Elucidating the Mechanism of the Ketogenic Diet as an Effective Adjuvant Therapy for Malignant Glioma: A Multiphase Study to Characterize Alterations in Tumor-Associated Inflammatory and Growth Factor Signaling

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In recent years, the ketogenic diet, a high-fat, low-carbohydrate and low-protein diet, has been shown to have potential as an effective adjuvant therapy for patients with malignant glioma. Nonetheless, its underlying mechanisms remain largely unknown. Although malignant gliomas are characterized by intrinsic heterogeneity, chronic inflammation and the overexpression of growth factor signaling pathways have emerged as common phenotypic traits throughout tumorigenesis. This study sought to reconcile such observations by exploring the effects of the ketogenic diet on the gene expression of key inflammatory regulators like NF-κB and the glucocorticoid receptor (GR) and of growth factor signaling proteins like AP-1 and MEK-4. It was hypothesized that the ketogenic diet would alter gene expression patterns by decreasing the expression of pro-inflammatory proteins like NF-κB, increasing the expression of anti-inflammatory proteins like GR, and decreasing the expression of growth factor signaling proteins. Immunofluorescence and western blotting were used on tumor and contralateral non-tumor tissue from mice fed a standard rodent diet, a 6:1 Bio-Serv F3666 ketogenic diet, or a 4:1 human ketogenic diet (Nutricia KetoCal). Experimental data clearly pointed to the reduction of inflammation and growth factor signaling as components of the diet's therapeutic mechanism. In particular, the 4:1 KetoCal significantly altered protein expression patterns by increasing the expression of GR and decreasing the expressions of NF-κB, AP-1, and MEK-4 in comparison to tumor tissue from animals fed a standard diet ($p < 0.05$; t-test). Such knowledge, in conjunction with more advanced in vivo studies, will be critical in the future to potentiate the therapy's transition from bench to bedside.

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