Regional brain glucose metabolism is differentially affected by ketogenic diet: A human semiquantitative positron emission tomography

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Abstract

Purpose

Ketogenic diet (KD) is recommended to avoid intense [^{18}F]FDG myocardial physiologic uptake in PET imaging. Neuroprotective and anti-seizure effects of KD have been suggested, but their mechanisms remain to be elucidated. This [^{18}F]FDG PET study aims to evaluate the effect of KD on glucose brain metabolism.

Method

Subjects who underwent KD prior to whole-body and brain [^{18}F]FDG PET in our department for suspected endocarditis were retrospectively included. Myocardial glucose suppression (MGS) on whole-body PET was analysed. The main exclusion criteria were brain abnormalities. Thirty-four subjects with MGS were considered the KD population, and 14 subjects without MGS were considered a KD failure. Brain SUVmax of these groups was compared. Second, the KD population (n = 34, mean age: 61.8 ± 17.2 years) was compared to a control group of 27 healthy subjects fasting for at least 6 h (mean age of 62.4 ± 10.9 years). A semiquantitative voxel-based intergroup statistical analysis was conducted using SPM.

Results

A 20% lower brain SUVmax was found in subjects under KD with MGS in comparison to those without MGS, p = 0.02. Whole-brain voxel-based intergroup analysis revealed that patients under KD had relative hypermetabolism of limbic regions including medial temporal cortices and cerebellum lobes and relative hypometabolism of bilateral posterior regions (occipito-parietal).

Conclusion

KD globally reduces brain glucose metabolism but with regional differences. These results have a clinical implication, since the realization of a KD could lead to misinterpretation of these regions, and a pathophysiological perspective as it could help understand underlying neurological effects of KD through possible decrease of oxidative stress in posterior regions, and functional compensation in the limbic regions.

Introduction

The brain is a major consumer of body energy, accounting for at least 20% of the whole energy consumption, while it is only 2% of body weight [1, 2]. Most of this energy is produced by aerobic metabolism utilizing glucose, with fat being a very low energy source under regular conditions. Brain

glucose metabolism can be affected by many parameters in physiological and pathological conditions, for example, age, glycemia, local damage, and neurodegenerative disorders such as Alzheimer's disease (AD). Ketogenic diet (KD) probably also influences brain glucose metabolism.

KD consists of reducing carbohydrate intake in favor of high-fat consumption to induce glucose metabolism shifting toward fatty acid metabolism. This last metabolism uses ketone bodies (mainly β hydroxybutyrate and acetoacetate) as a source of energy instead of glucose [3, 4]. KD has been proven beneficial in positron emission tomography (PET) imaging to avoid intense FDG myocardial physiologic uptake [5, 6]. For this reason, KD is done prior PET examinations indicated for endocarditis, sarcoidosis, or any disorder for which myocardial glucose suppression (MGS) is necessary. Interest in KD as a therapeutic strategy has risen since it was first proven useful in pharmacoresistant epilepsy in the 1920s [7, 8]. KD could have potential utility as an add-on therapy in several neurologic disorders, such as gliomas, head trauma, sleep disorders, stroke, and neurodegenerative disorders (AD, Parkinson's disease, multiple sclerosis) [4, 9–13]. However, the underlying mechanisms of the antiepileptic and neuroprotective effects of KD are still not fully understood [14].

On a cellular level, there is evidence that KD reduces reactive oxygen species and increases ATP and mitochondrial biogenesis [3, 15]. KD also leads to an increase in polyunsaturated fatty acids that regulate neuronal membrane excitability by blocking voltage-gated sodium channels [16] and modify glycolysis.

Preclinical and clinical studies have investigated the effects of ketone bodies on the brain and the interplay between glucose and ketone body metabolism. It is indeed assumed that during KD, ketone bodies are the main source of energy in the brain. This has been shown by catheterization of cerebral vessels in fasting humans [17], a reduction in cerebral metabolic rates of glucose (CMRglc) in ketotic rats on PET in the cortex and cerebellum using the Gjedde-Patlak model when plasma ketone bodies increased [18], and a proportionate decrease in CMRglc in humans with blood ketone increases [19]. Even if most authors agree [4, 18–20] that a global decrease in cerebral glucose metabolism occurs under KD toward the use of ketone bodies [21], the hypothesis that different brain regions have distinct utilization of glucose is left unanswered. Some authors found an increased cerebral metabolic rate of acetoacetate and a decreased cerebral metabolic rate of glucose in all regions [20], which was more marked in the caudal middle frontal cortex, while others found a preserved uptake in the basal ganglion and cerebellar hemispheres but did not identify regionally reduced uptake areas [22]. The aim of this study was to evaluate distinct regional metabolic changes on brain [^{18}F]FDG PET after KD using semiquantitative voxel-based analysis.

Materials And Methods

Population studied:

Patients who underwent a KD prior to brain and whole-body [^{18}F]FDG PET for suspected endocarditis between January 2019 and December 2020 in the Department of Nuclear Medicine at Timone Hospital in

Marseille were retrospectively included. Patients were hospitalized in cardiology units, with medical and paramedical teams used to KD rules. Our Nuclear Medicine department sends KD instructions to the units before examination. The dietary instructions were as follows: 12 hours minimum fasting, ideally 15 to 18 hours fasting before examination; no blood perfusion with glucose or parental nutrition 15 to 18 hours before examination; and a KD performed for 36 to 48 hours before examination. The minimum last two meals before fasting should be high-fat and low-carbohydrate meals. A list of permitted and banned foods is provided with menu examples.

Exclusion criteria were the following: presence of cerebral abnormalities on PET, CT, or MRI, such as brain embolies or abscess, brain sequelae (stroke, surgery, etc.), presence of neurologic symptoms suggestive of encephalitis or neurodegenerative disorders. Apparent normal brain PET on visual interpretation performed by two different independent readers was selected. Among the 152 patients selected (Fig. 1), 103 patients were excluded because of brain abnormalities. One patient was excluded because they were under 18 years old.

Myocardial metabolism was examined on whole-body PET for the 49 patients without neurologic lesions, and used as an indirect marker of KD adherence, since the study was retrospective. Images were classified in terms of the presence or absence of significant visual myocardial uptake. In this way, 14 patients were considered as a KD failure, in the absence of MGS, and 34 were considered as the KD population (Table 1) with 38% female, mean ± SD age of 61.8 ± 17.2 years. Brain and myocardial maximum standard uptake values (SUVmax) were collected. The brain SUVmax of the KD population (n = 34) was compared to the brain cortical SUVmax of the 14 patients without MGS using Student's t test. Glycemia before PET examinations was also recorded and correlated with brain SUVmax using the Pearson correlation coefficient. The study was approved by APHM institution with the reference PADS21-311.For semiquantitative brain regional analysis, the KD population was compared to a control group of 27 healthy subjects (Table 1) with a minimum 6 hours fasting, with a similar age and sex ratio (40% female), mean ± SD age of 62.4 ± 10.9 years with absence of neurological or psychiatric disorder, confirmed by neuropsychological testing and MRI (clinical trial reference NCT00484523).

Table 1
Patient characteristics of the KD population compared to the KD failure population, with brain and myocardial SUVmax.

Patients' characteristics	KD population n = 34	KD failure population n = 14	*p* value
Sex: Female (percentage)	n = 13/34 (38%)	n = 8/14 (57%)	0.25
Age: mean (range, ±SD)	61.8 (26–87, ± 17.2 years)	62.3 (27–81 ± 15.1 years)	0.92
Brain SUVmax: mean (range)	10.8 (3.9–19.6)	13.5 (9.8–17.2)	0.02
Myocardial SUVmax: mean (range)	3.2 (1.8–5.3)	9.5 (5.8–17)	< 0.001
Glycemia (g/ml)	1.07 (0.82–1.67)	1.03 (0.71–1.93)	0.69

[^{18}F]FDG PET acquisitions and reconstructions

A dose of 3 MBq per kilo of [^{18}F]FDG was injected followed by a 50 min rest in a dark quiet room for the KD population and a dose of 111 MBq followed by a 30-minute rest for the control population. Brain PET and then whole-body PET for the KD population were performed by a GE Discovery PET/CT camera. Whole-body images were iteratively reconstructed with CT-based attenuation correction. Brain PET-CT was acquired using a three-dimensional acquisition of 7 minutes when associated with a whole-body PET acquisition (endocarditis group) and 15 minutes when the brain was acquired alone (control group), with an axial resolution of 6.2 mm and 47 contiguous transverse sections of the brain of 3.27 mm thickness. Images were reconstructed using an OSEM-type iterative reconstruction algorithm with 5 iterations and 32 subsets and corrected for attenuation using a scan.

Brain post-reconstruction and semiquantitative analysis

A semiquantitative voxel-based intergroup statistical analysis was conducted. Images were processed using SPM8 (Welcome Department of Cognitive Neurology, University College, London, UK) run on MATLAB. Spatial normalization (MNI atlas) and smoothing with an 8 mm FWHM Gaussian filter were performed. A proportional scaling method was chosen to account for intersubject variability relying on different [^{18}F]FDG doses (111 MBq for brain alone or 3 MBq per kilo for brain and whole-body) and different times of acquisition after injection (30 minutes postinjection for 15 minutes versus 50 minutes postinjection for 7 minutes) [23]. Age and sex were added as covariables. A voxel p value of 0.001 was chosen for the voxel and combined with a p-cluster < 0.05, uncorrected. A familywise error (FWE-corrected) method was added to correct for multiple comparisons at the cluster level.

Results

Brain SUVmax comparison between the KD population with MGS and KD failure

The brain SUVmax of the KD population with MGS (n = 34) was compared to that of the population (n = 14) that was excluded from the regional metabolic analysis because of the absence of MGS, considered as a KD failure (Table 1). Brain SUVmax was lower in the KD population (SUVmax = 10.8) than in KD failure (SUVmax = 13.5), as expected, p = 0.02 (Student's T test), with a 20% brain SUVmax decrease under KD. No significant difference in glycemia levels was observed (p = 0.69). Glycemia was negatively correlated with brain SUVmax (Pearson coefficient correlation = 0.60, p < 0.01)

Semiquantitative voxel-based analysis between the KD population and the control group

Patient characteristics

Thirty-four subjects on KD (mean age: 61.8 ± 17.2 years, 38% female) were compared to a control group of 27 subjects (mean age of 62.4 ± 10.9 years, 40% female) (Table 2). No significant difference between the two groups' characteristics was found.

Table 2
Patient characteristics of the KD population compared to the control population

Patients' characteristics	KD population n = 34	Control population n = 27	*p* value
Sex: Female (percentage)	n = 13/34 (38%)	n = 11/27 (40%)	0.85
Age: mean (range, ±SD)	61.8 (26–87, ± 17.2 years)	62.4 (40–78 ± 10.9 years)	0.87

Between-group metabolism differences

All results are first expressed with a p value < 0.001 for the voxel and a p-cluster < 0.05, uncorrected. The findings that remained significant after correction of multiple comparison for the cluster by FWE method are specified. KD was associated with relatively increased FDG uptake in the bilateral limbic regions, bilateral cerebellum lobes, and left motor cortex (Fig. 2): right temporal medial cortex (peak T-score = 7.01; k = 1307 voxels; p-cluster < 0.001 FWEcorrected), left temporal inferior and medial cortex (peak T-score = 8.49; k = 3380 voxels; pcluster < 0.001 FWE-corrected; Fig. 2), bilateral frontal lobes: left frontal medial orbital (peak T-score = 7.03 and k = 1373; p-cluster < 0.001 FWE-corrected) and right frontal medial orbital (peak T-score = 6.46; k = 302; p-cluster = 0.133 FWE-corrected, and 0.031 uncorrected), left frontal superior cortex (peak T-score = 6.32; k = 359; p-cluster = 0.089 FWE-corrected, and 0.020 uncorrected), left frontal opercular cortex (peak T-score = 5.23; k = 663; p-cluster = 0.013 FWEcorrected and 0.003 uncorrected) in the cingulum (peak T-score = 6.64; k = 368; p-cluster = 0.084 FWE-corrected, and 0.019 uncorrected), in the left motor cortex (peak T-score = 6.94; k = 1500; pcluster < 0.001 FWE-corrected) and in both cerebellum

posterior lobes: left cerebellum (peak Tscore = 5.45; k = 852;; p-cluster = 0.004 FWE-corrected); and right cerebellum (peak T-score = 5.51;k = 695; p-cluster = 0.011 FWE-corrected). KD was also associated with a relatively decreased FDG uptake in bilateral posterior regions (occipital medial cortex, inferior parietal, precuneus and cuneus; peak T-score = 5.65; k = 6,099 voxels; p-cluster < 0.001 FWE-corrected Fig. 2) and left parieto-occipital cortex (peak Tscore = 4.51; k = 407 voxels; p-cluster = 0.064 FWE-corrected and 0.015 uncorrected).

Discussion

This study showed brain glucose metabolism modifications under a short KD prior to a PET examination. We first compared the KD population with MGS with the KD population without MGS, considered KD failure, and confirmed a significant 20% lower brain SUVmax in the KD population with MGS. These results are in concordance with those found in the literature, since most authors agree that under KD, there is a lower brain glucose uptake [4, 18–20]. However, the KD failure group was not used for the semiquantitative analysis, as subjects in this group could have performed a partial KD and because even when KD is well conducted, MGS is sometimes not achieved [6].

We then focused on regional brain metabolic changes using proportional scaling in the KD population with MGS compared to a healthy group and found a relatively increased FDG uptake mainly in bilateral limbic regions and cerebellum cortices and a relatively decreased FDG uptake in posterior regions (occipito-parietal). To date, only a few studies have investigated regional brain glucose metabolic changes during KD [20, 22]. Korsholm et al. [22] found a global hypometabolism of the cortex with preserved uptake in the basal ganglia and the cerebellum in an 11-year-old child with drug-resistant epilepsy on long-term KD using visual interpretation and quantitative analysis (Neurostat). No areas with focally reduced uptake were identified, but there was only one subject, and the effects could be partially explained by seizure relief itself. Courchesne-Loyer et al. [20] found on a sample of 10 young healthy adults (aged 35+/-15) that a four-day KD decreased CMRglc in all regions with the greatest decrease in the caudal middle frontal cortex. They compared the same subjects pre- to post-KD CMRglc using the quantification method of the multiple time graphical analysis of Patlak et al., but the sample was small and young.

On a cellular level, regional metabolic changes under KD probably rely on two opposite mechanisms that regulate glucose cell intake [4]. The first is the decrease in glucose cell uptake by the glucose transporter GLUT due to the accumulation of glycolytic intermediates secondary to an increase in ketone bodies. The second mechanism is the increase in cerebral blood flow that probably increases glucose uptake [4]. The downregulation of GLUT expression under KD is probably observed under long-term KD [4]. From a physiopathology point of view, neuroprotective effects of KD could be linked to the global decrease in brain FDG uptake, implying less oxidative stress. Interestingly, we found an even more marked hypometabolism in the posterior cortex under KD, regions that are affected in neurodegenerative disorders such as AD. On the other hand, the relative increase in glucose uptake in limbic regions, including temporal medial regions, might reflect functional compensation [24].

In our study, the fact that all patients who underwent a KD had suspicion of endocarditis could have been a recruitment bias since neurologic complications of endocarditis are found in approximately 25% of patients [25, 26]. However, we only selected patients without neurologic symptoms or abnormalities on neuroimaging and with apparent normal brain PET on visual interpretation. Additionally, out of 34 patients, only 59% had confirmed endocarditis on followup data. It would be interesting to verify our results in a larger population.

Additionally, the KD duration was 36–48 hours before examination, and it has been shown that a longer KD duration has a stronger effect on brain metabolism in rodents [19] and a stronger effect on MGS in humans [6]. The effect of a longer KD on brain metabolism could be investigated in a clinical study.

In this retrospective study, we chose the MGS as an indirect marker [5] of KD adherence before examination. A detailed questionnaire with ingested meals in a prospective study should be a more accurate way to evaluate KD than MGS.

Since our analysis is semiquantitative, we had to choose a method to correct individual brain metabolism variations. We used proportional scaling, focusing on regional metabolic changes. Even if this technique has some limitations, such as underestimating the extent of hypometabolic areas [23], it is justified considering that our two groups had different FDG doses and different times of acquisition after injection and by the objective of the study (i.e., the relative comparison of regional metabolism between 2 groups of patients with distinct whole-brain metabolism).

Conclusion

KD globally reduces brain glucose metabolism but with regional differences. It causes a relative hypermetabolism of limbic regions, including medial temporal cortices, and a relative hypometabolism of parieto-occipital regions. These results have a clinical implication, since the realization of a KD could lead to misinterpretation of these regions, and the findings also provide a pathophysiological perspective to help us understand underlying neurological effects of KD on neuroprotection and functional compensation.

Declarations

Financial support and disclosure: none to declare

FUNDING

The local PET database of healthy controls was funded by APHM (NCT00484523).

DATA AVAILABILITY

The PET data that support the findings are available from the corresponding author upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The retrospective observations required no ethical approval requirement other than informed consent. The local PET database of healthy controls was acquired in accordance with the Declaration of Helsinki, with informed written consent from the patients and approval from the “CPP Sud Méditerranée V” ethics committee. Informed consent was obtained from all individual participants included in the study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING

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COMPETING INTEREST

The authors have no relevant financial or non-financial interests to disclose.

DATASET

The datasets generated during analysis are available from the corresponding author on reasonable request.

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Figures

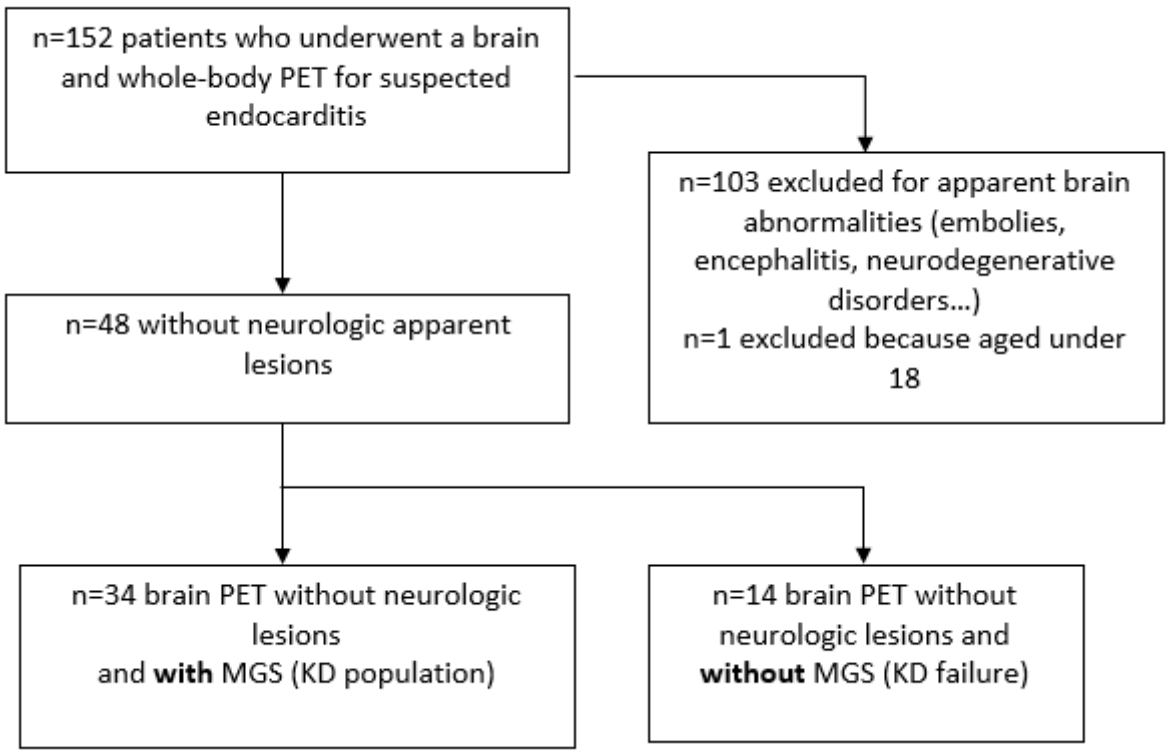

Figure 1

Flowchart of patient selection. KD= ketogenic diet, MGS= myocardial glucose suppression

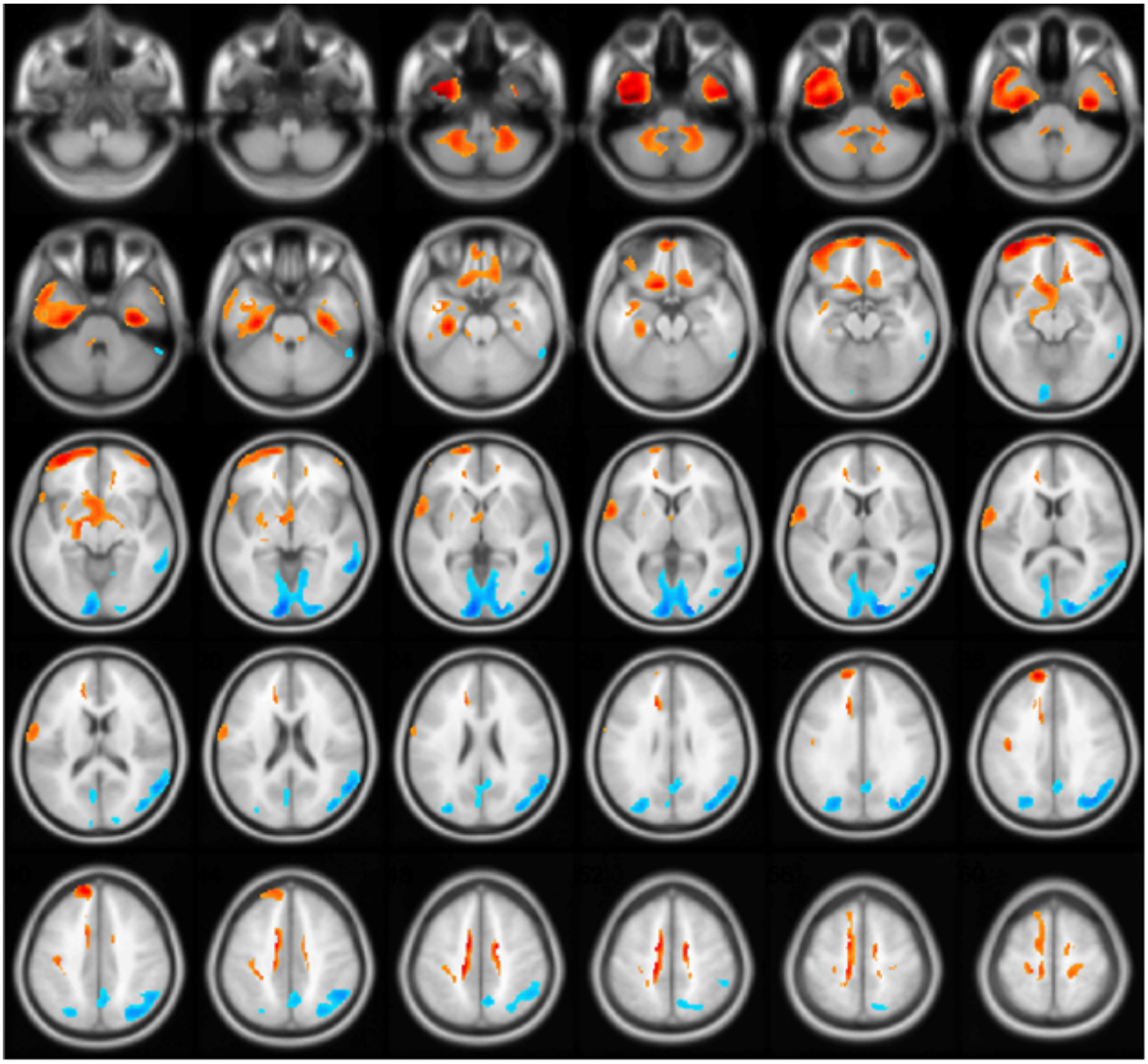

Figure 2

Whole-brain anatomical localization of significant metabolic changes after KD compared to a control population in axial slices. In orange, regions with increased metabolism include limbic regions, the left motor cortex, and the bilateral cerebellum. Blue indicates regions with decreased metabolism, including parietal and occipital cortices.