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ORIGINAL ARTICLE

Systemic arterial hypertension and metabolic profile: a systematic review

Gabriela B Souza[a], Marina Buchpiguel[a], Antonietta B Rossetto[a], Wanderley M Bernardo[b], Luiz A Bortolotto[c], Luca S Tristão[d], Guilherme Tavares[d], Edson G Lo Turco[e], Irineu F D S Massaia[a], José M Aldrighi[f,g]

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[a]Faculdade de Ciências Médicas da Santa Casa de São Paulo, São Paulo, Brasil;

[b]Departamento de Cirurgia Geral, Faculdade de Medicina de São Paulo, São Paulo, Brasil;

[c]Unidade de Hipertensão, Instituto do Coração (InCor), Faculdade de Medicina de São Paulo, São Paulo, Brasil;

[d]Departamento de Medicina Baseada em Evidências, Centro Universitário Lusíada, Santos, Brasil;

[e]Departamento de Cirurgia Urológica, Seção de Reprodução Humana, Universidade Federal de São Paulo, São Paulo, Brasil;

[f]Universidade de Saúde Pública de São Paulo, São Paulo, Brasil;

[g]Departamento de Ginecologia e Obstetrícia, Faculdade de Ciências Médicas da Santa Casa de São Paulo, São Paulo, Brasil.

Corresponding author
gabibsouza@hotmail.com

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ORCID authors:
Gabriela B Souza 0000-0002-0167-9479;
Marina Buchpiguel 0000-0002-9521-7549;
Antonietta B Rosetto 0009-0001-6804-3184;
Wanderley M Bernardo 0000-0002-8597-5207;
Luiz A Bortolotto 0000-0002-4865-6442;
Luca S Tristão 0000-0002-7197-0915;
Guilherme Tavares 0000-0001-6208-3743;
Edson G Lo Turco 0000-0002-3509-847X;
Irineu F D S Massaia 0000-0001-5584-9245;
José M Aldrighi 0000-0002-9521-7549;

Abstract

Introduction: Systemic arterial hypertension (SAH) is a significant cause of morbidity and mortality worldwide. Despite the difficulty in diagnosing SAH in the early stages, the rapid detection and management of SAH are essential in preventing the development of target organ injuries. Newer technologies such as metabolomics have been revealed as promising alternatives for SAH diagnoses.

Objectives: The purpose of this study is to evaluate, through a systematic review, the metabolomic profile of individuals with and without SAH.

Methods: This review followed the PRISMA guidelines on reporting items. It analyses articles selected from the EMBASE and MEDLINE databases that compares metabolites in a hypertensive group with a non-hypertensive group.

Results: The differences that reached statistical significance were a higher prevalence of lipids and lactic acid in the hypertensive group, as well as a reduction in methionine.

Conclusion: Future research should be conducted to establish a possible clinical implication to this metabolite alteration, by linking it to a potential target organ injury for SAH, such as atherosclerosis, renal failure, retinopathy our ventricular hypertrophy.

Keywords: systemic arterial hypertension, high blood pressure, metabolomic, review, systematic review.

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Authors summary

Why was this study done?
Systematic arterial hypertension is a highly prevalent disease, whose early diagnosis can prevent target organs injuries and reduce the morbidity of the disease. Therefore, newer diagnostic techniques have been developed such as metabolomics. The purpose of this study is to evaluate, through a systematic review, the metabolomic profile of individual with and without SAH, evaluating the impact metabolomics on the prevention and early diagnosis of the disease.

What did the researchers do and find?
This study followed the PRISMA guidelines on reporting items. It analyses articles selected from the EMBASE and MEDLINE databases that compares metabolites in a hypertensive group with a non-hypertensive group. The results found a sustained difference in metabolites between the hypertensive group and the non-hypertensive group, especially in relation to lipids, amino acids and lact acid.

What do these findings mean?
The altered metabolites in the group of hypertensive patients corroborate the greater cardiovascular risk found in patients with SAH. Despite this, the metabolic profile still has limitations in understanding the prognosis of the disease since there is no defined association between the metabolites and occurrence of a specific target lesion such as retinopathy, ventricular hypertrophy, atherosclerosis, and renal insufficiency.

Highlights
This systematic review highlights significant differences in the metabolomic profile between a group of patients with SAH and a group of healthy patients. Therefore, the present study seems to corroborate the use of metabolomics as a potential diagnostic tool for SAH, which could mean, soon, early screening for possible target lesions.

INTRODUCTION

Systematic arterial hypertension (SAH) is a major Public Health problem that affects about 30% of the adult population worldwide. Despite all the advances in its treatment, it is still a very prevalent disease in many countries, such as Brazil, in which less than 20% of the patients have the disease controlled1, and more than 22% of the population of its capitals already suffer from this condition[2].

Untreated SAH is one of the main risk factors for cardiovascular disease[3] and is considered the leading cause of death in the world[4]. Thus, it is of great importance to track its prevalence, especially through simple and low-cost methods to identify the condition early.

Brazilian and international guidelines consider as having hypertension every individual with values greater than or equal to 140x90 mmHg, in at least three different moments, always measured by a health professional, in an appropriate environment[5-7].

However, there are situations in clinical daily life that make it difficult to characterize the diagnosis of hypertension, and in those scenarios, it is necessary to perform a more accurate examination to define it. An exam called ambulatory blood pressure monitoring (ABPM) is indicated, which allows the measurement of blood pressure (BP) for 24 hours, including usual activities and sleep, utilizing a light and a small monitor placed at the individual's waist. ABPM is considered an important tool to exclude hypertension called "white coat hypertension" (higher pressure at the clinic, and normal in ABPM), as well as "masked" hypertension (normal pressure at the clinic, and higher in ABPM)[8,9].

Few symptoms are directly attributed to elevated BP, especially in the early stages of the disease10 making it difficult to identify SAH, delaying therapeutic intervention, and increasing the risk of cardiovascular comorbidities[8]. In fact, SAH treatment, introduced in earlier stages, such as in the range of values between 120x80 and 140x90 mmHg, considered by some guidelines as pre-hypertension, may prevent the development of severe target organ injuries and even reduce the risk of dementia[11].

Therefore, the identification of SAH at its earliest stages - when values are not yet higher - is of particular importance and represents a significant challenge to the medical community. Studies with metabolomics have been proving to reveal a promising alternative for early-stage SAH diagnoses once they are not only able to anticipate the diagnosis but also to direct new therapeutic alternatives[9].

Metabolomics consists of the study of the individual metabolite expression and reflects the "chemical signature" of their molecular phenotype. In diseases with an asymptomatic onset, such as SAH, metabolites may already present perceptible alterations in blood, urine, or other fluids well before the appearance of any symptom or clinical sign[12,13].

The identification of metabolites can be done using different techniques, but mass spectrometry (MS) is the most used in metabolomic studies because it is simple, fast, highly sensitive and enables the understanding of pathophysiological and diagnostic mechanisms involved in diseases[12-14]. The advantage of using this method when comparing to gene and protein analysis is that metabolites do not vary between species. By having the same chemical structure, it allows us to use similar methods in different organisms, which could make it a superior tool for research and diagnosis[15].

The purpose of this study is to evaluate, through a systematic review, the metabolomic profile of individuals with and without SAH.

METHODS

Study design

This systematic review followed the PRISMA guidelines on reporting items. A research strategy based on structured questions was adopted, according to the following initials: P - patient; I - intervention; C - control; O – outcome.

Study location and period

The selection of articles was made in the MEDLINE and EMBASE databases by two independent researchers, including articles from 2013 to 2019.

Study population and eligibility criteria

It was included researches with a group of individuals with SAH and a control group, both submitted to blood metabolic analysis. The outcome analyzed was the difference of metabolites between the study and control groups (composed of only normotensive individuals). Animal studies and studies including individuals with secondary hypertension or pre-eclampsia were excluded, as well as intermediate outcomes. There was no restriction on the date of publication of the article, language, or design of the study.

Data collection

The search that was carried out was: (Metabolomic OR Metabolomics OR Metabonomic OR Metabonomics) AND (Blood Pressure, High OR Blood Pressures, High OR High Blood Pressure OR High Blood Pressures OR hypertension OR Essential Hypertension OR Hypertension, Essential).

Initially, the titles of studies and then the summaries were evaluated. In the end, the full texts were analyzed. With this previous selection of articles in both databases, a manual search in the bibliographies of the systematic reviews and meta-analyses found and a gray literature search in the University of São Paulo's (USP) digital library was performed.

After the selection of the articles, data were extracted, which would allow future comparison between studies. The following information was collected: date of publication and author, number of patients and their inclusion and exclusion criteria, metabolic profile analyzed, and outcome. The outcomes sought were upregulation and downregulation of metabolites in individuals with and without SAH.

Data analysis

The data was collected from a series of cases. The risk of bias was calculated using the Checklist described by Joanna Briggs Institute.

Results were descriptive using absolute numbers, averages, percentages, and variations (standard deviation or confidence interval). The confidence level used was 95%.

Ethical and legal aspects of the research

This article does not contain any studies with human and/or animal participants performed by any of the authors.

RESULTS

From the initial search, 1055 articles were obtained in the MEDLINE database and 1703 articles in the EMBASE database. From this total, the replicated studies were excluded, leaving 1704 papers. Then, articles based on titles (n=1653), abstracts (n=24), and complex texts (n=19) were excluded, obtaining 8 articles. Finally, a manual search was made, which resulted in the addition of 2 more studies, with a total of 10 studies included in this systematic review (figure 1). No books or theses were found that could be part of this review.

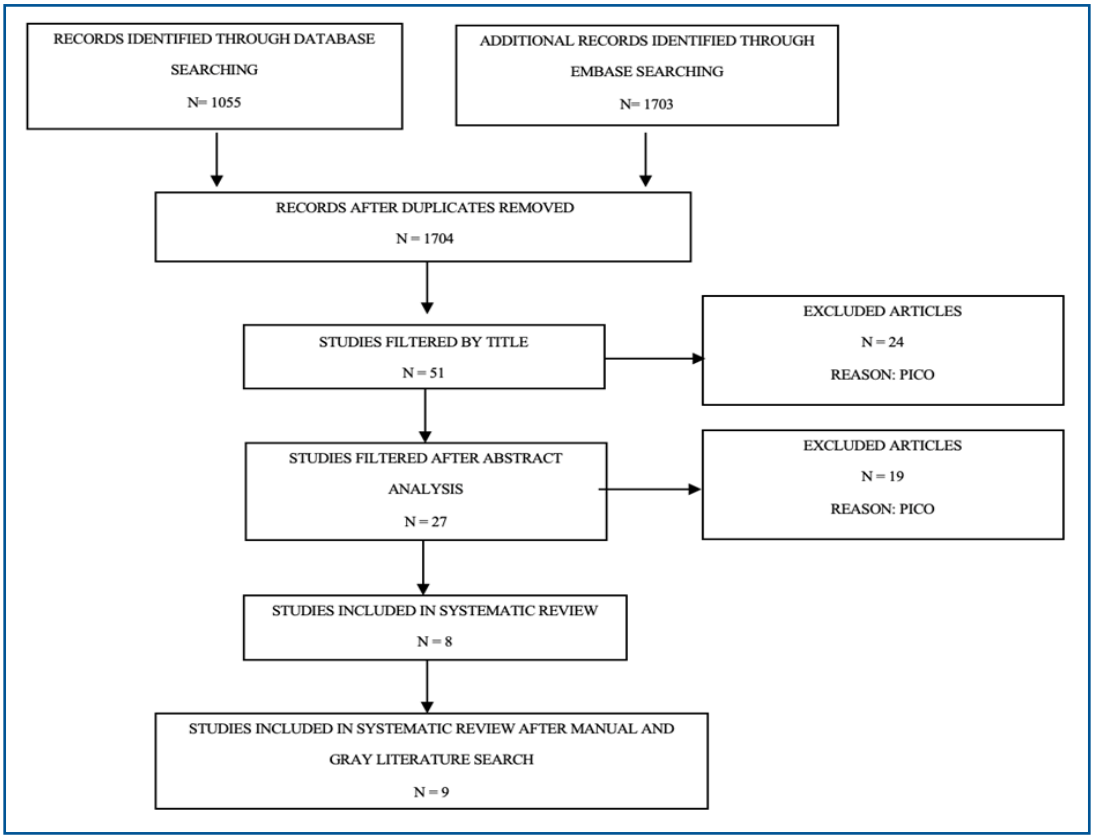

Figure 1: Flowchart for the selection of eligible studies

The bias analysis was done based on the Joanna Briggs questionnaire for case series16 and described in table 1. The overall risk of bias in this review was considered high.

Questionnaire:

1.Were there clear criteria for inclusion in the case series?

2.Was the condition measured in a standard, reliable way for all participants included in the case series?

3.Were valid methods used for the identification of the condition for all participants included in the case series?

4.Did the case series have consecutive inclusion of participants?

5.Did the case series have complete inclusion of participants?

6.Was there clear reporting of the demographics of the participants in the study?

7.Was there clear reporting of clinical information of the participants?

8.Where the outcomes of follow-up results of cases clearly reported?

9.Was there clear reporting of the presenting site(s)/ clinic(s) demographic information?

10. Was statistical analysis appropriate?

With the selected works, the significant metabolites were unified, divided, and analyzed in large groups (table 2):

1.Amino acids and derivatives: amino acids, and monoamine derivatives

2.Lipids and derivatives: lipids, steroids, cholesterol, fatty acids

3.Carbohydrates

4.Organic acids

5.Other

Table 1: Bias analysis based on Joanna Briggs questionnaire for case series. Answers' colors were marked according to the following: Yes (in green), No (in red), Not specified (in purple), and Not Applicable (in blue)

Article	1	2	3	4	5	6	7	8	9	10	Conclusion
Walajko, J M - 2015											High
Zhao, H 2018											High
Bai, Q 2018											High
Ameta, K 2017											Medium
Yang M. - 2016											High
Van Deventer, C.A. – 2015											Medium
Zhong L. - 2014											Medium
Li, Y – 2013											High
Brindle, J – 2002											High

Table 2: Ensemble of metabolites groups found throughout the research, and their outcomes on the studies

METABOLITE GROUPS	SAH	
	Up-Regulation	Down-Regulation
AMINO ACIDS AND THEIR DERIVATIVES	5-aminolevulinic acid, betaine, leucine, phenylalanine, 4-oxoproline, valine, alpha-tyrosine, ornithine, arginine, homocysteine, L-anserine	methionine, glycine, carnitine, arginine, valine, alanine, pyroracemic acid, inosose, p-hydroxyphenylalanine, methylhistidine, meatonine, 3,4-dihydroxyphenylethylenoglycine, 5-hydroxyndoleacetic acid
LIPIDS AND THEIR DERIVATIVES	Cortolone, 11-hydroxyandrosterone, VLDL, LDL, butyric acid, 5-hydroxyhexanoic acid, oleic acid	2-aminoctanoic acid
CARBOHYDRATES	d-glucose	
ORGANIC ACIDS	lathic acid, isovaleric acid, felinylactic acid, fumaric acid	glucuronide carboxylic acid, tricarballylic acid, acetyl-formic acid
OTHERS	sulfoacetaldeide, quinolinic acid, acetone	inositol, pyruvate

It was not possible to group the studies to perform a meta-analysis because the selected articles present different methodologies, selected metabolites, extraction techniques, and analysis methods. Therefore, a descriptive approach was chosen.

The studies were identified by their main author and date of publication. They were described based on the number of patients, metabolomics analyzed, and their outcome (table 3).

Table 3: Study description based on the number of patients, metabolomics analyzed, and their outcome

STUDY	PATIENTS	METABOLITE	OUTCOME
Walajko, J M - 2015	35 patients - 18 control - 17 hypertensive	Sulfoacetaldehyde, 5-aminolevulinic acid, quinolinic acid, 4-oxoproline, L-anserine, leucine, phenylalanine, valine, alpha-hydroxyisobutyric acid	Increase of the following metabolites in the sample with SAH: 5-aminolevulinic acid, sulfoacetaldehyde, betaine, L-leucine, quinolinic acid, phenylalanine, 4-oxoproline, L-anserine; valine
Zhao, H 2018	150 patients - 75 control - 75 hypertensive	5-Hydroxyndoleacetic acid, melatonin, 3,4-dihydroxyphenyl glycerol, 2-aminooctanoic acid, L-methionine, O-tyrosine, cortolone, 11-hydroxyandosterone, butyric acid, 5-hydroxyhexanoic acid	Increase of the following metabolites in the sample with SAH: cortolone, butyric acid, alpha-tyrosine, 5-hydroxyhexanoic acid, 11-hydroxyandrosterone Reduction of the following metabolites in the sample with SAH: melatonin, methionine, 3,4-dihydroxyphenyl ethylene glycol, 5-hydroxyndoleacetic acid, and 2-aminoctanoic acid
Bai, Q 2018	178 patients - 91 control - 87 hypertensive	Olicina, ornithine, carnitine	Increase of the following metabolites in the sample with SAH: ornithine Reduction of the following metabolites in the sample with SAH: glycine, carnitine
Ameta, K 2017	123 patients - 59 control - 64 hypertensive	Alanine, arginine, methionine, pyruvate, adenine, uracil	Increase of the following metabolites in the sample with SAH: arginine, homocysteine Reduction of the following metabolites in the sample with SAH: methionine, alanine, pyruvate
Yang M. - 2016	128 patients - 15 control - 113 hypertensive	Citrulline, D(+)galactose, glycine, frutose, L-tyrosine, oleic acid, myo-inositol, ureia, L-phenylanine, L-threonine, L(+)latic acid, L-valine, L-leucine, L-proline, betaine, palmitic acid, stearic acid, a-tocopherol, beta-sitoseterol, l-tryptophan, DL-glyceraldehyde, glycolic acid, eicosanoic acid, hexanoic acid, heptanoic acid, nanoic acid, sucrose, sorbitol, cellobiose, isoleucine, alanine, citric acid, azelaic acid, aspartic acid, 4-hydroxybenzoic acid, pimelic acid, L-serine, hypoxanthine, d-homoserine, uric acid, trimethylamine oxide, pentanedioic acid, allantoin, linoleic acid, oxaloacetic acid, sorbose, and alpha-ketoglutaric acid.	Increase of the following metabolites in the sample with SAH: oleic acid Reduction of the following metabolites in the sample with SAH: myoinosito

Continuation - Table 3: Study description based on the number of patients, metabolomics analyzed, and their outcome

STUDY	PATIENTS	METABOLITE	OUTCOME
Van Deventer, C.A. – 2015	25 patients - 13 control - 12 hypertensive	3-OH-sebacic acid; hesperetin, hexenoylcarnitine, fumaric acid, 2-OH-isovalerate, methylguanosine, N-acetylarylamine, 4-OH-phenylactate, quinurenic acid, phenylglyloxylate, methyluric acid, indole carboxylide glucuronide, tricarbalilic acid, lactic acid, dimethyluacil, trimethyl-L-lysine	Increase of the following metabolites in the sample with SAH: lactic acid, fumaric, 4-OH-phenylactic and 2-OH-isovaleric acid.
Zhong L. - 2014	265 patients - 99 control - 157 hypertensive	valine, alanine, pyroracemic acid, inose, p-hydroxyphenylanine, lactic acid, acetone, methylistidine. (does not describe all)	Increase of the following metabolites in the sample with SAH: lactic acid, acetone, VLDL and LDL Reduction of the following metabolites in the sample with SAH: valine, alanine, pyroracemic acid, p-hydroxyphenylanine inose, methylhistidine
Li, Y – 2013	86 patients - 22 control - 64 hypertensive	betaine, mevalonic acid, corticosterone, beta-leucine, propionic acid, methionine, D-glycose, glycine, tyrosine, malic acid	Increase of the following metabolites in the sample with SAH: D-glucose
Brindle, J – 2002	64 patients - 28 regular - 36 hypertensive / borderline high blood pressure	alpha-glycose, beta-glycose, lactate, glucose, glycerol, choline, lipids, alanine, valine, HDL, VLDL, LDL	Increase of the following metabolites in the sample with SAH: lipid components

The analysis of 35 patients identified the relative increase of the following metabolites in hypertensive individuals (n=17), when compared to normal individuals (n=18): 5-aminolevulinic acid, sulfoacetaldehyde, betaine, L-leucine, quinolinic acid, phenylalanine, 4-oxoproline, L-anserine; valine[17]. A second study involving 150 individuals, 75 of them hypertensive (systolic MAP: 139.95±10.09; Diastolic MAP: 89.92±7.54) and 75 normotensive individuals, found increased cortolone, butyric acid, alpha-tyrosine, 5-hydroxyhexanoic acid, 11-hydroxyandrosterone, and decreased melatonin, methionine, 3.4- dihydroxyphenylethyleneglycol, 5-hydroxindoleacetic acid, and 2-aminoctanoic acid in the hypertensive group compared to the control group18.

A Chinese study of 178 individuals revealed that the group of hypertensive patients (n=87; Systolic MAP: 182.39 ± 16.27; Diastolic MAP: 108.62 ± 11.83) exhibited abnormal amino acid metabolism when compared to the group of healthy individuals (n=91), presenting high levels of ornithine and low levels of glycine and carnitine[19]. Another investigation, when analyzing 123 patients (64 with SAH and 59 healthy individuals) found an increase in arginine and homocysteine and a decrease in methionine, alanine, and pyruvate in the metabolic pattern of hypertensive patients, compared to the normotensive group. However, it was not possible to obtain information on the statistical significance of these differences[20].

In a 2016 study, 128 patients were recruited, being 113 hypertensive individuals (Systolic MAP: 145.1 ± 9.28; Diastolic MAP: 88.35 ± 7.92) and 15 control patients without SAH. The results showed significant differences in the concentrations of oleic acid (higher values in individuals with SAH) and myoinositol (lower values in individuals with SAH)21 In another article, 13 normotensive individuals were compared with 12 individuals with SAH, the latter presenting higher concentrations of lactic acid, fumaric acid, 4-OH-phenylacetic acid, and 2-OH-isovaleric acid[22].

In a previous analysis carried out in 2014, it had already been found that patients with SAH (n=157) exhibited fewer amino acids (valine, alanine, pyroracemic acid, inososep-hydroxyphenylalanine, methylistidine) and more lactic acid, acetone, VLDL, and LDL than normotensive individuals (n=99)[23]. Unlike in another study that compared 22 healthy individuals with 64 hypertensive individuals with Ying and Yang deficiency syndrome, D-glucose was higher in hypertensive groups compared to the control group[24].

Finally, a study analyzing alpha-glucose, beta-glucose, lactate, glucose, glycerol, choline, lipids, alanine, valine, HDL, VLDL, LDL from normotensive (N-28), borderline (N=19), and hypertensive (N=17) patients noted that serum from the borderline and with HBP was similar and exhibited more lipid components[25].

DISCUSSION

The studies analyzed in this review show a high prevalence of lipids and their derivatives in the hypertensive

group when compared to healthy individuals. Several studies have already reported, even before the clinical finding of high blood pressure, that cholesterol represents an important biomarker of primary hypertension, as they have noted significant metabolic changes involving cholesterol, not only in hypertensive individuals but also in their children[26-28].

In addition, studies have shown that these metabolic changes in lipids express not only increased serum cholesterol concentrations but also saturated fatty acids; therefore, they are considered as a prognostic factor in hypertensive individuals, as they are also associated with coronary disease, diabetes mellitus, and a thrombotic risk[29,30].

In the present review, another interesting result was that the studies were able to identify a metabolic profile characterized by an increase in lactic acid in hypertensive individuals, possibly resulting not only from poor tissue perfusion, due to peripheral vasoconstriction (common in hypertension), but also by the use of anaerobic metabolic pathways that occur in the cells of the vascular smooth muscle, due to the high energy demand needed to maintain constant vasoconstriction[31].

Studies have also shown that in hypertension there is a reduction in methionine, an essential amino acid in protein synthesis and that has homocysteine as one of its intermediates. These low concentrations of methionine stimulate a greater conversion to homocysteine and this increase is associated with cardiovascular disease due to endothelial damage, reduced arterial elasticity, and greater local oxidative stress[32].

Regarding the metabolic pattern involving proteins and their derivatives (amino acids, dipeptides, and monoamine derivatives) the present review found that these were the substances that were most altered in studies involving hypertensive patients, both by upregulation and downregulation.

Lastly, the limitations of this review include the scarcity of published articles (which made it difficult to make a broad and detailed comparison), the small sample sizes, and the types of cross-sectional studies (which made it difficult to apply and extrapolate the results to the hypertensive population in general). Also, the failure to evaluate clinical outcomes and social demographic characteristic such as age, ethnicity, sex and comorbities associated with variations in metabolites found in hypertension, made it impossible to characterize a metabolic profile in the prognosis of the disease. Another limitation is the inclusion of targeted metabolomics studies, which can introduce bias into the systematic review and impact on the overall conclusions.

CONCLUSION

In conclusion, even though, significant differences in metabolic profiles were observed between normotensive individuals and those with SAH, it was not possible to establish a clinical significance for these findings, since no study associated the metabolic profile observed in the hypertensive group with a worse prognosis.

Future research should be conducted to evaluate a possible clinical/prognostic relationship of these altered metabolites in groups of individuals with SAH, without significant clinical impairment, and another with SAH, but with target organ damage, such as ventricular hypertrophy, atherosclerosis, renal failure, and retinopathy.

Author Contributions

GBS, MB, WMB, LST, GT and JMA conceived and designed research. GBS, MB and ABR conducted data analysis and research on EMBASE and MEDLINE database. WMB, EGLT, LST and GT contributed on analytical tools. GBS, MB, ABR, EGLT, IFDSM and JMA wrote the manuscript. All authors read and approved the manuscript.

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Conflicts of Interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Resumo

Introdução: a hipertensão arterial sistêmica (HAS) é uma causa significativa de morbidade e mortalidade em todo o mundo. Apesar da dificuldade de diagnóstico da HAS em estágios iniciais, a rápida detecção e manejo da HAS são essenciais na prevenção do desenvolvimento de lesões em órgãos-alvo. Tecnologias mais recentes, como a metabolômica, têm se revelado alternativas promissoras para o diagnóstico de HAS.

Objetivos: o objetivo deste estudo é avaliar, por meio de uma revisão sistemática, o perfil metabolômico de pacientes com e sem HAS.

Método: esta revisão seguiu as diretrizes PRISMA. Foram analisados artigos, selecionados nas bases de dados EMBASE e MEDLINE, que comparavam metabólitos entre um grupo de pacientes hipertensos e um grupo não hipertenso.

Resultados: as diferenças dos metabólitos que alcançaram significância estatística foram: a maior prevalência de lipídios e ácido lático no grupo hipertenso, bem como a redução de metionina neste mesmo grupo.

Conclusão: novas pesquisas devem ser realizadas para estabelecer qual a implicação clínica desta alteração metabólica, relacionando-a uma potencial lesão de órgão-alvo como a aterosclerose, a insuficiência renal, a retinopatia ou a hipertrofia ventricular.

Palavras-chave: hipertensão arterial sistêmica, metabolômica, revisão, revisão sistemática.

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