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Wilhelm Brünings' forgotten contribution to the metabolic treatment of cancer utilizing hypoglycemia and a very low carbohydrate (ketogenic) diet

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ABSTRACT

The growing interest in the alterations of tumor cell metabolism and their possible therapeutic exploitation also spurred new complementary and integrative approaches such as treating patients with a ketogenic diet (KD). KDs aim at inhibiting glycolytic tumor metabolism and growth, and have therefore been proposed as adjuncts not only to standard-of-care, but also to other therapies targeting tumor metabolism. Here I describe the life and forgotten work of one of the earliest researchers who realized the importance of altered tumor cell metabolism and its possible exploitation through metabolic modifications: Wilhelm Brünings. Brünings was a German natural scientist and physician famous for his innovative contributions to the fields of physiology and otorhinolaryngology. Based on the findings of Otto Warburg and his physiological reasoning he started to experiment with insulin administration and KDs in his patients with head and neck cancers, aiming to maximally lower blood glucose concentrations. He obtained encouraging short-term results, although most tumors became refractory to treatment after several weeks. His pioneering work is worth revisiting, especially for an international readership that may be unaware of his efforts, as hypoglycemic treatments, including the use of insulin injections and KDs, are currently being re-investigated as complementary and integrative cancer treatments.

1. Introduction

There is an increasing interest in the connection between metabolism and cancer and its potential for therapeutic interventions.[1–4] Among these are several approaches targeting the glucose metabolism of tumors such as the application of ketogenic diets (KDs) to cancer patients. KDs are very low carbohydrate, high fat diets that mimic certain characteristics of fasting, in particular through reduction of plasma insulin with an accompanying elevation of the ketone bodies acetoacetate and β-hydroxybutyrate. The state of nutritional ketosis in adults is typically characterized by concentrations of β-hydroxybutyrate in the range 0.5–3 mmol/l[5] and glucose in the range 85–95 mg/dl.[6] However, with concurrent calorie restriction much lower blood glucose concentrations (55–80 mg/dl[7]) can be achieved, resulting in a higher ketone-to-glucose ratio. This may be desirable for an optimal chance of disease management,[1] although in some animal models unrestricted KDs led to tumor growth retardation without lowering blood glucose levels.[8,9]

First clinical pilot studies on the KD and cancer have been conducted,[7,10–14] and several others are planned or currently running.[15–17] These studies are based on mainly three rationales.[18] First, KDs have been shown to be capable of slowing down tumor growth in many, although not all, animal models.[18,19] Second, the replacement of carbohydrates with fat that is characteristic for a KD is supposed to account for the increased fat oxidation rates in cancer patients that are due to tumor-induced insulin resistance, in this way possibly protecting against skeletal muscle loss.[20–22] Third, KDs are expected to sensitize tumor cells to radio- and chemotherapy, principally opening up a very broad range of applications as complementary cancer treatments. This at least partly relates to their ability to impair tumor cell glycolysis, reducing ATP levels and the ability to utilize substrates of glycolytic metabolism for protection against reactive oxygen species.[23–25]

From a historical point of view it is interesting that the major

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discoveries underlying the above rationales for KDs in cancer treatment were made approximately 100 years ago. Otto Warburg and coworkers performed systematic investigations of the high rates of fermentation of glucose to lactate in tumor versus normal tissues in the 1920s.[26–28] This is nowadays referred to as the Warburg effect and routinely employed via FDG-PET (2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography) imaging for clinical tumor assessment. While first preclinical studies into the effect of different forms of diet or macronutrient manipulation on cancer growth have roughly paralleled the early studies on cancer and metabolism,[29–31] the first clinical application of a KD to cancer patients is usually assumed to be much more recent, and usually attributed to Kenneth Fearon and co-workers who described the administration of a medium chain triglyceride-rich KD to five cachectic cancer patients in 1988.[32] Others mention the case study of two pediatric brain tumor patients by Nebeling et al.[33,34] from 1995 as the first clinical KD study (for example Hyde et al.,[35] Poff et al.[36] or we ourselves in our 2011 review[22]). Nevertheless, as I describe in the remainder of this paper, both assumptions are not correct: The first clinical study which included the description of a KD to treat cancer patients was published in 1941 by Wilhelm Brünings, a scientist and physician whose obituary has its 80th anniversary this year. His forgotten experiments are worth re-discovery and review for the international cancer and metabolism research community.

2. A brief review on the life and achievements of Wilhelm Brünings

Wilhelm Brünings was born on January 31st 1876 in Kustedt near Stade, Germany. He studied natural sciences, philosophy and medicine in Tubingen and later in Erlangen where he received his PhD in physics, chemistry and zoology in 1899. Afterwards, he turned to clinical research in Berlin and Tubingen, where he received his medical doctorate in 1901. After a round-the-world trip as a ship's doctor, Brunings joined the department of physiology at the university of Zurich, Switzerland, where he published several papers on electrophysiology[37–40] and instrumentation[41] and habilitated in 1904. His shift towards otorhinolaryngology was made when external reasons led him to Freiburg where he became the assistant of the famous laryngologist Gustav Kilian and earned the *venia legendi* for this field in 1908.[42] After World War I in which he served as a military doctor he became full professor and head of the university department for otorhinolaryngology first in Greifswald (1917), then Jena (1926) and finally Munich (1930).

Contemporaries described Brünings as an excellent lecturer, teacher, scientist, physician and mechanic.[42,43] His deep knowledge of the natural sciences combined with great technical and manual skills would have allowed him an efficient and unusually multidimensional way to approach and solve scientific problems. Indeed, his research spanned a diverse range of topics including cell electricity, X-ray diagnostics, radium treatment for cancer and, most importantly, instrumentation. Brünings' endoscopic instruments became world-famous and developed widespread utilization.[44] Among all these diverse activities, his passion was active patient care. When the Prussian Ministry of Culture offered Brünings his own Kaiser-Wilhelm research institute in Berlin after he had given a lecture on electroacoustic methods for treating amblyacousia, he declined because he preferred to continue treatment of patients.[42]

Until his death on October 3rd 1958 Brünings remained in Munich where he was full professor of otorhinolaryngology until his retirement in 1950 (Fig. 1).

It is against this background that we are going to examine Brünings' *Beiträge zum Krebsproblem* ("contributions to the cancer problem", Fig. 2), which include what is likely the first detailed description of a very low carb (ketogenic) diet to treat cancer patients – almost half of a century prior to the clinical study of Fearon et al.[32] that is usually cited as the first KD study on cancer patients.

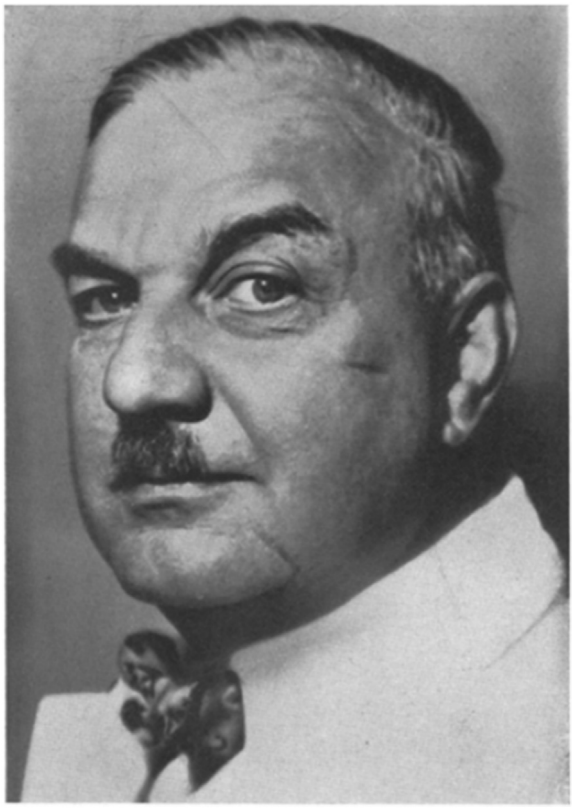

Fig. 1. Wilhelm Brünings as shown in a laudatory article by A. Greifenstein on the occasion of his 60th birthday celebration which was published in the journal *Archiv für Ohren-, Nasen-und Kehlkopfheilkunde* (now the *European Archives of Oto-Rhino-Laryngology*).[42]

3. Brünings' ketogenic diet studies

In the years 1941 and 1942, Brünings published two reports and a separate conclusion paper in the journal *Münchener Medizinische Wochenschrift* describing his experimental treatment of head and neck cancer patients in his Munich clinic by using insulin together with a KD in order to maximally lower blood glucose levels.[45–47] Having spent years studying parallels in the age-dependency, incidence rates and heritability among diabetes, hypertension and cancer, he developed a working hypothesis that there would likely also be a commonality concerning the etiology of these diseases. Combined with Warburg's findings this commonality would strongly implicate a disturbance of carbohydrate metabolism as a general factor necessary for cancer development. In the first report, titled "*Ueber eine diätetisch-hormonale Beeinflussung des Krebses*" ("On a dietetic-hormonal manipulation of cancer"), Brünings first described the case of a diabetic patient with a maxillary tumor who was referred to dietetic and insulin therapy for several weeks prior to planned surgery. During surgery, Brünings was completely surprised to find that large parts of the tumor had regressed and the remainder transformed into a viscous-elastic tissue.[45] This observation prompted him to quickly initiate some experiments that he had apparently planned for a long time, yet was reluctant to start due to the circumstances of the war:

Münchener
Medizinische Wochenschrift

Münch. med. Wschr.

Nr. 5. 31. Januar 1941 Schriftleitung: Dr. Hans Spatz und Dr. V. E. Mertens, Alfonsstraße 1
Unter Mitarbeit der Herren Albrecht, Magnus, Stepp und Straub
Verlag: J. F. Lehmann, Paul-Heyse-Straße 26
88. Jahrgang

Aufsätze und Vorträge

Aus der Universitätsklinik und Poliklinik für Hals-Nasen-Ohrenkranke in München
(Vorstand: Prof. Dr. med. et phil. Brüninga)

Beiträge zum Krebsproblem

Von W. Brüninga

1. Mitteilung:
Ueber eine diätetisch-hormonale Beeinflussung des Krebses

Ausgangspunkt neuen Fortschrittes sein in dem Kampfe, der zu einem resignierten Stellungskrieg zu werden droht.

Fig. 2. An excerpt from Brünings' first report.[45]

Die Versuche begannen zunächst mit Normalkost bei vorsichtig steigenden Insulindosen. In einer zweiten Reihe wurde lediglich Kh.-freie Ernährung ohne Insulin versucht. Es folgte eine Kh.-arme Diät (ca. 50 g oder 4 WBE Kohlehydrat) mit Steigerung des Insulins bis zur Toleranzgrenze und schließlich, als schärfste Form der Zuckerentziehung, eine praktisch kohlehydratfreie Ernährung mit gleichzeitig maximalen Insulingaben. Eine Beschreibung der ersten drei Behandlungsformen, ihrer Wirkungen und Ergebnisse ist unnötig, da ich mich schon nach kurzer Zeit auf die letzte, schärfste Form beschränkt habe, die sich als die wirksamste erwies.[45, p. 119]

(The experiments began with a normal diet and carefully increasing doses of insulin. In a second trial only a carbohydrate-free diet without insulin was tried. Subsequently, a low carbohydrate diet with increasing insulin doses until the tolerance limit and finally, as the strictest form of glucose deprivation, a practically carbohydrate-free diet with maximally tolerable doses of insulin was applied. A description of the results of the first three trials is unnecessary since after a short time of experimentation, I decided to restrict the trials to the strictest form which turned out to be the most effective)

Depot insulin was administered three times daily (at 7 a.m., 2 and 9 p.m.) by a nurse, starting with 0.3 cm^3 per injection and increasing by 0.1 cm^3 daily until signs of hypoglycemia appeared at which point the dose would be maintained. This usually occurred up to the fourth day.

Concerning the diet and its feasibility, Brünings wrote

Auch hat meine erfindungsreiche Küchenleiterin es verstanden, den Kranken aus Fleisch, Wurst, Fisch, Eiern, Fetten, Käse, Quark, Kh.-armen Koch-und Rohgemüsen, Sauerfrüchten, Nüssen, Sionon usw. eine abwechslungsreiche Kost herzustellen, gegen deren monatelange Verabreichung sich keiner von ihnen gesträubt hat.[45, p.119]

(My inventive kitchen leader figured out how to create a varied diet out of meat, sausages, fish, eggs, fat, cheese, curd, low-carbohydrate cooked, raw and fermented vegetables, nuts, Sionon[a] etc. that none of the patients was reluctant to eat for several months.)[b]

Brünings pointed out the importance of consuming large amounts of vegetables as a source of fiber and protection against acidosis. The diet was supplemented with twice-weekly vitamin C injections and two drops of vitamin D oil daily (with the argument that patients would have to stay in their rooms during the low-light winter). He also pointed out that he and his staff had never seen a subjective or objective deterioration of any patient caused by the combined insulin and "carbohydrate-free" diet treatment that he referred to as *Entzuckerungsmethode* ("de-glycation method").

His first report presents 14 cases with no further curative treatment options and tumors that could easily be measured by eye. Of these, 6 (43%) achieved a moderate remission, 7 (50%) an extensive remission and 1 (7%) a macroscopic complete remission.[45] In addition, there was a general improvement in the physical and psychological conditions of the patients as early as 8–10 days after therapy initiation. However, while the rate of remission appeared to peak at about 2–3 weeks, there also was a rebound effect after 2–3 months of which Brünings was apparently very disappointed. He was neither able to explain the fast regression nor the late-onset regrowth, but his observations allowed him to rule out several theories. In particular, he mentioned that:

Die naheliegende, primitive Vorstellung, daß der Krebs zu seinem Wachstum „Zucker braucht" und durch dessen Entziehung „ausgehungert werden kann", erwies sich von vornherein als unzureichend.[45, p. 122]

(The obvious, primitive belief that cancer "needs glucose" for its growth and can be "starved" through its deprivation turned out as insufficient right from the beginning.)

He was also able to conclude that neither insulin nor the KD alone could be responsible for the observed effects – only their combination was sufficient for efficacy.

His second report *"Klinische Anwendungen der diätetisch-hormonalen Krebsbeeinflussung ('Entzuckerungsmethode')"*[46] contained more practical details on the insulin dosing and diet.[c] Brünings was

[a] Sionon was the trade name for D-sorbitol.[111]

[b] This diet was estimated to contain <50 g carbohydrates and about 100 g fat and 200 g protein per day, although it seems that Brünings counted meat, sausages and eggs simply as "protein".

[c] Concerning beverages, it is interesting that Brünings wrote that no coffee or tea (which would be allowed) were available in Bavaria, but beer was. He cautioned against allowing beer which despite its "war dilution" with water still had too many carbohydrates.

eager to emphasize that even though the circumstances of the war made the provision of adequate foods difficult, one should not make compromises in the diet concerning its carbohydrate limitation and caloric adequacy – it would be better to limit the number of applications of the method. The second report contained another 30 cases of patients with various tumors that Brünings sampled from a larger collective of roughly 100 cases he had treated. The increased sample size had also increased the variance in the observed effects, with a larger percentage of tumors being refractory to the treatment. This, together with the rebound effect in those tumors that had responded, had apparently shifted Brünings' focus from a potentially curative intent to the general management of clinical symptoms that – contrary to the response of the tumor – had shown improvements in every single patient within a few days. Therefore, Brünings concluded his reports with the following suggestions for using his de-glycation method[47]:

1. Prior to surgery in order to improve post-surgery prognosis.
2. As a means to diagnose occult cancer based on the positive response of a patients' general condition to the insulin and KD treatment – known as *diagnosis ex juvantibus*.[d]
3. As palliative treatment of desperate cancer cases.
4. As a supportive treatment during radiotherapy or to make a patient eligible for radiotherapy in the first place.[e]

The suggested treatment duration was 5–7 days for the applications 1 and 2 and up to 14 days for the applications 3 and 4. Finally, given the simplicity of the approach, Brünings closed with the proposition to adopt his method for general clinical usage and further research.[47]

4. Discussion

The above summary shows that the idea to alter cancer patients' metabolism through a very low carbohydrate (ketogenic) diet is much older than usually acknowledged. The aim of this review was to reveal, 80 years after his death, Brünings' forgotten ingenious and original experiments to an international audience, especially given the recent renewed interest in metabolic therapies against cancer.[1,3,4]

A list of relevant KD studies published in peer-reviewed journals is given in Table 1, and Fig. 3 shows their chronological appearance relating to Brünings' publications.[7,10–14,32,34,48–65] It took almost half a century after Brünings' first publication until what is generally considered the first clinical study treating cancer patients with a KD was published (Fearon et al. 1988[32]), and 70 years until the publication of a study with a comparable number of cancer patients (Schmidt et al. 2011[50]). While Brünings' diet was based on whole foods with an emphasis on vegetables and animal products, the studies that followed were apparently influenced by the application of KDs against epileptic seizures where such diets typically consisted "*predominantly of heavy cream and butter fat*" so that the "*[u]se of vitamin/mineral supplements is essential to maintain nutrient adequacy in the ketogenic diet.*"[33] From the beginning, however, it was the goal to make the KDs for cancer patients more flexible by using ketogenic medium-chain triglycerides, and later allowing for a much larger percentage of whole foods and vegetables in so-called modified KDs. Together with other recent approaches such as the Paleolithic KD[58,62,65] at least part of the research community therefore seems to appraise KDs not as *per se* unhealthy, but as an holistic and from an evolutionary perspective natural approach to dieting, much in line with Brünings' experiences.[f]

While Brünings' experiments probably constitute the first clinical cohort study involving a detailed description of and focus on a KD, there exists one earlier report from 1927 by Fritz Silberstein and co-workers[66] involving 21 non-operable cancer patients who were also treated with insulin injections (partly into the tumor) and a concurrent high caloric, very low carbohydrate diet.[g] Again, beneficial effects of the insulin on the general condition of the patients were noted, and some cases responded with a local regression of their tumors. Silberstein et al. also compared blood glucose curves between the cancer patients and normal subjects and found not only elevated fasting glucose concentrations in the former, but also an abnormal postprandial elevation after a very low carbohydrate meal,[h] even after prior insulin administration, similar to what would be expected in diabetics. Indeed, later studies have justified the belief that insulin resistance is a general hallmark of advanced cancer patients.[67–71]

After Brünings had published his second report, there was a huge media coverage which motivated others to try reproducing his experiments. Among them were Schulte and Schütz in 1942, who were able to reproduce the short-term beneficial effects of insulin on the general condition of their patients, but not to induce macroscopic tumor regression or longer-term improvements, so that they discouraged clinicians from using the method.[72] However, in their paper no details of the "carbohydrate-free" diet are given, and it appears possible that – given the difficulties of obtaining the appropriate foods during the war as mentioned by Brünings – their diet was not as strict as demanded by Brünings. In 1957 Joseph Weiss published his results of treating 90 incurable cancer patients with depot insulin and a calorie restricted low carbohydrate diet containing 124 g carbohydrates, 66 g fat and 56 g protein per day.[73] He again reported pleiotropic effects such as pain reduction, euphoria and weight gain; 20 patients achieved stable disease and 9 patients tumor regression which lasted several months, in one case up to 4 years. This work was not directly comparable to Brünings', as the carbohydrate content was considerably higher and would certainly not have induced ketosis.

It is not straightforward to interpret Brünings' results and those of the replication studies in hindsight. The insulin administrations appear to have been responsible for short-term improvements in the general condition of the patients such as improved appetite, euphoria and weight gain. However, concerning pain reduction, at least in mice insulin does not appear to have analgesic effects.[74] What further complicates the interpretation is that insulin in former times used to be contaminated with other peptides including glucagon to varying degrees.[i] For example, Bishop and Marks explicitly mention the use of glucagon-free insulin in a 1959 study that also dealt with the dysregulated glucose metabolism and insulin resistance in cancer

[d] The general effects of the method appeared to be cancer-specific, since Brünings had seen no objective or subjective improvements in wellbeing, appetite or body weight in 20 healthy subjects and 6 non-cancerous patients.

[e] Brünings had observed mixed results in the response of tumors to radiotherapy when patients had been pre-treated with his method, with some tumors apparently becoming more radioresistant.

[f] An anonymous reviewer mentioned the potential role of bioactive peptides as anti-cancer agents.[112] As these are derived from whole animal and plant foods, their concentration would also be much higher in diets containing large amounts of vegetables and animal foods of marine and terrestrial origin.

[g] Brünings mentioned in an appendix that he became aware of Silberstein's work only after his experiments had been conducted.[47]

[h] This meal consisted of 500 ml whipped cream and 2 eggs. A typical breakfast described by Silberstein et al.[66] would consist of 250 ml whipped cream and one egg.

[i] I thank Dr. Michael Fink for first pointing this out to me.

Table 1
Human studies on the ketogenic diet and cancer published since Brünings' initial experiments. The list should contain all articles listed in PubMed upon a search using the keyword "ketogenic". Only studies published as peer-reviewed journal articles have been listed, while those mentioned solely in abstracts, comments or posters have been left out. In case of more than two study participants, their ages are given either as median (range) or mean ± standard deviation. CT: Chemotherapy; MCT: Medium chain triglycerides; N: Number of subjects on a KD; RCT: Radio-chemotherapy; RT: Radiotherapy.

Study author(s)	Year	Study type	N	Age [years]	Tumor	Concurrent treatment	KD/study duration	Concurrent calorie restriction prescribed	Supplements/artificial foods prescribed
Brünings[45]	1941	Intra-cohort study	14	56 (42–68)	Head and neck cancer	Insulin	≈12 weeks	No	No
Brünings[46]	1942	Intra-cohort study	30	55 (38–70)	Various extra-cranial tumors	Insulin	1.6 (0.3–3.0) weeks	No	No
Fearon et al.[32]	1988	Case study	5	59 (52–73)	Stage IV extra-cranial tumors	None	6 days control diet, then 7 days KD	No	Yes (MCT, arginine D-3-hydroxybutyrate, whey protein)
Nebeling et al.[34]	1995	Case study	2	3 and 8.5	Grade III anaplastic/cerebellar astrozytoma	None/CT	8 weeks	No	Yes (MCT, artificial flavorings, protein powder, multivitamins, vitamin D, multiminerals)
Chu-Shore et al.[48]	2010	Case study	5	8 (2–47)	Renal angiomyolipomas/ subependymal giant cell tumors	None	50 (3–66) months	No	Probably yes (hospital-prescribed KD with specified ratios)
Zuccoli et al.[49]	2010	Case study	1	65	Glioblastoma	RCT	2 months	Yes	Yes (4:1 KetoCal®, MCT, multivitamins, multiminerals)
Schmidt et al.[50]	2011	Intra-cohort study	16	50 (30–65)	Stage IV extra-cranial tumors	None	12 weeks	No	Yes (yoghurt drinks including MCT, vegetable oils and milk protein)
Fine et al.[10]	2012	Intra-cohort study (registered)	10	62 (52–73)	Stage IV extra-cranial tumors	None	4 weeks	No	No
Schroeder et al.[51]	2013	Intra-cohort study	11	67	Stage II-IV head and neck cancer	None	4 days	No	No
Champ et al.[52]	2014	Case study	6	59 (34–62)	Glioblastoma	RCT	32 (13–52) weeks	No (5), yes (1)	No
Rieger et al.[11]	2014	Intra-cohort study (registered)	20	57 (30–72)	Glioblastoma	None	5 weeks	No	Yes (commercial yoghurt drinks and plant oils)
Branca et al.[53]	2015	Case study	1	66	Grade 3 breast cancer	Vitamin D3 (10000 IU every other day)	3 weeks	No	Yes (commercial preparation of oleic acid associated with glycosylated vitamin D-binding protein, branched chain amino acids)
Schwartz et al.[7]	2015	Case study (registered)	2	55 and 52	Glioblastoma	None	4 and 12 weeks	Yes	Yes (KetoCal®)
Strowd et al.[54]	2015	Case study	8	41 ± 10	Low and high grade glioma	None/CT	2-24 (mean 13.2) months	No	Yes (multivitamins, vitamin D, calcium)
Jansen & Walach[55]	2016	Case study	13	68	Various curative (6)/palliative (6)/end stage (1) tumors	Mixed	≈1 year	No	Yes (commercial artificial foods)
Klement & Sweeney[56]	2016	Case study	6	54 (40–74)	Stage I-IV extra-cranial	RCT (5), CT (1)	6.6 (4.6–10.4) weeks	No	Yes (commercial crystalline amino acid formula)
Schwalb et al.[57]	2016	Case study	6	64 (55–73)	Stage IV extra-cranial	Complementary immunotherapeutic treatment	4.5 (1–34) weeks	No	Yes (commercial crystalline amino acid formula, fermented milk and colostrum product, emulsion with chondroitin sulfate, vitamin D3 and oleic acid, vitamin D3, curcumin, omega-3 fatty acids, ubiquinol, arginine, multivitamins)
Tan-Shalaby et al.[12]	2016	Intra-cohort study (registered)	17	65 (42–87)	Stage IV various tumors	None	16 weeks (with extension up to 131 weeks in 3 patients)	No	No
Tóth & Clemens[58]	2016	Case study	1	60	Grade 2 myoepithelial soft palate tumor	None	20 months	No	No
Artzi et al.[59]	2017	Controlled case study (registered)	5	42 (37–69)	Low and high grade glioma	None (1), bevacizumab (4)	8 (2–31) months	No	Yes (4:1 KetoCal®)
İyikesici et al.[60]	2017	Case study	1	29			1 year	No	No

Santos et al.[61]	2017	Case study	1	54	Stage IV triple-negative breast cancer	Metabolically (insulin-) supported CT, hyperbaric oxygen, hyperthermia	3 months	No	No	
					Recurrent glioblastoma	Intranasal perillyl alcohol				
Tóth & Clemens[62]	2017	Case study	1	62	Rectal cancer	RT (6 weeks), then none	24 months	No	No	
Zahra et al.[13]	2017	Intra-cohort study	9	67 (51–83)	Stage III/IV NSCLC (7) and pancreatic cancer (2)	RCT	1.1 (0–6) weeks	No	Yes (4:1 KetoCal®, artificial flavorings)	
Elsakka et al.[63]	2018	Case study	1	38	Glioblastoma	RCT, hyperbaric oxygen, metformin	24 months	Yes (9 months), then no	Yes (multivitamins, vitamin D, multiminerals, phytochemicals, MCT)	
Martin-McGill et al.[64]	2018	Intra-cohort study (registered)	6	46 (34–66)	High grade glioma	Lomustine (1), RCT (3), CT (2)	3 months	No	No	
Santos et al.[14]	2018	Controlled cohort study (registered)	9	53 (31–61)	Recurrent glioblastoma	Intranasal perillyl alcohol	3 months	No	No	
Tóth et al.[65]	2018	Case study	1	45	High-grade cervical intraepithelial neoplasia	None	26 months	No	No	

patients.[67] Still in 1985, substantial amounts of glucagon were found in insulin from three commercial manufactures.[75]

There is also the possibility that the diet itself mediated the pain reduction described by Brünings. Indeed, reduction in glycolytic metabolism and KDs are known to have anti-inflammatory and analgesic properties.[76] Brünings' observations concerning the superiority of a very strict carbohydrate restricted diet over milder versions provide some evidence that the diet has indeed played an important role. Concerning Brünings' descriptions of the influence on the tumor, two possible interpretations arise:

First, KDs by themselves have been shown to impair glycolytic tumor metabolism in humans, as demonstrated specifically in head and neck cancer patients in which tumor lactate levels dropped significantly after only a few days on the diet.[51] As discussed elsewhere this could be indicative of impaired growth and increased susceptibility to cytotoxic treatments.[24,25,77] One case study with 20 months follow-up even reports the halted progression of a soft palate tumor through initiation of an animal fat and meat-based Paleolithic KD with no further therapy.[58] An indication of the mechanisms at work can be derived from *in vitro* experiments showing that both ketone bodies[78,79] and free fatty acids[80] are able to impair tumor cell glycolysis. This is problematic for these cells because they frequently lack metabolic flexibility. On the one hand, many studies have found that tumor cells display decreased expression of ketolytic enzymes,[81–85] although more recently a few counterexamples were discovered.[6,7] On the other hand, a large part of a solid tumor would consist of hypoxic areas in which oxygen concentrations are too low to efficiently metabolize ketone bodies and fatty acids, even if the necessary enzymes would be expressed.[86] Furthermore, a hallmark of tumor cells appears to be dysfunctional mitochondria which generate large amounts of reactive oxygen and nitrogen species without effectively generating ATP.[87–91] A ketone- and fatty acid-mediated inhibition of glucose-6-phosphate in these cells induces a reduction of NADPH (required for regeneration of reduced glutathione) and lactate (a free radical scavenger) and therefore an increase in oxidative stress (reviewed in[23,24]). Accordingly, mouse studies have shown that the combination of KDs with pro-oxidative therapies such as chemotherapy,[92] ionizing radiation[93,94] or hyperbaric oxygen[95] works better than either of these treatments on its own, which emphasizes their role as complementary cancer treatments. Lastly, Martuscello et al. showed that KDs downregulated the mTOR (mammalian target of rapamycin) pathway in xenografted tumors derived from glioblastoma cells.[96] Collectively these examples show that KDs can exert pleiotropic effects on tumor cell metabolism and signaling pathways, providing some justification for their supportive application.

A second interpretation that a very strict low carbohydrate diet was found necessary by Brünings is that a KD would minimally compromise, and even support, hypoglycemic treatments. The switch to ketone body and fatty acid metabolism (known as keto-adaption) is able to protect against signs of hypoglycemia. This was impressively demonstrated when Drenick et al. infused insulin into keto-adapted obese subjects, resulting in serum glucose levels as low as 9 mg/dl without symptoms.[97] It is therefore possible that Brünings' diet contributed to improved tolerance of hypoglycemia, and that hypoglycemia in turn was the principle cause of the regression of tumors observed by Brünings and later by Joseph Weiss.

Proof-of-principle that hypoglycemia itself can induce tumor regression was provided in 1962 by Koroljow[98] who reported the achievement of a one-year complete remission in two metastasized cancer patients who were put into an insulin coma (lowest

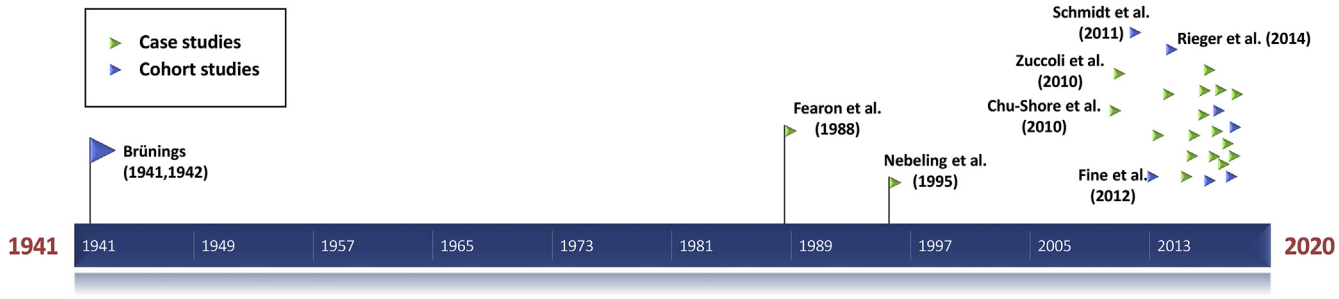

Fig. 3. Timeline of studies using ketogenic diets to treat cancer patients. The early studies are labeled with author names and the year of publication.

blood glucose reading 22 mg/dl).[j] A multitude of recent *in vitro* experiments have shown that in contrast to normal cells, many tumor cells are very vulnerable to glucose withdrawal by mechanisms involving both energy stress[99,100] and oxidative stress.[101–105] Again, this confirms the metabolic inflexibility of tumor cells arising from their dysfunctional mitochondria as described above.

Today, insulin administration is still in use in some centers with the aim of inducing hypoglycemia prior to administration of chemotherapy in what is referred to as "insulin potentiation therapy" or "metabolically supported chemotherapy". In a recently published combination of this concept with a KD, hyperthermia and hyperbaric oxygen, a metastasized breast cancer patient achieved a complete radiological and pathological response.[60] Insulin administration in these applications is usually limited to pulsed doses since it is now established that insulin is also a growth factor for many tumor cells.[106,107] Another drawback is that insulin also inhibits ketogenesis, reducing the possibility of utilizing ketone bodies as an alternative energy source for the brain, and exploiting their putative anti-tumor effects. Alternative proposals for hypoglycemic treatment of cancer patients therefore avoid using insulin; they include methods such as removal of glucose (and glutamine) through dialysis[108] or application of gluconeogenesis inhibitors in patients who have been keto-adapted.[109,110]

The examples above highlight the renewed interest in metabolic therapies of cancer, including KD interventions. My hope is that the discussion of Brünings' scientific reasoning and experimental data will further strengthen this interest. The significance of altered tumor and patient metabolism for the treatment of cancer as well as the supportive role of very low carbohydrate diets were already recognized and realized many decades ago by a remarkable investigator ahead of his time.

Compliance with ethical standards

The author declares that he has no potential conflicts of interest. The reader should be aware that many of the historical articles discussed in this review were performed prior to the Declaration of Helsinki and therefore that the ethical standards of today do not apply to these experiments.

[j] Koroljow's rationale was based on the theory that hypoglycemia reduces the oxidation of glucose, so that the unused oxygen raises the oxygen concentration which should retard tumor growth. Interestingly, Poff and colleagues have shown that only raising oxygen concentrations in tumor-bearing mice through hyperbaric oxygen breathing had no effect on tumor growth, but it augmented the anti-tumor effects of a KD.[95]

Data statement

All historical papers mentioned in this article are available from the author upon request.

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