, differentiation, and proliferation. The function that the cancer microenvironment plays in metastasis, dissemination, and response to treatment is now better understood. Cancer cells, healthy cells, the intracellular matrix, and the signals that envelop them make up this microenvironment. Cancer cells engage in interactions with fibroblasts, macrophages, lymphocytes, endothelial cells, and adipocytes among other host cell types found in solid tumors.

Research indicates that adipocytes, or cells found in adipose tissue, are involved in the initiation and spread of a number of different neoplasms, as well as treatment resistance and the recurrence of diseases that had previously been in remission. Adipocytes are abundant in bone marrow, which is also a key site of metastasis for solid tumors and a crucial microenvironment for hematological malignancies. In fact, adipocytes may be the main cell type in bone marrow following acute leukemia. This study aims to determine the association of adipocytes in acute leukemia.

METHODS
Protocol
By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility
For the purpose of this systematic review, we investigated the association of adipocytes in acute leukemia. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it should focus on determining the association of adipocytes in acute leukemia. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published within the last 10 years. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy
We used "adipocytes", "role", and "acute leukemia" as keywords. The search for studies to be included in the systematic review was carried out from January, 17th 2024 using the PubMed and ScienceDirect databases by inputting the words: adipocytes[MeSH Terms] OR adipocytes[All Fields] OR adipocyte[All Fields] OR adipocytic[All Fields] AND role[MeSH Terms] OR role[All Fields] AND ("acute"[All Fields] OR "acutely"[All Fields] OR "acutes"[All Fields] AND ("leukaemia"[All Fields] OR "leukemia"[MeSH Terms] OR "leukemia"[All Fields] OR "leukaemias"[All Fields] OR "leukemias"[All Fields] OR "leukemia s"[All Fields] AND (y_10[Filter]) AND (english[Filter]) used in searching the literature.

Data retrieval
After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.
Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis
Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT
In the PubMed database, the results of our search brought up 277 articles, whereas the results of our search on ScienceDirect brought up 281 articles. The results of the search conducted by title screening yielded a total of 14 articles for PubMed and 3 articles for ScienceDirect. We compiled a total of 12 papers, 10 of which came from PubMed and 2 of which came from ScienceDirect. We excluded 4 review articles, 2 articles having ineligible subjects, and 1 article having insufficient outcomes. In the end, we included five research that met the criteria.

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<tr>
<th>Author</th>
<th>Origin</th>
<th>Method</th>
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<td>Kononczuk, 2021</td>
<td>Poland</td>
<td>Cross-sectional study</td>
<td>62 patients</td>
<td>The findings suggested that ALL survivors present higher Adipocytes-FABP levels than the control group. Moreover, the elevated levels of Adipocytes-FABP and E-FABP were observed in overweight subjects and those with metabolic syndrome features. These findings showed that the increased levels of fatty acid-binding proteins may be involved in the pathogenesis of overweight and the onset of metabolic syndrome in acute lymphoblastic leukemia survivors.</td>
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<td>Tabe, 2017</td>
<td>Japan</td>
<td>Experimental study</td>
<td>NA</td>
<td>The results suggested that bone marrow adipocytes support acute monocytic leukemia cell survival by regulating their metabolic energy balance, and that the disruption of fatty acid β-oxidation (FAO) in bone marrow adipocytes may be an alternative, novel therapeutic strategy for AMoL therapy.</td>
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<td>Tucci, 2021</td>
<td>USA</td>
<td>Experimental study</td>
<td>NA</td>
<td>These findings uncover a previously unidentified interaction between acute lymphoblastic leukemia (ALL) cells and adipocytes, leading to transfer of free fatty acids (FFA) for use as a metabolic fuel and macromolecule building block. This interaction may contribute to ALL resistance to chemotherapy, and could potentially be targeted to improve ALL treatment outcome.</td>
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Yang, 2020\textsuperscript{12}  China  Cross-sectional study  16 patients  This findings showed that leukemia cells activate a transcriptional network that includes GDF15-related-PI3K/AKT activation and subsequent TRPV4 downregulation, which promotes bone marrow adipocyte remodeling. The morphological adaptation of bone marrow adipocytes and the modulation of lipolysis may represent a novel strategy for the treatment of hematologic malignancies, especially in elderly patients, whose aging and increased adiposity of the BM microenvironment reduce the efficacy of cytotoxic chemotherapy.

Zhang, 2022\textsuperscript{13}  China  Experimental study  NA  The data of this study showed that AML-educated multipotent mesenchymal stem/stromal cells (MSCs) tend to differentiate into adipocytes contributing to disease progression, which suggests complex interactions of leukemia with microenvironment components.

Kononczuk, et al. (2021)\textsuperscript{9} showed that acute lymphocytic leukemia (ALL) survivors had statistically higher adipocyte fatty acid-binding protein (A-FABP) level than the healthy controls (25.57 ± 14.46 vs. 15.13 ± 7.61 ng/mL, p < 0.001). In addition, all of the overweight and obese patients had a significantly higher level of A-FABP compared to the ALL group with normal BMI (32.02 ± 17.10 vs. 20.33 ± 9.24 ng/mL, p = 0.006). In the analysis by gender, female subjects with normal BMI showed a higher concentration of A-FABP compared to the control group (22.74 ± 8.28 vs. 11.87 ± 6.77 ng/mL, p < 0.001), whereas the male subjects with normal BMI did not reveal significant statistical differences compared to the control group (A-FABP: 16.80 ± 9.75 vs. 17.30 ± 7.56 ng/mL, p = 0.717). Additionally, the higher levels of A-FABP was found in females with high BMI in comparison to the control group (A-FABP: 34.32 ± 20.23 vs. 11.87 ± 6.77 ng/mL, p = 0.001). In addition, the participants with two or more metabolic risk factors (16.13%) presented significantly higher levels of A-FABP (33.62 ± 17.16 vs. 15.13 ± 7.61 ng/mL, p = 0.001) than the control group.

Tabe, et al. (2017)\textsuperscript{10} showed that bone marrow adipocytes had antiapoptotic effects on acute monocytic leukemia (AMoL) cells in co-culture, effects of metabolic alterations in AMoL cells, effects of gene expression changes in U937 cells, effects on transcriptional network in AMoL cells, and effects on upregulation of AMPK signaling and HSP in AMoL cells. BM adipocytes supported viability of U937, MOLM13, and MV4;11 AMoL cells and OCI-AML3 AMMoL cells in these conditions showed by low rates of annexin positivity as effectively, or more, than undifferentiated mesenchymal stem/stromal cells (MSCs). Similarly, co-culture with BM adipocytes protected primary AMoL cells from spontaneous apoptosis to a greater extent than those co-cultured with MSCs. In U937 and THP1 cells, co-culture with BM adipocytes frequently altered 585 genes in a CAGE-mapped TSS signature: 366 upregulated and 219 downregulated (false discovery rate < 0.05). Moreover, in two independent experiments, iTRAQ proteomic analysis detected a total of 1609 and 940 proteins in U937 cells cultured in the absence or presence of adipocytes, respectively, and identified replicated significant expression changes of 13 proteins upregulated (> 1.2-fold) and 19 proteins downregulated (< 0.8-fold) compared to control conditions (p < 0.05).

Tucci, et al. (2021)\textsuperscript{11} showed that ALL cells stimulate adipocyte lipolysis. Lipid staining confirmed that adipocytes cultured directly with murine or human ALL, or in their conditioned media (LCM), had less lipid, though this did not reach significance for all conditions. In this experimental study, the results also showed that ALL cytokines may not drive
adipocyte FFA release. This study selected six cytokines with known effects on lipolysis [TNFa, RANTES (CCL5), CCL17, MCP-1 (CCL2), IL-16, PDGF-AA], and cultured adipocytes in their approximate measured concentrations. All six cytokines together induced modest adipocyte FFA release, but substantially less than LCM. Monoclonal blocking antibodies to four of the cytokines did not attenuate this effect, though Infliximab, a monoclonal antibody to TNFa, tended to reduce LCM-stimulated FFA release. Moreover, ALL cells take up adipocyte-derived FFA, it was proven with differentiated 3T3-L1 adipocytes in the presence of the fluorescent-labeled palmitate analogue, BODIPY-FFA. BODIPY fluorescence incorporated into adipocyte triglycerides and phospholipids. We found that ALL cells generally contain lipid droplets, as they were present in all five ALL cell lines tested and all three ALL patient bone marrow aspirate smears.

Yang, et al. (2020) showed that downregulated TRPV4 contributes to increased bone marrow adipocyte lipolysis. To investigate whether TRPV4 plays an important role in BM adipocytes, this study used TRPV4 inhibitor (RN1734) and agonist (4aPDD) to verify the function of TRPV4 in BM adipocytes, respectively. 4aPDD at a concentration of 0.25 mg/mL resulted in an acceptable level of toxicity of adipocytes, while allowing Ca2+ influx to reach the level required for the experiment. To further confirm that TRPV4 regulates lipolysis of BM adipocytes, this study used shTRPV4 lentivirus to knock down TRPV4. Quantitative analysis showed that the number (control vs. shTRPV4, 528.1±46.4/mm2 vs. 298.9±48.3/mm2, 454.7±54.0 mm2, P<0.01) of BM adipocytes decreased in TRPV4 knockdown samples. ATGL and HSL mRNA levels were also increased in TRPV4 knockdown adipocytes. These data indicate a critical role for TRPV4 in the regulation of lipolysis in BM adipocytes.

In addition, when BM adipocytes were co-cultured with leukemia cell lines (THP-1, K562, HL-60), the expression of TRPV4 changed significantly. These results further suggest that TRPV4 may play an important role in GDF15-induced remodeling of BM adipocytes. GDF15 secreted by leukemia cells promoted BM adipocyte lipolysis, decreasing the number and area of BM adipocytes. As shown by western blot analysis, TRPV4 expression was inhibited in BM adipocytes when co-cultured with leukemia cell lines (THP-1, K562, HL-60), whereas anti-GDF15 neutralizing antibodies partly reversed the effect.

Zhang, et al. (2022) showed that acute myeloid leukemia (AML) patient-derived MSCs exhibited increased adipogenic differentiation capacities. There was a significantly increased number of differentiated adipocytes from AML-hMSCs on day 14 of differentiation. Zhang, et al. (2022) cultured AML-hMSCs and N-hMSCs in 24-well plates in adipogenic or osteogenic differentiation medium to extend these observations. In addition, this study showe AML cell incubation facilitated normal hMSCs to differentiate into the adipogenic lineage. OCI/AML3-cocultured N-hMSCs exhibited lower osteoblastic differentiation but higher adipogenic differentiation potential than hMSCs in control groups. This was proven by adopting an in vitro transwell co-culture system to see whether the alteration in MSCs could be reproduced. First, N-hMSCs at passage 3 were cocultured with fresh AML blasts for nine days using a Transwell system and then induced for adipogenic or osteogenic differentiation.

**DISCUSSION**

The purpose of this research was to review studies published after January of 2014 and up to January of 2024 that investigated the association of adipocytes in acute leukemia. This review included three experimental study and two cross-sectional study. Overall, the studies showed that acute leukemia (AML or ALL) and adipocytes were associated.

Adipocytes, endothelial cells, hematopoietic cells, mesenchymal stromal cells, and pericytes are among the many cell types found in the bone marrow compartment. The composition of these cells essentially varies across the course of an individual's life. Adipose tissue might finally account for >70% of the bone marrow space. White adipose tissue (WAT), which surrounds internal organs and is located subcutaneously, is the predominant type of adipose tissue in the body. Although its primary role is energy storage, WAT also serves as an endocrine organ, a reservoir for hematopoietic cells, and has immunomodulatory properties. Brown adipose tissue (BAT) is the main thermogenic organ, which is responsible for generating heat via the action of uncoupling protein-1. Bone marrow adipose tissue (MAT) exhibits heterogeneous qualities and may constitute a discrete class with particular attributes. Divergent responses between MAT and physiological needs such bone remodeling and hematopoiesis are possible.

Bone marrow, a major site of metastasis for solid tumors and an important microenvironment for hematological malignancies, is also rich in adipocytes. In hematological malignancies such acute myeloid leukemia (ALL), multiple myeloma (MM), chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (AML), bone marrow adipocytes play a crucial role by creating a rotumoral microenvironment. Bone marrow adipocytes envelop tumor cells, which demonstrate decreased rates of spontaneous apoptosis and extended survival duration.

Historically, the BM niche has been divided into two categories: the perivascular (also known as endothelial) niche and the endosteal (also known as osteoblastic) niche. The first niche is larger and contains a higher concentration of mesenchymal stem cells (MSCs), which can differentiate into adipocytes, osteoblasts, chondrocytes, and fibroblasts. It is also distinguished by the paracrine interactions that occur between HSCs and non-hematopoietic cells to preserve homeostasis and promote healthy hemopoiesis. Adipocyte differentiation from MSCs is a complicated process that includes morphological changes, the expression of multiple lipogenic enzymes, the cessation of cell growth factor, substantial lipid buildup, and sensitivity to most or all of the major hormones (glucocorticoids, growth hormone). The
Adipokines, a class of hormones and cytokines secreted by adipocytes, influence a wide range of paracrine and endocrine targets. According to a study, a unique chemoprotective niche from the metabolic protection may arise from the intercalation of ALL cells and adipocytes in the bone marrow and adipose tissue microenvironments. As a result, the adipocyte secretome interacts with ALL at several different locations but does not directly affect the survival of ALL cells. Though most of these have not yet been studied in relation to ALL, adipocytes also secrete a wide range of additional hormones and cytokines, including as adipins, RBP4, FGF21, resistin, and omentin. Furthermore, it can be hypothesized that adipocytes aid in the survival of tumor cells by both secreting adipokines and inhibiting the antitumor effect of chemotherapy agents, as they alter the pharmacokinetics of chemotherapy and supply additional energy to stimulate the proliferation of tumor cells. The impact of adipokines, particularly chemokines and inflammatory cytokines, on medication resistance and tumor progression presents a novel avenue for therapeutic intervention. Additionally, it is thought that the adipocyte microenvironment serves as a protective niche for ALL cells, as fat deposits shield these cells from the harmful effects of chemotherapy.

Adipose tissue in the bone marrow allowed AML blasts from patients to survive and proliferate by taking over adipocyte metabolism and triggering lipolysis, which released free fatty acids. Fatty acid binding protein-4 (FABP4) was required mechanistically for the proliferation of AML blasts in co-culture with adipocytes since its silencing by shRNA inhibited the proliferation of AML blasts and improved mouse survival in a model of Hoxa9/Meis1-driven AML. Additionally, it was discovered that b-adrenergic receptor expression on stromal cells, which triggers AML-induced sympathetic signaling, causes MSC differentiation shift to osteoblasts at the expense of adipocytes, hence impeding normal granulocyte maturation.

CONCLUSION
Acute leukemia cells have various effects on adipocytes which alter adipogenic differentiation capacities or adipocyte lipolysis and promote bone marrow adipocyte remodeling. Adipocytes play a crucial role in acute leukemia cell survival and their treatment.

REFERENCES


