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Review

Ketogenic Diet in the Management of Glioblastomas: A Bibliometric Analysis

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Abstract: Glioblastoma is a highly aggressive brain tumor that has a poor prognosis despite various treatments like surgery, chemotherapy, and irradiation. However, a restricted ketogenic diet (RKD), which has been proven to be effective in treating drug-resistant epilepsy, could be a potential adjunct in the treatment of certain GBM cases. Our study aimed to highlight the existing knowledge, identify collaboration networks, and emphasize the ongoing research based on highly cited studies. During the literature search, we found 119 relevant articles written between 2010 and 2023. Among the top 20 most cited articles, there were seven laboratory and five clinical studies. The works of Olson LK, Chang HT, Schwartz KA, and Nikolai M from the Michigan State University, followed by Seyfried TN and Mukherjee P from Boston College, and Olieman JF, and Catsman-Berrevoets CE from the University Medical Center of Rotterdam, were significant contributions. The laboratory studies showed that RKD had a significant antitumor effect and could prolong survival in mouse glioblastoma models. The clinical studies verified the tolerability, efficacy, and safety of RKD in patients with GBM, but raised concerns about whether it could be used as a single therapy. The current research interest is focused on the efficacy of using RKD as an adjunct in selected chemotherapy regimens and demonstrates that it could provide GBM patients with better treatment options.

Keywords: bibliometrics; glioblastoma; ketogenic diet; treatment; feasibility; efficacy; tolerability

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1. Introduction

Glioblastoma multiforme (GBM) is one of the most aggressive primary brain neoplasms, accounting for 14.5% of all neoplastic brain lesions and 48% of all CNS malignancies [1,2]. According to the World Health Organization (WHO), GBM can be further subdivided into isocitrate dehydrogenase (IDH) wild-type, which is the most common, and IDH mutant [3]. The reported incidence ranges from 0.76/100,000/year to 4.8/100,000/year, depending on the age, sex, and origin of the population studied [1]. According to the Central Brain Tumor Registry of the United States, GBM incidence peaks in the 75–84 age group [1,2]. Several genetic (mutations in the ATRX, TERT, TP53, B-TAF V600E, GATA4, FGFR1, EGFR, and MGMT genes) and acquired risk factors (tobacco smoking, nitrosamines, head trauma, ionizing radiation, obesity, and excessive alcohol consumption) have been mentioned in the relevant literature with wide variations [1]. The standard treatment for GBM includes surgical resection supplemented by radiotherapy and temozolomide chemotherapy [4,5]. In recent years, non-conventional therapies have been gaining attention as standard treatments often provide poor prognosis. One such treatment is Boron neutron capture therapy (BNCT), which is a novel radiotherapy used for brain and head and neck tumors. BNCT uses boron-10 to target malignant cells when irradiated with neutrons, while sparing normal tissues [6]. This reduced irradiation to healthy tissues allows for potential reirradiation of recurrent tumors. Studies by Kawabata et al. and Chen et al. have shown that BNCT could be a viable option for prolonging overall survival

in recurrent GBM [7,8]. A critical review of 21 studies from 13 countries showed that the treatment of GBM is costly, reaching up to 204,284 $ per patient, despite the considerable variation in the treatment delivered [9]. However, a review by Grochans et al. showed that the prognosis of GBM remains poor regardless of the treatment given, with reported 5-year survival rates ranging from 3.3% to 10.1% [1,2,10,11].

On the other hand, a restricted ketogenic diet (RKD) may offer an effective and safe treatment adjunct in patients with GBM [12–21]. Its use is based on the concept that brain cancer is partly a metabolic disorder, which could be controlled by depriving cancer cells of essential metabolic substrates, such as glucose and glutamine [12–21]. This metabolic effect is achieved by decreasing the intake of calories and carbohydrates while increasing the relative proportion of lipids in the diet [12–21]. Evidence from in vitro studies shows that a RKD has an anti-angiogenic, anti-invasive, anti-inflammatory effect on GBM cells [12–21]. A recent systematic review showed that the mean overall survival was 15.3 months using adjunct RKD, with significant improvement in the quality of life in 44% of the studies [13]. A review based on Bayesian models showed a prolongation of the mean survival time ranging between 30 and 70% [22]. The major side effects of RKD were weight loss, constipation, fatigue, and poor diet adherence [13,14]. It has been observed that the ketogenic diet holds potential as a promising therapeutic intervention not only for GBM patients, but also for other solid tumors. This is because most tumors exhibit metabolic characteristics that include increased glucose uptake and dependence on glycolysis. Current preclinical studies are underway to investigate the effects of the ketogenic diet on tumor progression and survival in cases of lung, prostate, pancreatic, and breast cancers, among others. Notably, the ketogenic diet has shown promise in various aspects of daily life as well as in medical cases, such as managing patients with drug-resistant epilepsy, Alzheimer's disease, Parkinson's disease, motor neuron disease, multiple sclerosis, and migraine. Therefore, the ketogenic diet may prove to be a valuable tool for managing these conditions [17,18,23,24].

Several systematic reviews summarized the evidence in the literature for the efficacy and safety of the RKD in GBM patients [12–21]. However, no study has provided a knowledge map using high-impact articles. Our current study aimed to carry out a bibliometric analysis of articles on the use of the RKD in GBM treatment to describe (1) the background knowledge, (2) identify the current research front, (3) visualize cooperation networks between experts in the field, and (4) construct a historiography overview map. This study is relevant to healthcare professionals who specialize in GBM management, such as neurosurgeons, neurologists, oncologists, dieticians, oncology nurses, and policymakers. Our current manuscript offers a wealth of valuable information for those seeking specialized training in a particular field, as well as those interested in research collaboration and publication. In addition, the manuscript is designed to provide readers with a comprehensive understanding of the subject matter at hand. We believe that anyone interested in furthering their knowledge in this area will find our manuscript to be a valuable resource. However, its primary importance lies in its potential to benefit GBM patients. Given the lack of a universally effective treatment protocol, any safe intervention that could improve the efficacy and safety of treatment would be immensely valuable.

2. Materials and Methods

2.1. Study Design

We conducted a bibliometric analysis according to the workflow recommended for science mapping by M. Aria and C. Cuccurullo, which included three stages [25]. In the first stage, we carried out a literature search, while in the second step, we described the gathered evidence using descriptive and inferential statistics, as described below in greater detail. In the third and final stage, we summarized the findings from our search's 20 most cited documents, providing a historiographic overview. Since the current study included input data from a literature database and involved no patients, it was exempted from Institutional Review Board (IRB) approval and patient informed consent.

2.2. Literature Search

In the present study, a comprehensive search was performed using the "Web of Science" database to retrieve all relevant articles regarding RKD and GBM management. Key terms like "keto diet", "high-fat low carbohydrate", or "ketogenic diet" along with "glioblastoma" or "high-grade glioma", and the Boolean operators "AND" and "OR" were applied in our search algorithm. Inclusion criteria were met in publications that were relevant to our subject. No exclusion criteria were applied. In January 2024, the data were acquired and meticulously reviewed to extract pertinent information. The search string of our study in the Web of Science is depicted in Table 1. Lastly, we exported all gathered articles' full records and cited references in the BibTeX format.

Table 1. Search string of our study in the Web of Science.

https://www.webofscience.com/wos/woscc/summary/9c5ac2ac-0b72-42c3-9931-b23b7ad4b4e5-b89a8e8e/relevance/1 (accessed on 5 January 2024)

2.3. Bibliometric Analysis

We conducted the bibliometric analysis using the statistical environment R, the biblioshiny interphase (package bibliometrix), and the analysis from the online platform of the Web of Science Core Collection [25]. We identified the background knowledge regarding the most cited documents and hosting journals, authors, their affiliations, and keywords. The publication density per author was estimated based on Lotka's law [26]. The core journals publishing on RKD and GBM were identified using Bradford's law [27]. Both Lotka's and Bradford's laws are extensions of the well-known Pareto's law in bibliometrics [26]. We identified potential cooperation networks from the co-author affiliations. Trend topics were identified by plotting the logarithmic keyword frequency and the cumulative keyword occurrence over time. Furthermore, we plotted the historiographic network based on the citations.

3. Results

3.1. Literature Search

The gathered 119 records were published in 70 books and journals and included 4647 citations (Table 2). Several types of documents existed among these records, including 61 original studies, 35 reviews, and 17 meeting abstracts. Altogether, 568 authors participated in the manuscript writing, with an average of six authors per document. A total of 269 author keywords described the content of the relevant documents. All articles were written between 2010 and 2023.

Table 2. Basic information regarding the literature search that was performed.

Main Information about	Description	Results
Data		
	Timespan	2010:2023
	Sources (Journals, Books, etc)	70
	Documents	119
	Average years from publication	5.66
	Average citations per document	36.85
	Average citations per year per doc	4.26
	References	4647
Document types		
	Article	60

Table 2. *Cont.*

Main Information about	Description	Results
	Article; early access	1
	Correction	2
	Editorial material	2
	Letter	2
	Meeting abstract	17
	Review	35
Document contents		
	Keywords Plus	424
	Author's Keywords	269
Authors		
	Authors	568
	Author Appearances	714
	Authors of single-authored documents	1
	Authors of multi-authored documents	567
Author collaboration		
	Single-authored documents	1
	Documents per Author	0.21
	Co-Authors per Documents	6
	Collaboration Index	4.81

3.2. Background Knowledge

Table 3 shows the top 20 most cited documents reporting on the usage of RKD in the management of GBM. The study by Tennant et al. in Nature Review Cancers achieved the highest impact in the field with 863 citations, followed by the study by Abdelwahab et al. in Plos One with 183 citations, and Haar et al. in Neurochemistry Research with 183 citations [28–30]. It is worth noting that there were only five clinical studies among the top 20 most cited articles [31–35]. On the contrary, there were seven laboratory studies [21,29,36–40] and an equal number of reviews [17,19,28,30,41–43].

Table 3. The 20 most cited articles regarding glioblastoma (GBM) and restricted ketogenic diet (RTD).

Paper	Year	Study Design	Journal	Total Citations	Total Citations per Year
Tennant DA et al. [28]	2010	Review	Nature Review Cancers	863	57,533
Abdelwahab MG et al. [29]	2012	Laboratory study	Plos One	186	14,308
Haar CP et al. [30]	2012	Mini review	Neurochem Res	183	14,077
Rieger J et al. [31]	2014	Case series (N = 20)	Int J Oncol	179	16,273
Zuccoli G et al. [44]	2010	Case report	Nutr Metab	171	11.4
Champ CE et al. [32]	2014	Case series (N = 6)	J Neuro-Oncol	138	12,545
Seyfried TN et al. [19]	2015	Mini review	Cancer Lett	128	12.8
Poff AM et al. [36]	2014	Laboratory study	Int J Cancer	125	11,364
Vidali S ET et al. [17]	2015	Review	Int J Biochem Cell Biol	115	11.5

Table 3. *Cont.*

Paper	Year	Study Design	Journal	Total Citations	Total Citations per Year
Lussier DM et al. [37]	2016	Laboratory study	Bmc Cancer	99	11
Schwartz L et al. [41]	2017	Review	Semin Cancer Biol	95	11,875
Woolf EC et al. [38]	2015	Laboratory study	Plos One	75	7.5
Woolf EC et al. [42]	2016	Review	Front Molec Neurosci	74	8222
Martuscello RT et al. [39]	2016	Laboratory study	Clin Cancer Res	71	7889
Mukherjee P et al. [45]	2019	Laboratory study	Commun Biol	67	11,167
Chang HT et al. [33]	2013	Case series (N = 22)	Nutr Metab	67	5583
Tan-Shalaby Jl et al. [34]	2016	Case series (N = 17)	Nutr Metab	63	7
De Feyter HM et al. [40]	2016	Laboratory study	Euro-Oncology	63	7
Feichtinger RG et al. [31]	2014	Case series (N = 25)	Glia	62	5636
Landis CJ et al. [43]	2018	Review	Biochim Biophys Acta-Rev Cancer	61	8714

Regarding the most common author keywords, and after excluding the search keywords, "ketogenic diet", "glioblastoma", "glioma", "glioblastoma multiforme", the terms "metabolism", "Walburg effect", "glucose", "glycolysis", and "metabolic therapy" were most frequently used with more than five occurrences (Figure 1).

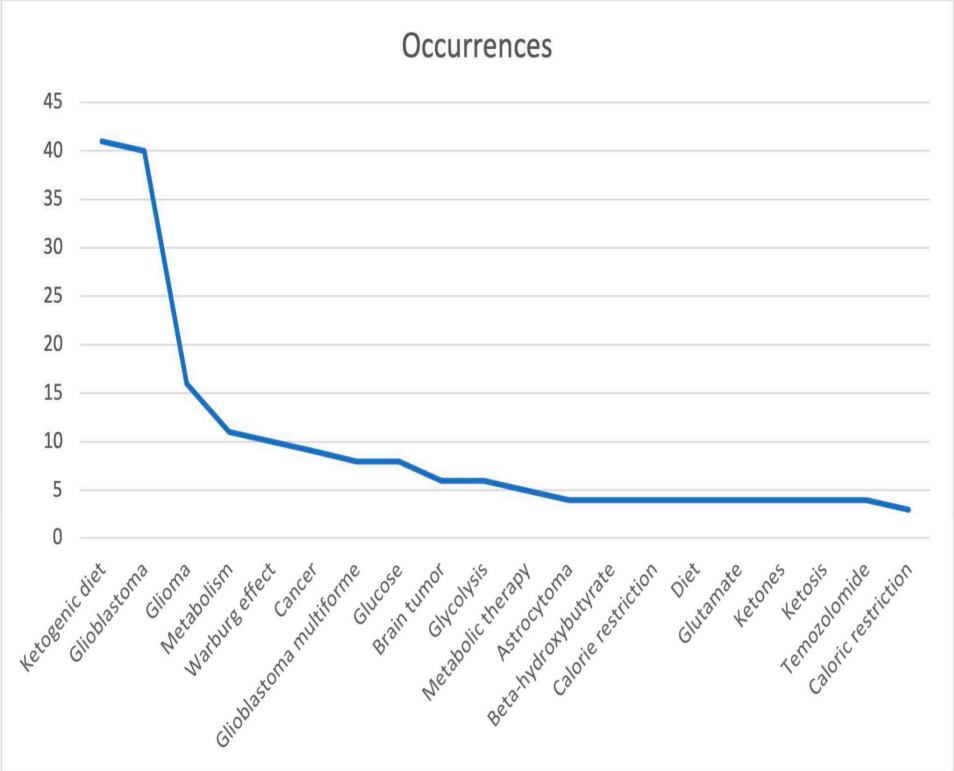

Figure 1. The most common keywords in the studies regarding glioblastoma (GBM) and restricted ketogenic diet (RTD).

The articles were mostly funded by the National Institutes of Health (N = 13) and the United States Department of Health and Human Services (N = 13), followed by the

Boston College Research Expense Fund (N = 6), CrossFit Incorporation (N = 5), and the Foundation of Metabolic Cancer Therapies (N = 5). The results are shown in Figure 2.

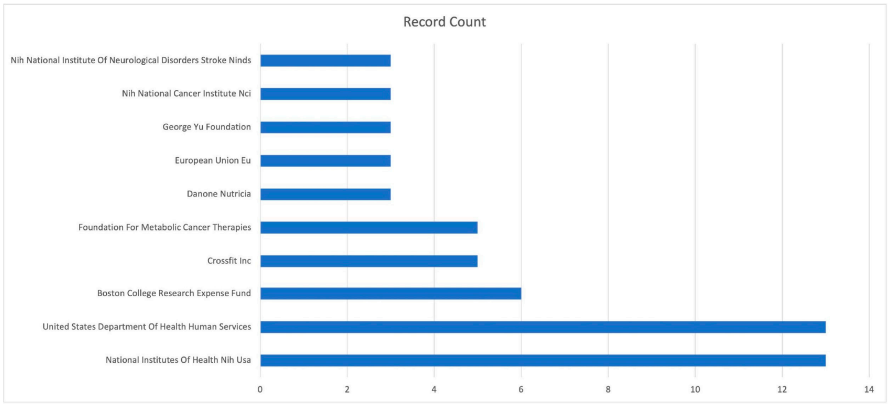

Figure 2. The most common sources of funding for articles regarding glioblastoma and restricted ketogenic diet.

The contribution of Michigan State University was most significant with the works of Olson LK, Chang HT, Schwartz KA, Noel M and Nikolai M, followed by the Boston College (Seyfried TN and Mukherjee P) and the University Medical Center of Rotterdam (Olieman JF, and Catsman-Berrevoets CE). The results are shown in Figures 3 and 4. Figure 5 shows the top authors' contributions to the literature over time. Seyfried TN, Mukherjee P, and Zuccoli G. were among the pioneers in the field with continuous contributions throughout the years. Ten percent of the authors were involved in at least two articles (Figure 6).

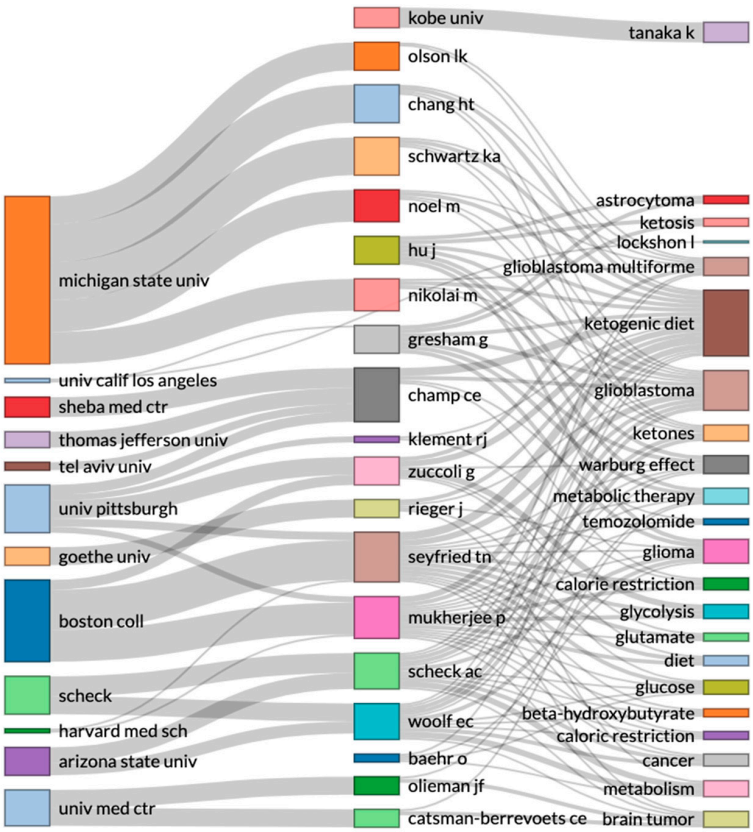

Figure 3. A Sankey three-field diagram associating the most impactful institutions, the contributing authors, and the authors' keywords. This figure highlights the involvement of universities of high impact and their researchers in various fields related to using the ketogenic diet in GBM management.

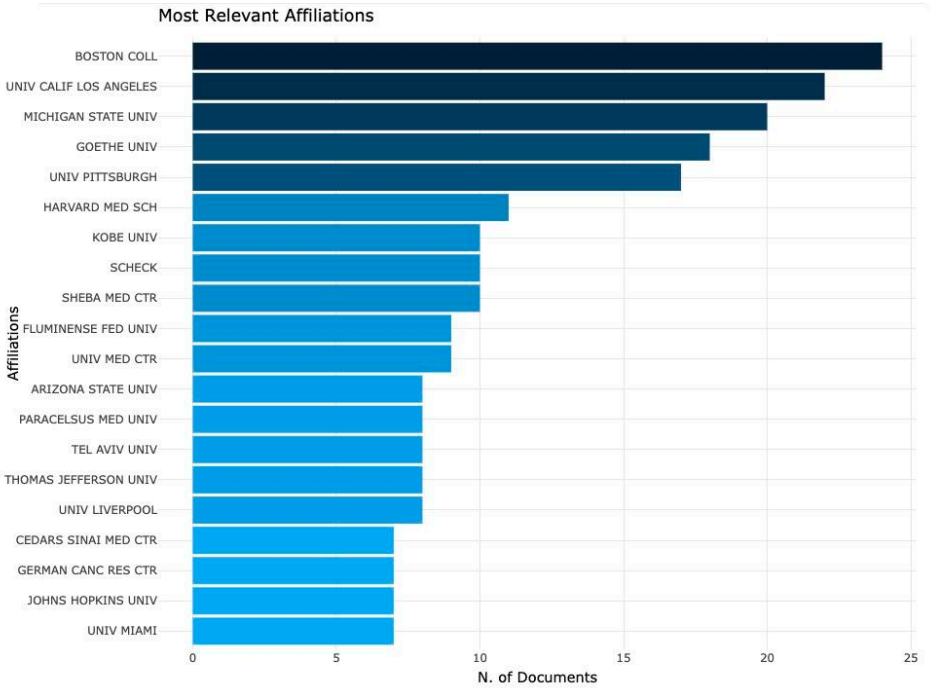

Figure 4. A bar plot showing the most impactful institutions involved in the research on using a restricted ketogenic diet in glioblastoma management.

Figure 5. Top author's contribution regarding glioblastoma and restricted ketogenic diet throughout the years.

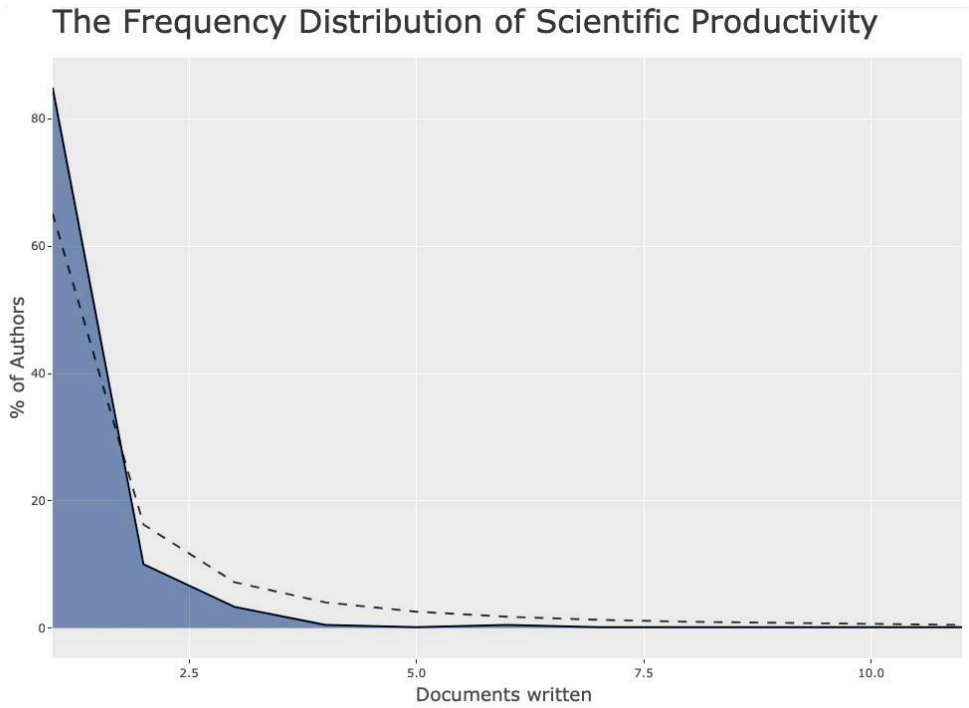

Figure 6. A line diagram showing the publication density of authors in the field of glioblastoma and restricted ketogenic diet, according to Lotka's law.

The top 20 sources are depicted in Figure 7. According to Bradford's law, Neuro-oncology, the Frontiers in Nutrition, the Journal of Neuro-oncology, Cancers, Nutrition and Metabolism, International Journal of Oncology, and Neurochemical Research published the bulk of the relevant literature (Figure 8).

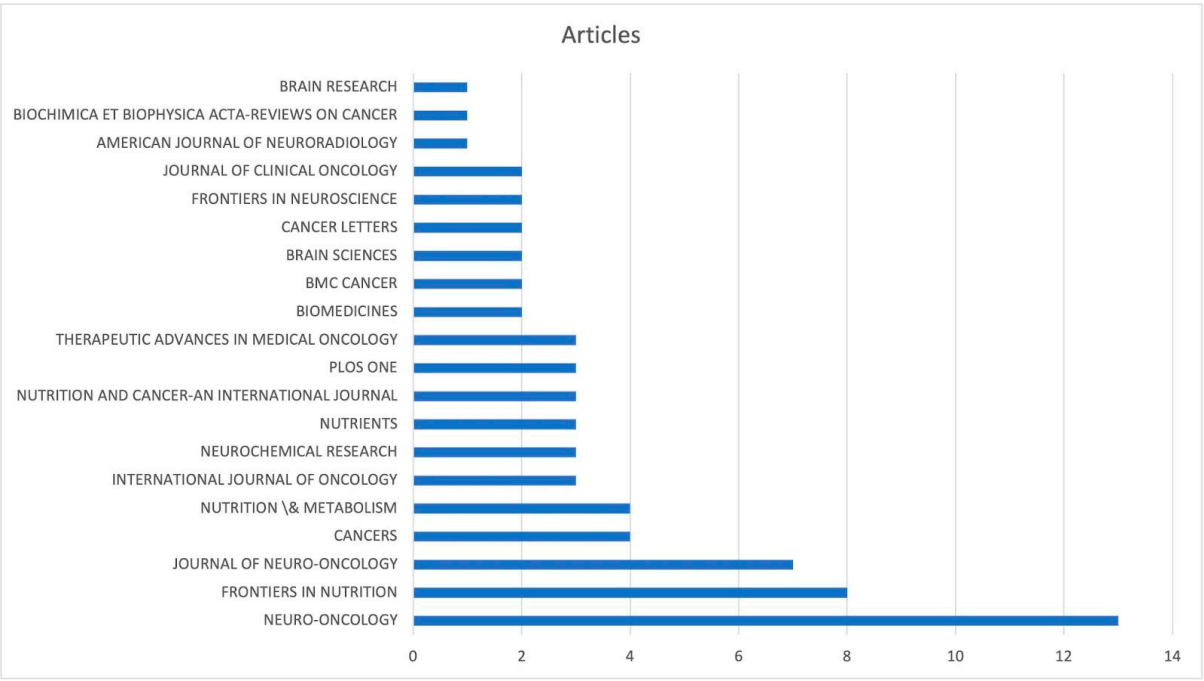

Figure 7. A bar plot showing the 20 most influential scientific journals in the field of GBM and RTD.

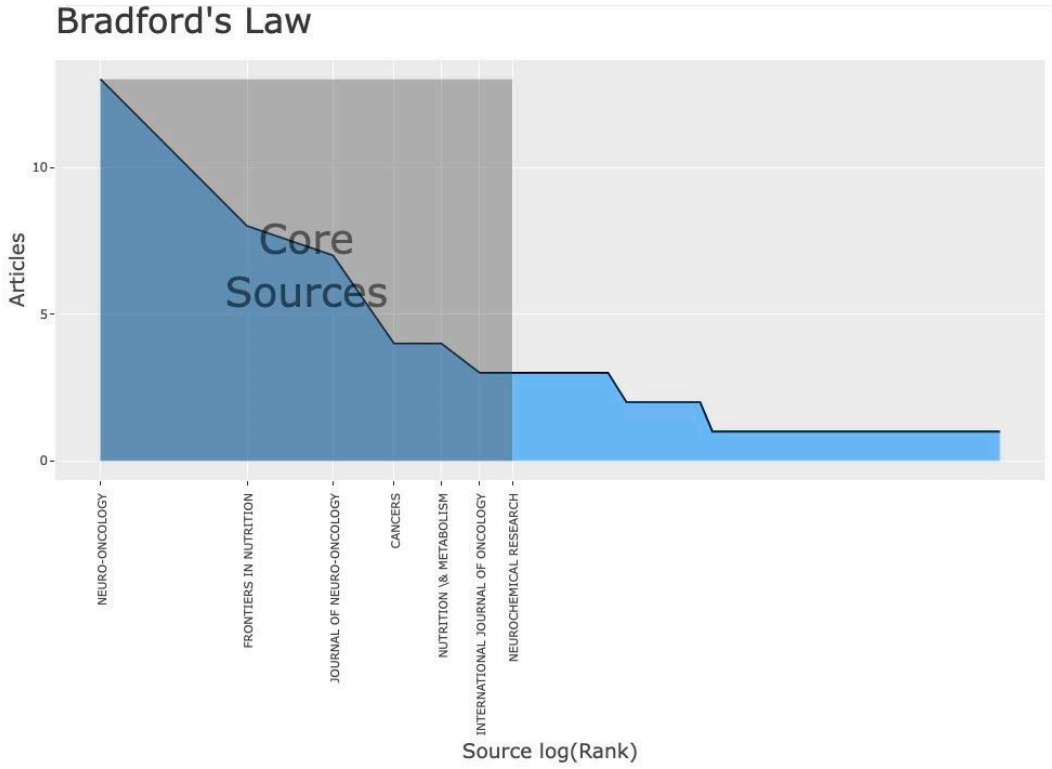

Figure 8. A line diagram identifying the core sources according to Bradford's law.

3.3. Cooperations

As shown in Figure 9, there are several cooperation networks between the United States and Europe, and to a lesser extent with countries from South America. Figure 10 shows two small cooperation networks with at least six members. The first cooperation is between the University of Pittsburg (USA), Boston College (USA), the Semmelveis University (Hungary), the University of Zulia (Venezuela), the Leopoldina Hospital Schweinfurt (Germany), and the University of Florida (USA). The second network is between the Thomas Jefferson University (USA), the Dukes University (USA), the Sheba Medical Center (Israel), and the Tel-Aviv University (Israel).

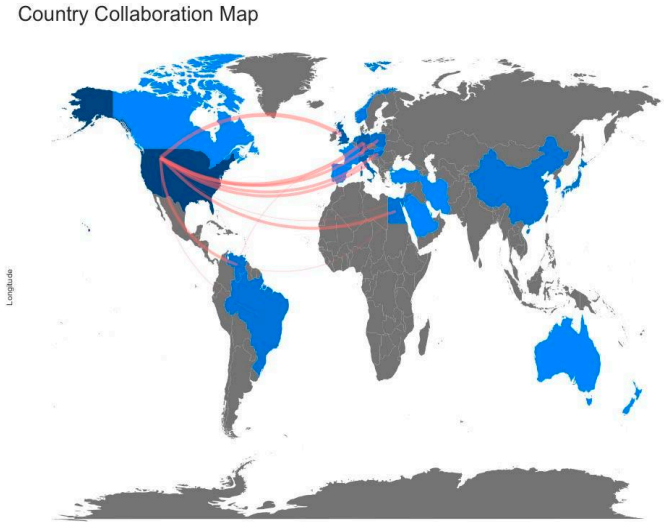

Figure 9. The reader may track the global interest in restricted ketogenic diet and glioblastoma from a world map visualizing international cooperation research networks.

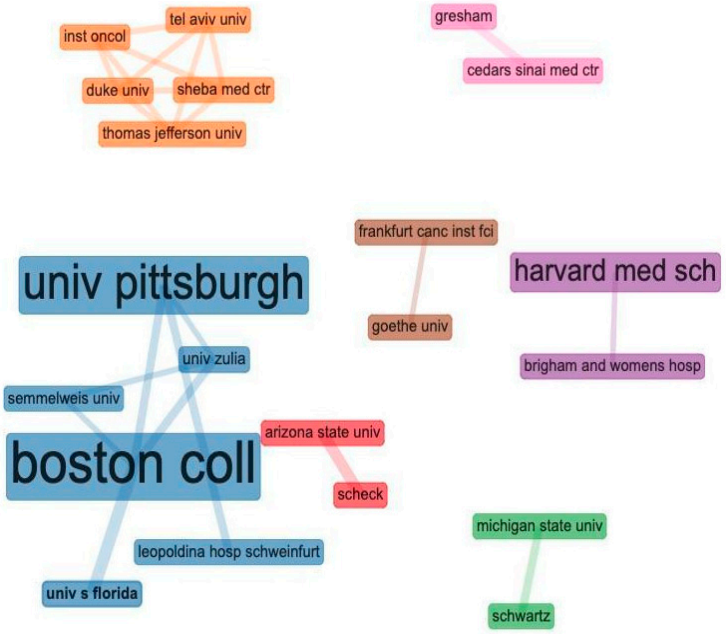

Figure 10. We identified two medium-sized cooperation networks focusing on the implementation of restricted ketogenic diet and glioblastoma, involving the United States and Europe.

3.4. Research Front

The current research interest has shifted from more general terms such as "cancer cells", "tumors", and 'glioblastoma multiforme" in 2010 to more focused keywords, including "ketogenic diet", "chemotherapy", "radiotherapy", and "temozolomide". The research is led by Gresham G. and Hu J., along with Kant S and Kesarawi P. (Figure 11). Finally, it seems that the journals of Cancers and Nutrition and Metabolism show a rising interest in the field of RKD and GBM (Figure 12).

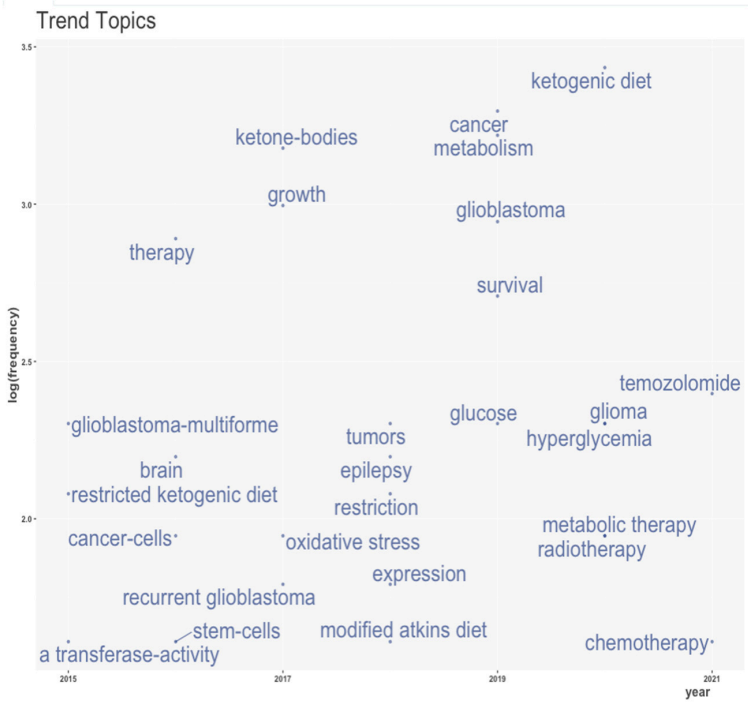

Figure 11. A word trend map showing the shift from more general to more focused keywords throughout the years.

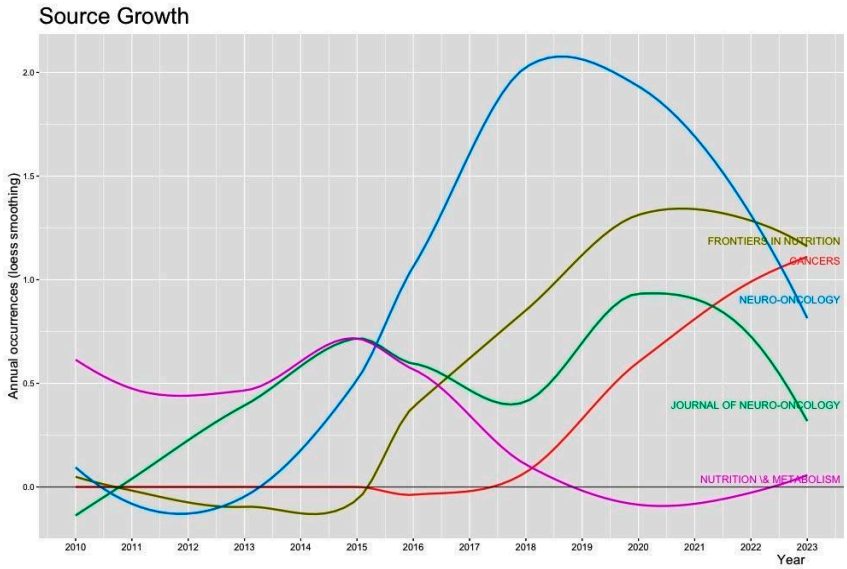

Figure 12. A timeline graph showing the trends in journal interest in publishing research articles focusing on GBM and RTD throughout the years.

3.5. Historical Overview

In 2010, Tennant et al. published a review on the general concept that cancer cells manifest an altered metabolic phenotype, which is partially driven by important signaling pathways, such as PI3K and mTOR, transcription factors, and the hypoxia-inducible factor [28]. These changes lead to a hypermetabolic state with an overuse of glucose which could be used as potential targets for future drugs [28]. The same year, Zuccoli et al. reported the case of a 65-year-old patient suffering from a confirmed GBM, which was successfully treated with subtotal resection and an RKD [44].

In 2012, Abdelwahad et al. published a laboratory study confirming that an RKD significantly enhances the antitumor effect of radiation in malignant glioma mouse models, in terms of survival and recurrence when compared to the standard diet [29]. The results were verified by another laboratory study from Poff et al., who found that mice receiving the RKD outlived mice with other diets [36]. The authors attributed their results to the fact that ketone administration manifested anticancer effects, independent of glucose levels or calorie restriction [36].

Between 2013 and 2014, four clinical studies were published. Chang et al. studied the expression of ketolytic and glycolytic enzymes involved in 22 brain biopsies with high-grade gliomas [33]. The authors reported the downregulation of the mitochondrial enzymes OXCT1 and BDH1 coupled with the overexpression of the glycolytic enzymes HK2 and PKM2, concluding that high-grade gliomas express a different metabolic profile to normal cells [33]. Likewise, Feicthinger et al. reported that the enzymatic activity of citrate synthase and oxidative phosphorylation complexes decreased with increasing grade in astrocytic neoplasms [35]. Champ et al. studied the feasibility and safety of RKD in patients with GBM undergoing chemotherapy [32]. Their study showed that the adjunct RKD was well tolerated without any major toxicities [32] The ERGO trial focused on the feasibility and efficacy of the RKD in 20 patients with recurrent GBM [31]. Once again, the authors reported that an RKD could be well tolerated, but with questionable efficacy, particularly if used as a monotherapy [31]. A couple of years later, Tan-Shalaby et al. recruited 17 patients with cancer and studied the safety and efficacy of a modified Atkins diet as a monotherapy [34]. The authors found that their quality of life was preserved, despite the apparent weight loss, and without any disturbances in their laboratory findings [34].

In the following years, five laboratory studies were added [37–40,45]. Woolf et al. reported that an RKD alters the expression of proteins involved in the disease progression in a mouse glioma model [38]. In addition, Lussier et al. postulated that the antitumor

effects of RKD in mice could be attributed to the tumor-reactive immune responses [37], while Martuscello showed that low glucose and high ketone levels inhibit glioma cell proliferation in vitro [39]. However, it was De Feyter et al. who, in contrast to the existing knowledge, supported that rat gliomas could oxidize ketone bodies with an upregulation of ketone body transport when fed a ketogenic diet [40]. Only recently, Mukherjee et al. reported that an RKD combined with a glutamine antagonist killed glioblastoma cells while reversing symptomatology and improving survival [45]. Figure 13 visualizes the historical network based on the retrieved citations.

Figure 13. The historical overview of authors publishing in the field of GBM and RTD based on citation networks based on bibliometric principles [19,29,32,33,35–42,44,45].

4. Discussion

Our ongoing inquiry presents a thorough survey of the academic literature concerning the function of a ketogenic diet (RKD) in managing glioblastoma (GBM). It is apparent that the emergence of the significance of an RKD in this particular context is relatively recent, with the evidence suggesting its emergence around the year 2010. Since then, there has been a burgeoning interest in this area of study, resulting in the publication of approximately one thousand academic papers. Notably, authors affiliated with institutions such as Michigan State University and Boston College have made noteworthy contributions to the literature, often collaborating with researchers from Europe and South America.

A number of diligent research endeavors have resulted in the publication of several noteworthy articles in esteemed academic journals, including Neuro-oncology, Frontiers in Nutrition, and Nutrients. These publications have garnered significant attention and recognition for the potential of an RKD as a promising therapeutic approach for GBM. The vast body of published research encompasses a broad spectrum of studies, ranging from laboratory investigations to clinical trials. Collectively, these studies present compelling evidence attesting to the antitumor effects of the use of the RKD in GBM treatment, and have demonstrated a notable extension of survival for affected patients.

The standard of care in GBM management includes surgical resection, chemotherapy, and irradiation [4,5]. Tumor Treating Field therapy, targeted therapy, immunotherapy, and BNCT constitute other promising GBM therapies [46–49]. The research in the field of GBM therapy is gradually moving towards identifying and selecting patients with specific genetic profiles who are likely to benefit from RKD therapy (Figure 14). In addition, there is now an increasing emphasis on developing customized treatment protocols that are tailored to individual patient needs. With the refinement of patient selection criteria and treatment strategies, researchers aim to optimize the therapeutic efficacy of RKD in the

management of GBM. This, in turn, is expected to improve patient outcomes and enhance their quality of life.

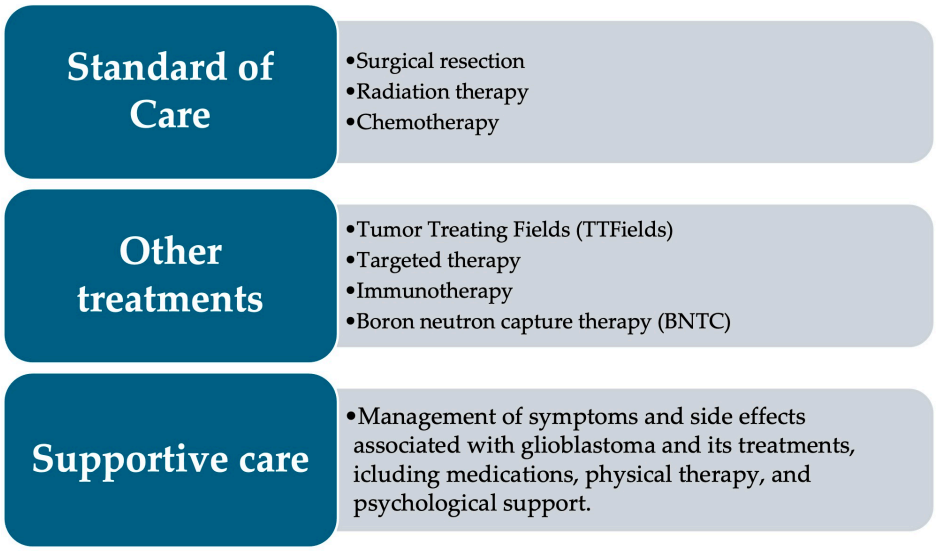

Figure 14. Overview of currently available treatment options in the management of GBM.

Notably, seven (35%) of the twenty most frequently cited articles were literature reviews. It is noteworthy that a considerable number of reviews have been published regarding the use of the ketogenic diet in various medical fields, including oncology and the treatment of glioblastoma (GBM). This indicates the potential role of the ketogenic diet in managing GBM and highlights the enthusiasm surrounding this approach. These reviews may serve as a basis for future original studies in the field of GBM management and beyond. The original concept of using the ketogenic diet in several clinical entities has resulted in broadening the scope of research in this area, with review studies examining its possible applications in diverse medical fields. Moreover, our bibliometric analysis entailed comprehensive and inclusive eligibility criteria to achieve a higher sensitivity in identifying new concepts, ideas, and trends surrounding the application of ketogenic diet in GBM. It is important to note that trends and concepts are not limited to original studies, but rather encompass any document, regardless of publication type. Additionally, we acknowledge the significant impact that high-quality review papers and meeting abstracts can have on our understanding of this subject matter, and therefore, these sources were considered in our analysis.

The most frequently cited article, which reached 863 citations, was a literature review by Tennant et al. published in 2010 [28]. The authors investigated the changes in the metabolism of cancer cells and postulated that they offer potential targets for new cancer therapies [28]. Another mini-review by Haar et al. with 183 citations summarized the main mechanisms of drug resistance, including drug efflux, hypoxic areas of tumor cells, cancer stem cells, DNA damage repair, and miRNAs [30]. In five different reviews (Seyfried et al., Schwartz et al., Woolf et al., and Landis et al.), the authors provided an excellent overview of the reasons for the metabolic disease in GBM known as the Warburg effect, the role of an RKD as a potential metabolic therapy, and the underlying pathogenetic mechanisms [12,19,41–43]. Figure 15 summarizes the mechanisms associated with the beneficial effect of the ketogenic diet in managing GBM.

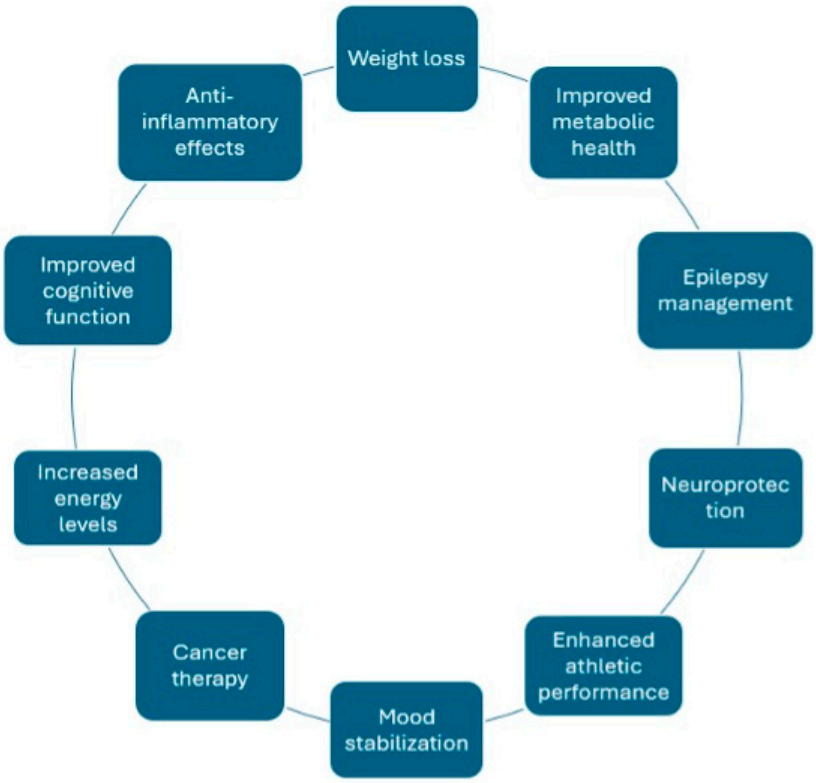

Figure 15. Overview of mechanisms associated with the beneficial effect of the ketogenic diet in managing GBM.

The study of the use of RKD for GBM treatment is not without obstacles. First, an RKD cannot be used as a sole treatment, but rather as an adjunct. Rieger et al. reported that the RKD is ineffective in the treatment of malignant melanoma alone [31]. In addition, serious ethical concerns may exist about using the RKD as a sole treatment. The second major obstacle in the implementation of the RKD regimen as an adjunct therapy for GBM is patient tolerance and dietary compliance, as highlighted in a recent study [31]. Patients undergoing this regimen may experience persistent feelings of hunger and various minor side effects such as fatigue, weight loss, and gastrointestinal disturbances including diarrhea or constipation. These challenges require a high level of motivation and commitment from patients to sustain adherence to the RKD regimen over prolonged periods. The failure to maintain dietary compliance can potentially compromise the effectiveness of the RKD as an adjunct therapy for GBM [31]. Therefore, it is imperative to address these challenges to ensure the optimal benefits of the RKD regimen for GBM patients [31]. Equally important is the fact that there is great heterogeneity in the so-called RKD, with large variations in total calories and the relative proportion of proteins, lipids and carbohydrates [29,34,39,50]. This heterogeneity precludes a direct comparison of the results of different studies. Furthermore, there is no gold standard diet to which the RKD could be compared [29,34,39,50]. Therefore, there is considerable heterogeneity in the comparators used in the published studies [29,34,39,50]. In addition, the analysis of add-on treatments such as the RKD is quite complex and requires studies with large patient populations.

Future studies should standardize the relative proportions of proteins, lipids, and carbohydrates in brain cancer patients as well as total calorie requirements. It may also be necessary to modify existing protocols, such as the Enhanced Recovery After Surgery (ERAS) protocol, accordingly. Once this is achieved, ready-to-eat meals could be labelled to allow for more individualized nutrition. On the other hand, the role of multidisciplinary teams cannot be overstated. Clearly, a dietitian is required to tailor the diet to the patient's needs and the targeted metabolic therapy. Similarly, a psychologist and family members can improve adherence to the diet despite the minor adverse effects. Another area of

research needs to address the efficacy of the RKD in the different subtypes of GBM. GBM is not a uniform disease and has differences in genotypic profile, response to treatment, and survival [14].

Limitations

The current bibliometric study is characterized by some important limitations. Firstly, due to the inherent limitations of the available software for bibliometric analysis, only a single database was searched. We preferred to use the Web of Science since it provides the largest volume of exportable metadata. Secondly, the literature search yielded a small number of studies. Thirdly, important studies without citations could be disregarded and poor-quality studies with a high number of citations could be over-emphasized. Finally, there are no established guidelines for reporting bibliometric studies. Therefore, the current manuscript was written as dictated by the aims of our study.

5. Conclusions

The use of the restricted ketogenic diet (RKD) in the management of GBM has emerged as a new and increasingly important topic in the field of neuro-oncology. Collaborative efforts between researchers from Michigan State University and Boston College, in conjunction with their European and South American counterparts, have led to several high-impact publications (Q1) in prominent journals such as Neuro-oncology, Frontiers in Nutrition, and Nutrients. Preclinical studies have demonstrated the antitumor properties of the RKD, while clinical studies have confirmed its good tolerability, its efficacy in prolonging survival, and the absence of major side effects. Ongoing research is geared towards identifying specific patient subgroups with tailored genetic profiles and customized treatment protocols. Taken together, these findings suggest that the RKD, in combination with standard care, could present a promising new therapeutic avenue for GBM patients, with more encouraging outcomes than existing treatments.

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