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"JÚLIO DE MESQUITA FILHO"
FACULDADE DE MEDICINA

Carolina Fumico Massuda Araujo

Metformin for the treatment of breast cancer: a scoping review of randomized clinical trials

Tese apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Doutora em Saúde Coletiva.

Orientador: Prof. Dr. Edison Iglesias de Oliveira Vidal

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UNIVERSIDADE ESTADUAL PAULISTA

Câmpus de Botucatu

ATA DA DEFESA PÚBLICA DA TESE DE DOUTORADO DE CAROLINA FUMICO MASSUDA ARAUJO, DISCENTE DO PROGRAMA DE PÓS-GRADUAÇÃO EM SAÚDE COLETIVA, DA FACULDADE DE MEDICINA - CÂMPUS DE BOTUCATU.

Aos 10 dias do mês de novembro do ano de 2023, às 08:00 horas, por meio de Videoconferência, realizou-se a defesa de TESE DE DOUTORADO de CAROLINA FUMICO MASSUDA ARAUJO, intitulada **Metformina para o tratamento de câncer de mama: uma revisão de escopo de ensaios clínicos randomizados**. A Comissão Examinadora foi constituida pelos seguintes membros: Prof. Dr. EDISON IGLESIAS DE OLIVEIRA VIDAL (Participação Virtual) do(a) Depto. de Clínica Médica / FM/Botucatu - Unesp, Profa. Dra. CRISTIANE MURTA RAMALHO NASCIMENTO (Participação Presencial) do(a) Depto. de Saúde Pública / FM/Botucatu - Unesp, Prof. Dr. MÁRIO CÍRIO NOGUEIRA (Participação Virtual) do(a) Depto. de Saúde Coletiva / FACMED/Juiz de Fora - UFJF, Prof. Dr. LEONARDO ROBERTO DA SILVA (Participação Virtual) do(a) Centro de Atenção Integral à Saúde da Mulher (CAISM/Unicamp), Prof. Dr. MAXIMILIANO RIBEIRO GUERRA (Participação Virtual) do(a) Depto de Saúde Coletiva / Universidade Federal de Juiz de Fora, Faculdade de Medicina. Após a exposição pela doutoranda e arguição pelos membros da Comissão Examinadora que participaram do ato, de forma presencial e/ou virtual, a discente recebeu o conceito final:_ _ APROVADA _ _ _ . Nada mais havendo, foi lavrada a presente ata, que após lida e aprovada, foi assinada pelo(a) Presidente(a) da Comissão Examinadora.

Prof. Dr. EDISON IGLESIAS DE OLIVEIRA VIDAL

DEDICATÓRIA

Aos meus amados pais, Tochie e Edilberto, por todo o amparo, confiança, dedicação e incentivo ao longo desta vida.

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Ao meu orientador Prof. Edison Vidal, pela oportunidade de imenso aprendizado. Com você aprendi a navegar a literatura científica com outros olhos. Obrigada pela paciência e pelo precioso tempo gasto oferecendo-me muito de sua experiência e visão de pesquisa.

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“Queres de verdade ser santo? - Cumpre o pequeno dever de cada momento; faz o que deves e está no que fazes”.

São Josemaria Escrivá

Resumo

ARAUJO, C. F. M. **Metformina para o tratamento do câncer de mama: uma revisão de escopo de ensaios clínicos randomizados**. 2023. 161f. Tese (Doutorado) – Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Botucatu, 2023.

Objetivo: Mapear a literatura de ensaios clínicos randomizados (ECRs) com metformina no tratamento do câncer de mama.
Delineamento: Revisão de escopo.
Fontes de dados: Entre abril e outubro de 2021, foram pesquisadas cinco bases de dados eletrônicas (MEDLINE, EMBASE, CENTRAL, LILACS e Web of Science), bem como literatura cinzenta em OpenGrey, National Library of Medicine Bookshelf e ClinicalTrials.gov, a Plataforma Internacional de Registro de Ensaios Clínicos da Organização Mundial da Saúde, o Google Scholar e pesquisamos manualmente listas de referências, resumos de conferências e referências de especialistas.
Critérios de elegibilidade: Eram elegíveis quaisquer ECRs em que a metformina tenha sido usada para o tratamento de pessoas adultas com câncer de mama. Não foram impostas restrições de contexto, idioma, data de publicação ou desfechos.
Extração e síntese de dados: Dois revisores independentes mapearam os dados dos estudos incluídos com base nos fenótipos do câncer de mama, estágios e modalidades de tratamento.
Resultados: Vinte e cinco dos 40 estudos incluídos apresentavam alguma forma de resultado (artigos completos ou resumos), correspondendo a um total de 5.623 participantes. A maioria dos ensaios não forneceu resultados específicos por fenótipo. Ao todo, 107 desfechos diferentes foram relatados, dos quais os mais comuns foram: sobrevivência geral (SG), sobrevida livre de doença (SLD), sobrevivência livre de progressão, taxa de resposta objetiva, resposta patológica completa, taxa de benefício clínico, cirurgia conservadora e qualidade de vida. Há evidência limitada de uma análise de subgrupo de pacientes HER2+ de um único ensaio clínico grande sugerindo que a metformina possa melhorar a SG e SLD.
Conclusões: Os presentes achados destacam a necessidade de padronizar a publicação de resultados dos ECRs por fenótipo do câncer de mama e revelam o potencial para expandir o conhecimento neste campo a partir da determinação retrospectiva dos fenótipos dos participantes, o que poderia permitir metanálises de dados de pacientes individuais.

Palavras-chave: metformina; câncer de mama; revisão; ensaio clínico.

Abstract

ARAUJO, C. F. M. **Metformin for the treatment of breast cancer: a scoping review of randomized clinical trials**. 2023. 161f. Thesis (Doctorate) – Faculty of Medicine of Botucatu, Universidade Estadual Paulista, Botucatu, 2023.

Objective: We aimed to map the literature of randomized clinical trials (RCTs) of metformin for the treatment of breast cancer.
Design: Scoping review.
Data sources: Between April and October 2021, we searched five electronic databases (MEDLINE, EMBASE, CENTRAL, LILACS, and Web of Science), as well as grey literature on OpenGrey, National Library of Medicine Bookshelf, and ClinicalTrials.gov. the World Health Organization's International Clinical Trials Registry Platform, and Google Scholar, hand-searched reference lists, conference abstracts, and sought specialist input.
Eligibility criteria: We included any RCT where metformin was used for the treatment of adult patients with breast cancer. We did not impose any restrictions on context, language, publication date, or outcomes.
Data extraction and synthesis: Two independent reviewers charted the data from the included studies based on breast cancer phenotypes, stages, and treatment modalities.
Results: Twenty-five out of 40 included studies had some form of published results (full text or abstracts) amounting to 5,623 participants. Most trials did not provide phenotype-specific results. In total, there were 107 different reported outcomes, the most frequent of which were: overall survival (OS), disease-free survival (DFS), progression-free survival, objective response rate, pathological clinical response, clinical benefit rate, breast conservation rate, and quality of life. There is limited evidence from a subgroup analysis of HER2+ participants from a single large study suggesting that metformin might improve OS and DFS.
Conclusions: Our findings emphasize the need to standardize the reporting of trial results by breast cancer phenotype and reveal the potential to expand the current knowledge base in this field through the retrospective determination of participant phenotypes that could allow cost-effective individual patient data meta-analyses.

Keywords: metformin; breast cancer; review; clinical trial.

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List of abbreviations and acronyms

AC	adriamycin, cyclophosphamide
AC-T	adriamycin, cyclophosphamide, paclitaxel
AC-TH	doxorubicin/cyclophosphamide/paclitaxel/trastuzumab
AMH	anti-mullerian hormone
ANZCTR	Australian New Zealand Clinical Trials Registry
BC	breast cancer
BCR	breast conservation rate
BMI	body mass index
CBR	clinical benefit rate
CBS	conservative breast surgery
cCr	clinical complete response
CI	confidence interval
CRC	colorectal cancer
CRP	C-reactive protein
CT	chemotherapy treatment
DFS	disease-free survival
DIN	ductal intraepithelial neoplasia
DLT	dose limiting toxicity
DRFS	distant recurrence–free survival
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EC-T	epirubicin/cyclophosphamide/paclitaxel
EC-TH	epirubicin/cyclophosphamide/paclitaxel/trastuzumab
EORTC-QLQ-C30	European Organization for Research and Treatment for Cancer Quality of Life Questionnaire
ER	estrogen receptor
EUCTR	European Union Clinical Trials Register
FBG	fasting blood glucose
FDA	Food and Drug Administration
FDC	fluoruracil, doxorubicin, cyclophosphamide
FMD	fasting-mimicking diet
GLOBOCAN	Global Cancer Observatory
HbA1c	glycated hemoglobin
HC	homocysteine
HER2	human epidermal growth factor receptor 2
HOMA-IR	homeostasis model assessment for insulin resistance
HT	hormonal therapy
IARC	International Agency for Research on Cancer
ICTRP	International Clinical Trials Registry Platform
IDFS	invasive disease–free survival
IGF-1	insulin-like growth factor 1
IGFBP-3	insulin-like growth factor binding protein 3
IPD	individual patient data

IQR	interquartile range
ISRCTN	International Standard Randomised Controlled Trial Number
LIN	lobular intraepithelial neoplasia
LVEF	Left Ventricle Ejection Fraction
MLT	melatonin
MMA	methylmalonic acid
MRI	magnetic ressonance imaging
MTF	metformin
NACT	neoadjuvant chemotherapy
NAST	neoadjuvant systemic therapy
NCIC CTG MA.32	National Cancer Institute of Canada - Clinical Trials Group MA.32
NeoCT	neoadjuvant chemotherapy
NI	not informed
NPLD	non-pegylated liposomal doxorubicin
NSAI	non-steroid aromatase inhibitor
OpenGrey	System for Information on Grey Literature in Europe
ORR	objective response rate
OS	overall survival
PCC	population, concept, and context
PCOS	polycystic ovarian syndrome
pCR	pathological complete response
PD	pharmacodynamic
PFS	progression-free survival
PgR	progesterone receptor
PI	principal investigator
pPR	partial pathological response
PRISMA-ScR	preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews
QoL	quality of life
RFS	recurrence-free survival
RR	response rates
RRR	radiological response rate
SAI	steroid aromatase inhibitor
SAP	statistical analyses plan
SHBG	sex hormone-binding globulin
SNP	single nucleotide polimorphism
T2DM	type 2 diabetes mellitus
TCb-H	docetaxel/carboplatin/ docetaxel/trastuzumab
TCH+P	Taxotere, Carboplatin, Herceptin + Pertuzumab
TEC	docetaxel, epirubicin and cyclophosphomide
TNBC	triple-negative breast cancer
WHO	World Health Organization

Contents

1. Introduction[1]

Breast cancer is the most common cancer worldwide and has a significant impact on the global number of cancer deaths [1]. In December 2020, the International Agency for Research on Cancer (IARC) updated the online database GLOBOCAN (Global Cancer Observatory), which estimated that 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred around the world [2].

According to the agency, female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer in both sexes and all ages [1]. Worldwide, there are over 2.3 million new cases of breast cancer, accounting for 11.7% of all new cancer cases and making up 24.5% of all cancers in women. Continuing with the statistics, lung cancer appeared next at 11.4%, followed by colorectal at 10.0%, prostate at 7.3%, and stomach cancer at 5.6%. Nevertheless, lung cancer remained the leading cause of cancer-related deaths, accounting for an estimated 1.8 million deaths (18%). It was followed by colorectal cancer at 9.4%, liver cancer at 8.3%, stomach cancer at 7.7%, and female breast cancer at 6.9%. In 2020, 685,000 deaths occurred due to breast cancer.

There are predictions for the year 2040 that the burden of breast cancer will increase to over 3 million new cases and 1 million deaths every year due to population growth and aging alone [3]. Therefore, global initiatives are essential to counteract its growing burden, particularly in low and middle-income countries experiencing a rapid increase in incidence rates and persistently high mortality rates.

Breast cancer treatments are expensive and chemotherapy treatments are related to major toxicities. In the USA, the disease has the highest treatment cost of any cancer, accounting for 14% of all cancer treatment costs [4]. In 2020, the cost of medical services for breast cancer was $26.2 billion, with an additional $3.5 billion spent on prescription drugs. Furthermore, chemotherapy is a common treatment for breast cancer and has been shown to improve survival. However, it often leads to adverse effects,

[1] A presente tese de doutorado será utilizada na submissão do manuscrito para apreciação de revisores de revista científica para publicação dos resultados da revisão de escopo. Por essa razão o texto encontra-se em inglês.

including nausea, dysgeusia, peripheral neuropathy, loss of appetite, myalgia, and peripheral edema, which can significantly impact various aspects of quality of life [5]. Due to the high cost and toxicity associated with treatment, less aggressive and more affordable breast cancer treatments are desirable.

Metformin is one of the most common medications used worldwide and has been used for more than 60 years proving its efficacy and safety [6]. It is a synthetic biguanide often prescribed as the drug of choice to treat type 2 diabetes mellitus (T2DM). The usual dose of metformin (0.5–2.5 g daily), administered orally, is effective for long-term glycaemic control, with notable improvements in glycated hemoglobin (HbA1c) [7]. In addition, it is an extremely inexpensive medication, costing about 15 cents per tablet [6]. Nowadays, it is used daily by more than 200 million diabetic patients around the world as monotherapy or in combination with other medications. Nevertheless, the precise mechanisms responsible for its therapeutic benefits are still not fully comprehended [8].

In 2011, the World Health Organization (WHO) recognized the significance of metformin in managing individuals with T2DM globally by adding it to their list of essential medicines, alongside sulfonylureas and insulin [9]. In the United Kingdon, the prescription rate of metformin as antidiabetic drug showed a significant increase, rising from 55.4% in 2000 to 83.6% in 2013, among those who were using at least one medication for managing diabetes [10]. Similarly, metformin use as first-line treatment increased from 60% in 2005 to 77% in 2016 in the USA [11], demonstrating the influence of national and international prescribing guidelines [7].

There are several public health interests in the repurposing of old generic drugs [12]. Repositioning involves the investigation of existing medications for new therapeutic purposes. There is no doubt that it is a unique cheaper strategic way of innovation with some advantages if compared with the long process of developing new drugs from the scratch. Generic drugs have already passed all the phases required by regulatory agencies to be approved for commercialization with their initial indication. They have a well-established pharmacodynamics and pharmacokinetics profile, in addition to a safety profile with well-mapped adverse effects.

It is important to note that in the past decade, additional applications for metformin use have increased. Over the past few years, we now have evidence of

several other beneficial roles of metformin such as preventing diabetes, managing gestational diabetes [13], and treating polycystic ovarian syndrome (PCOS) [14]. Indeed, metformin has shown promising effects against certain types of cancers and are being investigated in several experimental studies including *in vitro* and/or *in vivo* [15], observational studies [16], and interventional trials [17].

The number of RCTs in breast cancer is increasing, but the landscape remains unclear [18]. Breast cancer is a heterogeneous disease with great variation in its morphological and molecular characteristics, as well as in its clinical response treatment. Moreover, different stages of breast cancer are associated with distinct treatment modalities, which are associated with a variety of specific outcomes.

Importantly, a recent systematic review attempted to assess the evidence from RCTs on the effectiveness of metformin in the treatment of breast cancer [17]. However, the study has methodological limitations, was restricted to a limited range of outcomes and did not consider the different phenotypes, stages of breast cancer, or the treatment modalities examined in the original studies. These factors are central to the appropriate interpretation of the effectiveness of any breast cancer treatment.

To date, metformin does not have an established role in breast cancer therapy. However, public health systems can be more efficient by offering the population more benefits to an increasing and mortal disease like breast cancer at a low cost. Given the sources of clinical heterogeneity underlying breast cancer and the many clinical trials conducted or planned to be initiated in this field, a scoping review is needed to show the extent of the unclear landscape. Therefore, our goal in this scoping review was to map the literature on RCTs of metformin for the treatment of breast cancer.

5. Conclusion

In summary, the proposed scoping review illuminated the growing body of evidence from RCTs about metformin in the treatment of breast cancer. We mapped the landscape of existing studies according to phenotypes, staging, treatment modality, types of interventions, comparators, outcomes, and their main findings. Given the clinical heterogeneity underlying breast cancer itself and the current existence of 40 different primary studies in this field, by charting that literature we were able to identify new opportunities for clinical trials and systematic reviews. Specifically, we emphasize the necessity for standardizing the presentation of results from breast cancer clinical trials by phenotype and envision the potential for collaboration among researchers to retrospectively ascertain the phenotypes of breast cancer participants in previous

studies. This could substantially enhance the possibility of conducting better and more cost-effective meta-analyses in this field, including IPD meta-analyses.

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