Review Article

Fasting or fasting mimicking diet as a strategy for managing adverse effects in patients undergoing chemotherapy: a systematic review

Jejum ou fasting mimicking diet como estratégia para manejo de efeitos adversos em pacientes submetidos a quimioterapia: uma revisão sistemática

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ABSTRACT

Introduction: Fasting and the fasting-mimicking diet are strategies to reduce adverse effects (AEs) by increasing differential stress sensitization in tumor cells and enhancing chemotherapy uptake, causing oxidative stress and DNA damage. **Methods:** A systematic review was conducted using PubMed and Scopus databases, following the PRISMA method and utilizing the Cochrane Collaboration RoB 2.0 tool to assess risk of bias. **Results:** A total of 7 randomized clinical trials (RCTs) were included. The RCTs evaluated fasting over different periods: 18, 48, 60 and 96 hours. Most trials used the Common Terminology Criteria for Adverse Events (CTCAE) to assess AEs. No grade V AEs were observed. Most AEs were grade I or II, and in all RCTs, both groups experienced some type of treatment-related toxicity. Stomatitis, headaches, weakness, mucositis, diarrhea, vomiting, nausea, self-reported toxicities, and chemotherapy delay were significantly lower during fasting ($p=0.013$; $p=0.002$; $p=0.024$; $p=0.004$; $p<0.001$; $p<0.001$; $p=0.009$; $p=0.023$, and $p=0.034$, respectively). Both groups reported clinically significant worsening of fatigue, pain, dyspnea, loss of appetite, and constipation during treatment ($p<0.01$). **Conclusion:** Due to the scarcity of studies, it is not possible to confirm that fasting or similar strategies can mitigate chemotherapy-induced AEs compared to a regular diet.

RESUMO

Introdução: O jejum e a *fasting mimicking diet* são estratégias para reduzir os efeitos adversos (EA), aumentando a sensibilização diferencial ao estresse em células tumorais e aumentando a captação do quimioterápico, ocasionando estresse oxidativo e dano ao DNA. **Método:** Foi realizada uma revisão sistemática, utilizando as bases de dados Pubmed e Scopus, por meio do método PRISMA e a ferramenta de Colaboração Cochrane RoB 2.0 para avaliar o risco de viés. **Resultados:** Foram incluídos 7 ensaios clínicos randomizados (ECRs). Os ECRs avaliaram o jejum por diferentes períodos: 18, 60, 48 ou 96 horas. A maioria dos ensaios utilizou os Critérios de Terminologia Comum para Eventos Adversos (CTCAE) para avaliar os EA. Não foram observados EA grau V. A maioria dos EA foi grau I ou II, e em todos os ECRs, ambos os grupos apresentaram algum tipo de toxicidade relacionada ao tratamento. Estomatite, cefaleias, sensação de fraqueza, mucosite, diarreia, vômito, náusea, toxicidades auto-relatadas e menor adiamento da quimioterapia foram significativamente menores durante o jejum ($p=0,013$; $p=0,002$; $p=0,024$; $p=0,004$; $p<0,001$; $p<0,001$; $p=0,009$; $p=0,023$ e $p=0,034$, respectivamente). Nos dois grupos, houve piora clinicamente significativa de fadiga, dor, dispneia, perda de apetite e constipação ($p<0,01$). **Conclusão:** Devido à escassez de estudos, não é possível afirmar que o jejum, ou estratégias similares, amenizam os EA da quimioterapia em comparação a uma dieta regular.

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INTRODUCTION

The word cancer is used to describe a group of more than 100 diseases that undergo genetic mutations and have the ability to resist treatments, with the potential to cause the host's death. It represents one of the major public health problems in Brazil, with an increasing number of cases each year[1].

Cancer treatment can be carried out through several therapeutic modalities, either in isolation or in combination, with chemotherapy being one of these strategies[1]. However, although this treatment has benefits, the toxicities caused by this therapy can affect the gastrointestinal tract, leading to various adverse effects (AEs) that may persist for days after the application and impact the outcomes of this technique[2-5]. Fasting, which involves consuming only water for several hours or days, has emerged as an option for reducing the adverse effects caused by antineoplastic drugs. Due to the difficulty of implementation, the fasting mimicking diet appears as an alternative, as it can exert similar functions to fasting by reducing the activation of glucose/insulin signaling pathways[6,7].

Short-term fasting increases differential stress sensitization in cancer cells compared to healthy cells. During the period of nutrient deprivation, healthy cells deactivate pathways that promote cell growth and reproduction, a factor that favors greater tolerance to various stressors, such as chemotherapy[8]. Cancer cells, however, are unable to inactivate these pathways, resulting in a loss of ability to adapt to nutrient deprivation. The persistent growth of these cells causes fasting to enhance differential stress sensitization in tumor cells and increase the uptake of chemotherapy drugs, leading to increased oxidative stress and DNA damage[8].

Fasting leads to profound metabolic changes and favors an anti-Warburg effect, reducing glucose availability, decreasing ATP synthesis, and increasing the production of reactive oxygen species, which is important for inducing apoptosis[9]. It is also associated with a reduction in the number and severity of toxicities caused by chemotherapy[10].

Thus, the present study aimed to evaluate scientific evidence in the literature related to fasting or the fasting mimicking diet as a strategy for reducing adverse effects in cancer patients undergoing chemotherapy treatment.

METHODS

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to assist in the organization of this study through its checklist[11]. This was a systematic review study conducted according to the Cochrane Handbook for Systematic Reviews of Interventions[12,13], with the aim of gathering and summarizing results found in randomized controlled trial (RCT) research, registered in PROSPERO (CRD42024529246).

The guiding question was based on the PICO strategy, resulting in the question: "Can fasting or a fasting mimicking diet help in managing adverse effects caused by chemotherapy in cancer patients?".

The search for original articles occurred between March and August 2023, using the PubMed and Scopus databases. The keywords used were "fasting", "caloric restriction", and "cancer", limited to title and abstract, using Boolean logic terms "AND" and "OR", with filters applied for a 10-year limit, including only articles in English, Portuguese, and Spanish, with full text, clinical trials, and randomized controlled trials. The inclusion criteria were: (1) studies in humans; (2) studies that evaluated fasting or fasting mimicking diet in cancer patients undergoing chemotherapy with the aim of improving adverse events and (3) adult patients. The exclusion criteria were: (1) duplicate studies; (2) studies not available as full original articles; (3) studies with uncharacterized samples and that used other strategies for managing toxicity and (4) *in vitro* studies.

The search results were imported into the Rayyan tool[14], and the abstracts deemed relevant to the topic of interest were selected by two researchers and assessed according to the eligibility criteria. Possible discrepancies between the authors were resolved through a third reviewer. The risk of bias in the studies was assessed using the Cochrane Collaboration's RoB 2.0 tool[15,16].

RESULTS

A total of 247 articles were found in the databases. After removing duplicates, title/abstract screening was conducted, resulting in the exclusion of 232 articles. The reasons for exclusion included animal studies, *in vitro* studies, study type, incomplete text, and papers going over other topics. Out of these, 11 full-text articles were reviewed, of which 7 met the inclusion criteria (Figure 1). The information from the selected articles is described in Table 1. Regarding the types of tumors studied, all RCTs were conducted on female tumors, with six studies including patients with breast cancer, three with ovarian cancer, and two with cervical cancer. The participants in the RCTs did not present malnutrition, heart disease, diabetes, a history of eating disorders, were not pregnant, and had not lost weight in recent months.

The RCTs utilized various fasting strategies to mitigate adverse effects, such as fasting mimicking diet, short-term fasting, and intermittent fasting. To assess toxicities, five RCTs[17-19,21,22] used the Common Terminology Criteria for Adverse Events (CTCAE). Bauersfeld et al.[20] used the Functional Assessment of Chronic Illness Therapy (FACIT©) system, the Functional Assessment of Cancer Therapy - General (FACT-G), and the Trial Outcome Index (TOI) score. Lugtenberg et al.[23] applied the European Organization for Research and

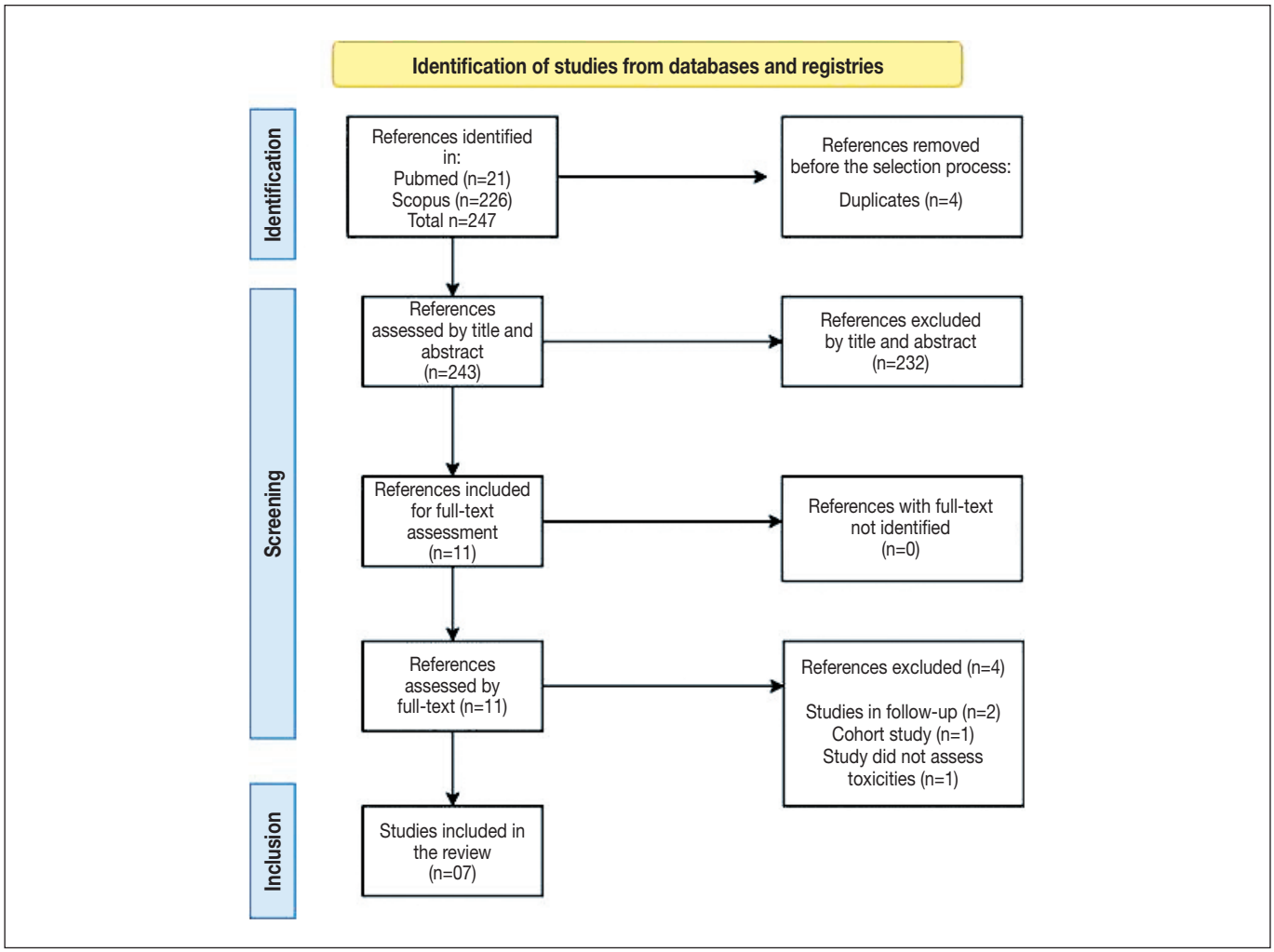

Figure 1 - *Adapted PRISMA 2020[12] flowchart with study selection process.*

Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) and the Breast Cancer Questionnaire (EORTC-QLQ-BR23) to measure adverse events.

Regarding other medications included in the RCTs, antiemetics[17,19-21,23] and dexamethasone were administered to all participants in both groups. Only two RCTs[18,22] did not document whether these medications were used.

Regarding the results obtained, there were no grade V adverse events in the RCTs. In the RCTs by Groot et al.[21] and Groot et al.[17], participants experienced grade III/IV toxicity, with febrile neutropenia, fatigue, and infection present in 6 patients in the fasting group and 3 in the control group[21], and neutropenia and febrile neutropenia present in 75.4% and 65.6% in the fasting and control groups, respectively[17]. Regarding grade III toxicities, one case of nausea was recorded during the fasting cycle[18], two control group patients presented with neutropenia[19,22], and two others experienced syncope and dehydration caused by vomiting[22]. In the RCT by Bauersfeld et al.[20], there were no grade III toxicities.

Most articles reported grade I and II adverse events. Zorn et al.[18] reported that fatigue, nausea, and stomatitis were the most frequent toxicities, with the latter being reduced during fasting cycles. Riedinger et al.[22] observed a tendency for improvement in hematological parameters, with lower toxicity present in the fasting group (p=0.73). Additionally, there was similarity between the two groups regarding chemotherapy-induced neuropathy[22].

Groot et al.[21] demonstrated more side effects related to fatigue, mucositis, and dizziness in the control group, while the fasting group showed more infection, neuropathy, diarrhea, nausea, eye problems, and constipation, but without significant differences between the groups. Similarly, the RCT by Zorn et al.[18] demonstrated that infection and neuropathy were more present in the fasting group, fatigue was present in the fasting group, and nausea was more prevalent in the control group. Diarrhea and constipation occurred similarly in both groups[18]. In the RCT by Omar et al.[19], constipation was significantly present (p=0.004) only in the fasting group.

Tabele 1 – Characteristics of studies included in the systematic review.

Author / Year	Type of Cancer	Study Size	CT	Intervention	Comparison	Number of Dropouts	Results	Conclusion
Groot et al., 2020[17]	Breast. HER2-negative, Stage II/III (cT1cN+ or ≥T2 any cN, cM0). Majority with ductal tumor and ER+/PR+.	131	8 cycles of neoadjuvant AC-T chemotherapy or 6 cycles of neoadjuvant FEC-T chemotherapy, all every 3 weeks.	- FMD (low amino acid, plant-based diet consisting of soups, broths, liquids, and tea) for 4 days (3 days before and on the day of chemotherapy); - Caloric content decreased from day 1 (~1200 kcal) to days 2–4 (~200 kcal).	RD	2	65 received FMD and 64 were part of the CG. Neutropenia and febrile neutropenia (Grade III/IV) showed no significant difference between groups (27.7% FMD versus 23.8% CG, p=0.580).	No difference was observed between FMD and RD.
Zorn et al., 2020[18]	Breast, endometrial, ovarian, and cervical. - 73% breast cancer; - 80% between T1 and T2; - 93.4% between N0 and N1; - 10% with metastasis,	51	Neoadjuvant or adjuvant chemotherapy with a minimum of 4 cycles of the same chemotherapy protocol at intervals of 3 to 4 weeks: - Paclitaxel/ carboplatin - Epirubicin/ cyclophosphamide - Docetaxel/ cyclophosphamide	- Group A: mSTF (2-3 cycles of CT) after RD (2-3 cycles of CT); - Group B: RD (2-3 cycles of CT) after mSTF (2-3 cycles of CT); - Group C: Ketogenic + mSTF after RD; - Group D: RD after Ketogenic + mSTF, - mSTF: 25% of caloric needs (400 to 600 kcal/day) consisting of 75% fat, 15% protein, and 10% carbohydrates + 2.5 l of non-caloric liquids (water, herbal tea, and caffeine- and alcohol-free diet drinks); - 96-h fast (3 days before CT and 1 day after CT).	-	21	7 patients in Group A and 9 in Group B were considered. Stomatitis, headache, and weakness were significantly less frequent during fasting cycles (p= 0.013; p= 0.002; and p= 0.024, respectively). The overall severity of toxicities was significantly reduced during fasting cycles (p= 0.023). Fewer chemotherapy delays during fasting cycles (p= 0.034); No significant change in fatigue.	No difference between mSTF and RD.
Omar et al., 2022[19]	Breast. - HER2-negative; - Majority with ER+/PR+, Stage II or III.	48	AC repeated every 3 weeks for 4 cycles.	- 18-hour IF, allowing up to 750 kcal during the 6-hour eating window; - They could drink water during the fasting period and consume small amounts of foods mainly consisting of vegetables, fruits, and a small number of proteins and carbohydrates with limited sugar and fats; - The IF occurred on 3 consecutive days, starting 1 day before chemotherapy, on the day of chemotherapy, and 1 day after, repeated every 3 weeks for four cycles.	RD	0	24 patients in the IF group and 24 patients in the CG. Mucositis, diarrhea, vomiting, and nausea were higher in the RD group (p=0.004, p<0.001, p<0.001, and p=0.009, respectively). Constipation was present in the IF group (p=0.004). No significant difference between the two groups in the incidence of thrombocytosis, neutropenia, headache, hair loss, or fatigue.	No difference was observed between IF and RD.

Continuation Tabele 1 – Characteristics of studies included in the systematic review.

Author / Year	Type of Cancer	Study Size	CT	Intervention	Comparison	Number of Dropouts	Results	Conclusion
Bauersfeld et al., 2018[20]	Breast and ovarian. - 30 breast cancer and 4 ovarian cancer cases; - 97% between T1-T3; - 50% pN1; - 30% triple-negative breast cancer and 36.7% Luminal B/HER-2	50	- For breast cancer patients: EC, FEC-D; FEC-D + trastuzumab, AC-T, EC-T, ACT, and D + pertuzumab + trastuzumab. - For ovarian cancer patients: P mono, P + T, EC-T + P, and P + T + bevacizumab.	- Group A was randomized to a 60-h STF during the first 3 of 6 scheduled CT sessions (36 h before to 24 h after CT) followed by RD during the next 3 CT sessions; - Group B was assigned to RD during the first 3 CT sessions, followed by STF during the last 3 CT sessions. STF: unlimited amounts of water, herbal tea, 200 calories of vegetable juice, and standardized small amounts of light vegetable broth, with a maximum total daily energy intake of 350 calories.	RD	16	18 participants in Group A and 16 in Group B. - Group A showed a statistically and clinically significant beneficial effect on QoL and fatigue during fasting cycles; - Group B did not show a significant reduction in QoL and fatigue during fasting cycles. Significant increase in QoL in Group A according to the FACT-G Scale, FACIT Scale, and TOI.	No difference was observed between STF and RD.
Groot et al., 2015[21]	Breast. - HER2-negative, Stage II and III; - 8 in adjuvant treatment; - 9 were N+; - 9 were ER+ and 6 PR+.	13	ACT on the first day of each three-week cycle (six cycles in total)	- STF group (24 h before chemotherapy and 24 h after chemotherapy), allowed to drink water, coffee, or unsweetened tea.	RD	0	7 patients in the STF group and 6 in the CG. Grade I/II side effects: - fatigue, mucositis, and dizziness were higher in the RD group; - infection, neuropathy, diarrhea, nausea, and constipation were higher in the fasting group. No significant difference in the incidence of Grade III/IV side effects between the groups.	No difference was observed between STF and RD.
Riedinger et al., 2020[22]	Ovarian, uterine, and cervical. - 9 ovarian cancer, 8 uterine cancer, and 1 cervical cancer; - 13 in Stage III and 3 in IV; - 17 with primary diagnosis. Neoadjuvant treatment	24	- CT: bevacizumab, carboplatin, cisplatin, docetaxel, doxorubicin, gemcitabine, and paclitaxel; - CT sessions every 3 weeks, with at least 6 cycles.	- FG and RD; - Fasting for 24 h before and 24 h after CT treatments; - Allowed to m aintain adequate hydration with water, black coffee, or unsweetened tea.	RD	4	10 participants in the FG and 10 in the CG. Grade III neutropenia was present only in the CG. Improvement in hematological parameters with less Grade II or higher toxicity in the fasting group (p=0.73). Grade I or II neuropathy was similar between the groups.	No difference was observed between F and RD.

Continuation Tabele 1 – Characteristics of studies included in the systematic review.

Author / Year	Type of Cancer	Study Size	CT	Intervention	Comparison	Number of Dropouts	Results	Conclusion
Lugtenberg et al., 2021[23]	Breast. HER2-negative, Stage II/III (cT1cN+ or ≥T2 any cN, cM0). Majority with ductal tumor and ER+/PR+.	131	8 cycles of neo-adjuvant AC-T chemotherapy or 6 cycles of neoadjuvant FEC-T chemo-therapy all every 3 weeks.	- FMD (low amino acid, plant-based diet consisting of soups, broths, liquids, and tea) for 4 days (3 days before and on the day of chemotherapy); - Caloric intake decreased from day 1 (~1200 kcal) to days 2–4 (~200 kcal).	RD	2	65 received FMD and 64 were in the CG. The fasting group showed better scores in insomnia (p=0.068). Physical, functio-nal, and cognitive functioning scores decreased in both groups (p<0.01). In both groups, clinically relevant and significant wor-sening of fatigue, pain, dyspnea, loss of appetite, and constipation was reported (p<0.01), as well as worse-ning of nausea.	No difference was observed between FMD and RD.

CT = chemotherapy; F = fasting; IF = intermittent fasting; FG = fasting group; ER = estrogen receptor; PR = progesterone receptor; CG = control group; CA = cancer; AC-T = doxorubicin and cyclophosphamide + docetaxel; FEC-T = 5-fluorouracil, epirubicin, and cyclophosphamide + docetaxel); FMD = fasting mimicking diet; mSTF = modified short-term fasting; STF = short-term fasting; EC = epirubicin and cyclophosphamide; FEC-D = fluorouracil, epirubicin, and cyclophosphamide + docetaxel; ACT = doxorubicin, cyclophosphamide, and paclitaxel; EC-T = epirubicin and cyclophosphamide + paclitaxel; D = docetaxel; P = carboplatin; T = paclitaxel; ECT+P = epirubicin and cyclophosphamide + paclitaxel + carboplatin; P+T = carboplatin + paclitaxel; NC = caloric need; AC = doxorubicin + cyclophosphamide; RD = regular diet; QoL = quality of life.

In addition to these adverse effects, the RCT by Zorn et al.[18] reported other toxicities, with insomnia and arthralgia being more present in the fasting group, and reduced appetite, stomatitis, and pain being more present in the control group. Depression and esophagitis symptoms were similar between the two groups, and hunger, stomach pain, and headaches were only observed in the control group. On the other hand, dyspnea, edema, and vomiting were only present in the fasting group. Lugtenberg et al.[23] demonstrated that the fasting group showed better results regarding insomnia, but without statistical difference compared to the control group (p=0.068) in the per-protocol analysis.

Fatigue did not show a statistically significant difference during fasting cycles in the RCT by Zorn et al.[18]. In contrast, Bauersfeld et al.[20] demonstrated better results regarding fatigue in the fasting group when analyzed per protocol. In the RCT by Lugtenberg et al.[23], fatigue significantly worsened throughout the treatment in both groups, as did pain, dyspnea, loss of appetite, and constipation (p<0.01).

Groot et al.[17] did not observe significant differences between the groups regarding patients who discontinued chemotherapy (p=0.580). However, Zorn et al.[18] demonstrated that patients in the fasting group had significantly fewer chemotherapy treatment delays compared to the control group (p=0.034). In the RCT by Riedinger et al.[22], there were two hospitalizations. One was due to syncope and dehydration caused by emesis. The other was due to an axillary abscess, which was not related to chemotherapy, occurring only in the control group.

Regarding nausea, the RCT by Lugtenberg et al.[23] demonstrated that both groups reported a significant worsening throughout the treatment. Omar et al.[19] observed a significantly higher presence of nausea and emesis in the control group compared to the fasting group (p=0.009 and p<0.001, respectively).

Some symptoms caused by the fasting protocol were hunger[18,20], dizziness[18], weakness[18], headaches[18,20], mild nausea[20], and orthostatic reaction[20]. In the RCT by Omar et

al.[19], only the control group presented significantly higher mucositis and diarrhea (p=0.004 and p<0.001, respectively). In the RCT by Zorn et al.[18], the frequency and severity scores of self-reported weaknesses decreased significantly during fasting cycles compared to regular diet cycles (p=0.024).

Regarding hair loss, there was no difference between the two groups[19,23]. The RCT by Omar et al.[19] did not observe significant differences between the groups regarding thrombocytosis, neutropenia, and headache. However, in the RCT conducted by Zorn et al.[18], the frequency and severity of self-reported headaches decreased significantly during fasting cycles compared to regular diet cycles (p=0.002).

Zorn et al.[18] observed that the overall severity of self-reported toxicities by participants was significantly lower during fasting cycles compared to regular diet periods (p=0.023). Bauersfeld et al.[20] reported that during fasting, all adverse effects were of low grade and did not interfere with the participants' daily activities.

In all RCTs, there were participant dropouts throughout the study, except in the RCT by Groot et al.[21]. The RCT by Omar et al.[19] concluded the trial with the proposed number of participants at the start, but included two new participants during the study after two dropouts in the intermittent fasting arm. However, the timing of the dropout and inclusion of the new participants was not reported. The reasons for dropout included the emergence of metastasis[17,23], abandonment before the start of the study[17,18,23], discontinuation of chemotherapy, adjustments to the protocol or chemotherapy delays[18,20,22], death[22], not feeling socially comfortable with fasting[22], deterioration of general condition independent of fasting[18], discomforts related to fasting[18,20], feeling of additional burden due to participation in the study[18], desire not to continue participating in the study[19,20], and aversion to the nutrients imposed by the study[20].

The assessment of the risk of bias in the RCTs is presented in Figure 2. Overall, all RCTs included in this study had some level of bias, with three of them[18,20,21] being classified as having a high risk of bias. Notably, none of the RCTs demonstrated bias in relation to domain 3.

DISCUSSION

To date, RCTs indicate that fasting is safe and well-tolerated only in patients with gynecological tumors, such as breast, ovarian, and uterine cancers, with no serious complications reported. More specifically, in the case of breast cancer, the practice is considered safe for HER2-negative tumors and estrogen and progesterone receptor-positive tumors[17,18,21,23] in stages I, II, and III[17-21,23]. In other types of cancer, the patients analyzed ranged from stage I to IV[18,20,22], with only one study, conducted by Zorn et al.[18], including patients with metastasis.

The study published by Safdie et al.[10] describes ten cases where patients voluntarily fasted for a period of 48 to 140 hours before and/or 5 to 56 hours after chemotherapy, with various types of tumors. In this study, symptoms of hunger, dizziness, and headaches were observed without interfering with daily activities during fasting cycles, with similar results occurring in two RCTs in this review[18,20]. In agreement with the RCT by Safdie et al.[10], the RCT by Omar et al.[19] reported a higher prevalence of nausea, mucositis, and diarrhea in the control group.

Dorff et al.[24] conducted a cohort study that evaluated fasting during chemotherapy, where patients were divided into 3 cohorts (24 hours, 48 hours, and 72 hours of fasting), consuming up to 200 kcal/day. Fasting-related symptoms included fatigue, headache, dizziness, hypoglycemia, hyponatremia, and hypotension, which were symptoms similar to those presented in two studies here[18,20]. Regarding other toxicities[24], nausea, vomiting, diarrhea, and constipation were present in the fasting group, with results similar to the RCTs presented in this review[18,19,21]. Grade III and IV neutropenia was present in 7 patients in the cohort[24], as well as in two

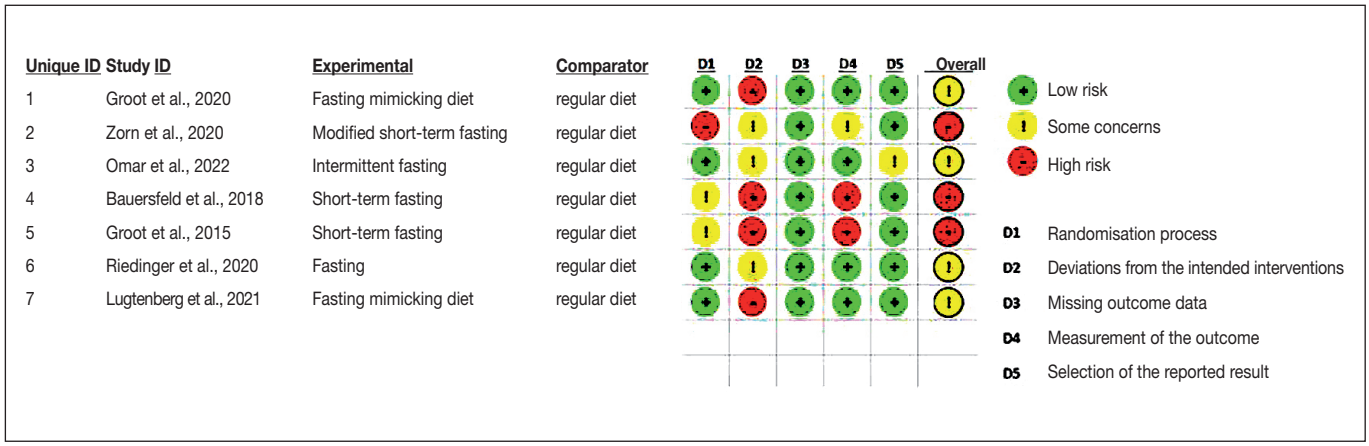

Figure 2 - *Assessment of risk of bias among included studies according to the Rob 2.0 Tool[15].*

RCTs in this review[17,21]. In contrast, in the RCTs by Omar et al.[19] and Riedinger et al.[22], neutropenia was present only in the control group.

Valdemarin et al.[25] presented a single-group clinical trial conducted with 90 patients who underwent the fasting mimicking diet protocol for 3 to 4 days. The symptoms reported by the patients were only grade I and II, similar to the RCT reported in this work[20]. The most common symptoms were headache, fatigue, diarrhea, abdominal pain, nausea, constipation, and hypoglycemia[25]. Some of these symptoms corroborate the results obtained in studies included in this review[18,20]. Fatigue showed controversial results in some RCTs presented in the review[18,20,23].

Given that cancer patients have a high chance of developing malnutrition[26], the RCT by Bauersfeld et al.[20] analyzed the change in participants' body weight throughout the study and observed that there was no significant change ($p>0.3$), similarly to Riedinger et al.[22], who observed an average reduction of 1.1 kg in the fasting group and 0.84 kg in the control group ($p=0.81$). The study by Valdemarin et al.[25] also assessed the potential alteration in the nutritional status of patients in the fasting group. On average, participants lost 2 to 2.5 kg after each fasting cycle. However, they regained the weight during the refeeding period, resulting in an increase in handgrip strength and a significant increase in phase angle and fat-free mass. In contrast, the RCT conducted by Lugtenberg et al.[23] demonstrated that patients in the fasting group experienced a significant reduction in body mass index (BMI) midway through the chemotherapy protocol ($p=0.002$) and at the end ($p=0.026$). Among the control group, BMI was higher at the end of treatment compared to the beginning ($p=0.006$). Similar results were found in the study by Zorn et al.[18], where the fasting group also experienced significant weight loss ($p=0.002$), which remained significantly reduced at the end of the study ($p<0.005$). The results of the studies conducted by Kikomeko et al.[27], Drexler et al.[28], and Caccialanza et al.[29] reinforce that it is not possible to assert if fasting or fasting-like strategies, despite being safe, would be effective for cancer patients during chemotherapy, corroborating results similar to those obtained in this work. The systematic review with meta-analysis conducted by Ferro et al.[30], like this review, evaluated fasting as a strategy to reduce side effects caused by chemotherapy and also did not demonstrate any significant effect of fasting in reducing toxicities related to antineoplastic therapy.

There are some limitations to this systematic review. Firstly, the search was restricted to only two databases, which may have limited the number of articles included and affected the representativeness of the results. Expanding the search in future studies may offer a more comprehensive view of the effect of fasting on chemotherapy adverse events. Additionally, most of the randomized controlled trials (RCTs) included relied on self-reported results by participants, which, along with high dropout rates or deviation from the proposed intervention, may have introduced bias in the results. Finally, there is a scarcity of studies investigating the role of fasting or similar strategies in reducing the side effects of antineoplastic therapy.

CONCLUSION

Due to this scarcity of studies, we cannot assert that fasting or similar methods are effective in reducing chemotherapy adverse effects compared to a regular diet. However, all the included RCTs indicate that fasting during cancer treatment in patients with gynecological female tumors and without malnutrition is safe. More studies are needed to clarify the effectiveness of fasting techniques in managing toxicities. It is crucial to conduct RCTs with a significant number of participants, minimizing intervention deviations and comparing different fasting strategies to determine their relative effectiveness. Additionally, further studies considering variables such as nutritional status, muscle mass, dietary history, age, comorbidities, chemotherapy protocols, and tumor type are essential.

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