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Therapeutic effect of ketogenic diet treatment on type 2 diabetes

Fang Li[a,1], Yang Shen[b,1], Qun Chen[a], Xingyu Li[a], Hongnan Yang[c], Canyang Zhang[a], Jinjun Lin[b], Zhicheng Du[a], Chenyao Jiang[a], Chengming Yang[d], Dongmei Yu[e,*], Peiwu Qin[a,*]

[a] *Institute of Bio-pharmaceutical and Health Engineering, Tsinghua Shenzhen International Graduate School, Shenzhen 518101, China*

[b] *Department of Endocrinology, Baoan Central Hospital of Shenzhen, the Fifth Affiliated Hospital of Shenzhen University, Shenzhen 518055, China*

[c] *Department of Automation, Hangzhou Dianzi University, Hangzhou 310016, China*

[d] *Southern University of Science and Technology Hospital, Shenzhen 518055, China*

[e] *Department of Electromechanical and Information Engineering, Shandong University, Weihai 264209, China*

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A B S T R A C T

Diet plays an important role in diabetes development. The effect of ketogenic diet on type 2 diabetes remains elusive. In this study, we collect diabetes related physiological parameters and abdominal MRI images to evaluate the effect of ketogenic diet after 3-months of consecutive treatment. Ketogenic diet mitigates the diabetes symptom inferring from the statistically significant reduction of key diabetic physiological parameters such as Hemoglobin A1c (HbA1c) concentration, Triglyceride (TG), Fasting blood glucose (FBG), Body Mass Index (BMI), and adipose tissue volume. Moreover, we propose a new parameter to quantify the treating effect of ketogenic diet since Slope and Offset of Oral Glucose Tolerance Test (SOOGTT) incorporate more sampling points by fitting OGTT (Oral Glucose Tolerance Test) curve. SOOGTT shows statistically significant (P < 0.001) treating effect of ketogenic diet on type 2 diabetes. We use artificial intelligence to segment adipose tissue for treatment evaluation, which shows that ketogenic diet reduces the amount of adipose tissue.

1. Introduction

According to the 2017 International Diabetes Federation's (IDF) report, 451 million people (age ≥ 18) suffer from diabetes globally [1]. The patient number will reach 693 million in 2045 by prediction. Diabetes is a type of metabolic disease with high blood glucose levels. Hyperglycemia is caused by insufficient insulin secretion or disordered biological action [2]. Diabetes has 4 categories: Type 1 diabetes, type 2 diabetes, gestational diabetes mellitus, and specific types of diabetes [3]. Type 2 diabetes (T2D) has the highest prevalence among the 4 types of diabetes, accounting for more than 90% of diabetics [4]. Persistently high blood glucose induces various complications, such as hypertension, nervous, eyes and kidney impairments [5,6], and increases the risk of cardiovascular disease [7], cancer, and mortality [8,9]. Diabetes and its complications cause tremendous physical and psychological suffering to patients and financial burden to the social medical system.

T2D is an incurable chronic disease due to limited therapeutics. The best treatment only alleviates the symptoms and slows down the progress of diabetes. The World Health Organization (WHO) suggested (2016) that weight loss and calorie restriction can reverse T2D [10]. Many studies have shown bariatric surgery, low-calorie diets (LCD), and low carbohydrate diets (LC) improve T2D symptoms [11]. Surgery causes complications and even death. The LCD treatment reduces the blood glucose of diabetics in a short time, which is associated with cholesterol-rich gallstones.

[1] These authors contribute equally to this work.

[*] Corresponding authors.
E-mail address: yudongmei@sdu.edu.cn (D.M. Yu); pwqin@sz.tsinghua.edu.cn (P.W. Qin)

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However, long-term use of LCD leads to serious complications [12]. Non-surgical methods are prior strategies to alleviate diabetes [13].

Diet planning and nutrition intake play an indispensable role in the overall management and treatment of T2D diabetes [13,14]. The American diabetes association recommends that diabetics should receive individualized nutrition therapy [15]. LC diet is the most frequently prescribed treatment for diabetes [16,17], which focuses on nutrient content rather than calorie intake [18], limiting the proportion of diet carbohydrates. LC diet improves blood lipid and glucose stability and reduces the demand for diabetes drugs [19]. Short-term treatment shows that LC diets can significantly improve T2D [20]. The improvement in blood glucose control and reduction in drug therapy associate with the lowest carbohydrate intake [21]. Therefore, a more rigorous low carbohydrate diet-the ketogenic diet potentially may have a better therapeutic effect on T2D.

Ketogenic diet limits total carbohydrates to 20–30 g per day in contrast to 130 g/day or less in LC diet [22]. Protein consumption accounts for around 20% of intake and the rest of energy requirement is from dietary or body fat. Carbohydrate sources are mainly non-starchy vegetables, nuts, dairy products, and fruits [23,24]. Longer ketogenic diet intervention reduces HbA1c level below the risky threshold among 55% of total diabetes [25]. Another one-year study finds that the ketogenic diet significantly reduces HbA1c in T2D patients [26]. These studies evaluate the effects of ketogenic diets on a few parameters and a study including all the physiological parameters is still missing.

In this study, we collected all relevant physiological and abdominal MRI data before and after ketogenic diet treatment. With the tremendous increase of medical images, deep learning facilitates the segmentation of subcutaneous adipose tissue from participants' abdominal MRI [27-32]. Deep learning has been used in computer-aided diagnosis, disease detection, and lesion segmentation due to its strong nonlinear modeling and feature extraction capability [33-35]. Deep learning revolutionizes medical image processing including tumor segmentation [36-38], detection of retinal diseases [39,40], and Alzheimer's disease [41-43]. With the patients' subcutaneous fat content segmented by deep learning, we perform statistical analysis with other physiological parameters to analyze the effect of ketogenic diet systematically. Meanwhile, we build the first subcutaneous fat MRI dataset for model development.

2. Materials and methods

2.1 Study design

We select adults with T2D (n = 8, from 18 to 65 years old) who are willing to follow our treatment guidance. Their BMI is > 25 kg/m^2 and the duration of diabetes are less than 3 years. The following prerequisites are used to exclude and select patients: a) Type 1 or steroid diabetes; b) Diabetes with severe chronic complications such as nephropathy, retinopathy, and diabetic foot; c) Heart and lung diseases such as acute or chronic heart failure, coronary artery disease, and chronic obstructive pulmonary disease; d) Liver and gallbladder diseases such as poor digestion, hepatic cirrhosis, or severe abnormal liver function; e) Abnormal renal function (creatinine (Cr) increased or glomerular filtration rate (GFR) less than 90 mL/min); f) Secondary or malignant hypertension; g) Hematological system disorders and rheumatism disease; h) Infection and stress states; i) Surgery, cardiovascular and cerebrovascular accidents in last 3-months; j) Cancer; k) Pregnancy or lactating postpartum patients; l) Psychopath.

2.2 Intervention

We treat patients after obtaining their consents to participate in the study and strictly restrict their carbohydrate intake (20 to 30 g/day) for three months. We encourage participants to get adequate sleep, increase physical activity, and report their daily diet. After a 3-month ketogenic diet intervention, we re-measure the participants' physiological parameters and collect abdominal MRI.

2.3 Assessments

The diagnostic criteria of type 2 diabetes are: a) FBG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h; b) 2 h plasma glucose (PG) ≥ 200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO using a glucose load with 75 g anhydrous glucose in water; c) For patients with classic symptoms of hyperglycemia or hyperglycemic crisis with random PG ≥ 200 mg/dL (11.1 mmol/L). In the absence of unequivocal hyperglycemia, results are confirmed by the second test.

TG, Alanine aminotransferase (ALT), and FBG are measured with an automatic biochemical analyzer. HbA1c is measured with an automatic glycosylated hemoglobin analyzer. Weight, blood pressure, fat volume, and other relevant indicators are included. We calculate the slope and the offset of OGTT, which might be a new index for a diabetes evaluation.

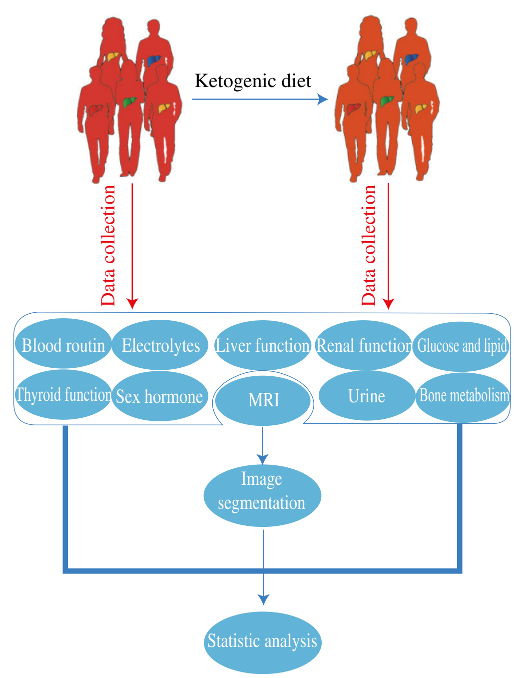

Fig. 1 Schematic of experimental design and data analysis. We collect physiological parameters and abdominal MRI of participants for statistical analysis and image segmentation respectively.

2.4 Statistical analysis

The statistical analysis is performed in Python. We use the paired *t*-test to compare the changes in the physiological parameters of the participants after a 3-months treatment with the ketogenic diet. The mean value, the *P*-value, and *t*-value for each indicator are calculated (*t*-test and spearman function is in the SciPy library). Spearman correlation between the number of segmented pixels of subcutaneous fat in participants' abdominal MRI images and physiological parameters is calculated. After excluding the outliers of OGTT, we perform the curve fitting of OGTT and record the slope and offset, which is a newly proposed parameter to evaluate the effect of the ketogenic diet on T2D.

2.5 Medical image segmentation

We collect abdominal MRI for the subjects involved in this study. This dataset contains 315 individual images, which are preprocessed, labeled, and saved in PNG (Portable Network Graphics) format with the size of 512 × 512. 70% of total images are used for training and the rest are for validation. We compare the segmentation accuracy of four different deep learning networks (FCN, UNet, PSPNet, and Deeplabv3) and the number of segmented fat pixels is used to evaluate the effect of ketogenic diet on T2D.

3. Results

3.1 Participant information

The subjects are selected according to the rules mentioned in the methods section. We record the physiological parameters and MRI images of eight participants before and after ketogenic diet treatment. The subjects involved are willing to follow our guidance of ketogenic diet treatment and report their progress occasionally upon request. We calculate the mean value, *P*-value, and *t*-value for all the parameters and use deep learning networks to segment subcutaneous fat from abdominal MRI slices. The schematic of experimental design and data analysis is shown in Fig. 1.

3.2 New parameter for evaluation of diabetes symptoms

The participants' blood concentration of GLU (mmol/L) is recorded at 0, 30, 60, 120, and 180 min respectively in OGTT. We select the points from the rising phase for linear curve fitting since dropping-points mean that the body absorbs GLU (Fig. 2). The offset of the green curve (after ketogenic diet treatment) is significantly smaller than the red curve (before treatment), which demonstrates the ability of glucose metabolism increases in the participants after a 3-months treatment. FBG level is significantly lower after ketogenic intervention, which also shows that ketogenic diet can relieve diabetes symptoms.

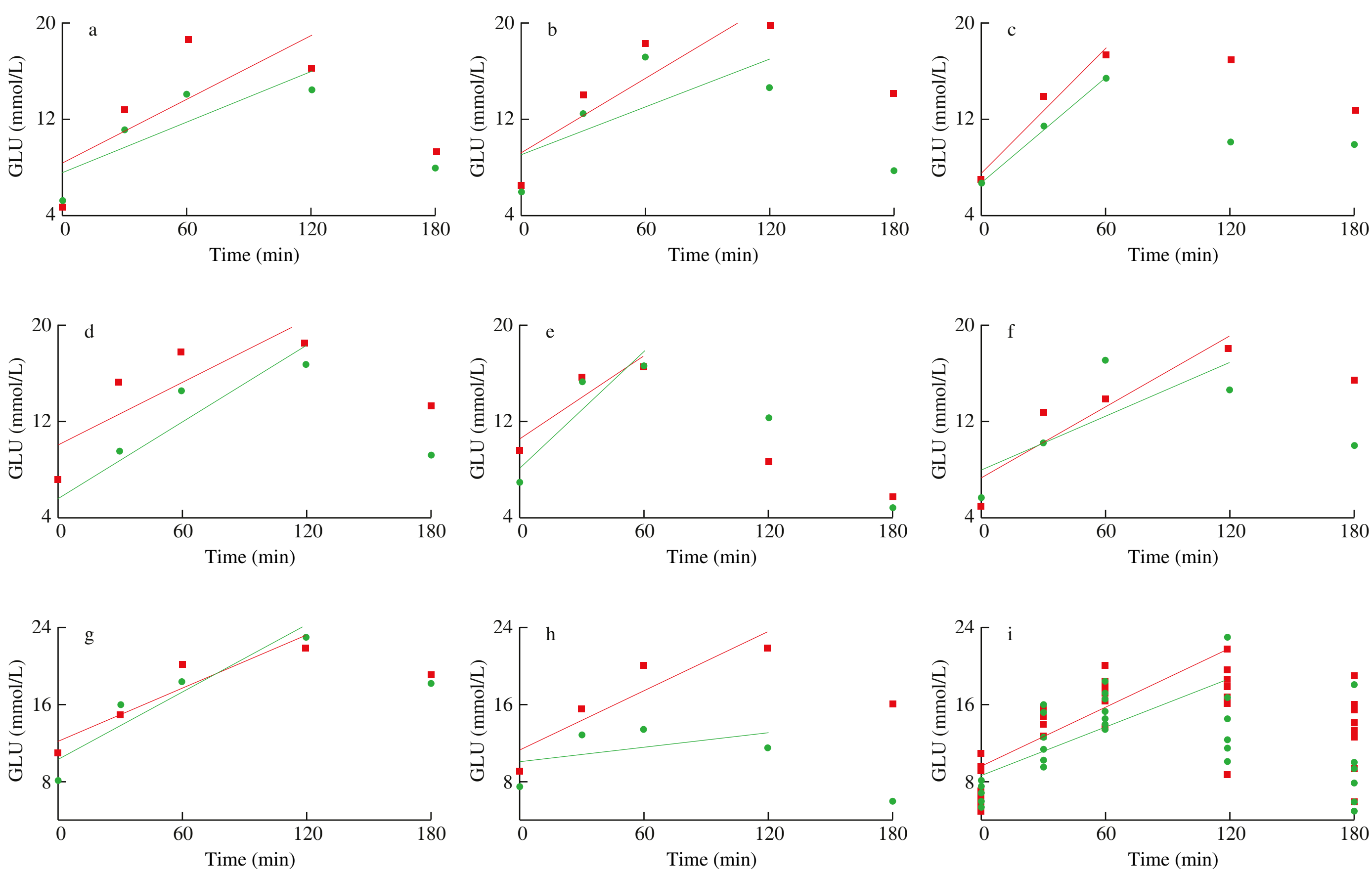

Fig. 2 Changes of physiological parameters after ketogenic diet treatment. a-h correspond to participant 1-8, respectively; i represents the curve fitted by summarizing 8 participants' dataset. Red curve is before the ketogenic diet and green curve is after the ketogenic diet. The *X*-axis represents time (min) and the *Y*-axis represents GLU concentration (mmol/L).

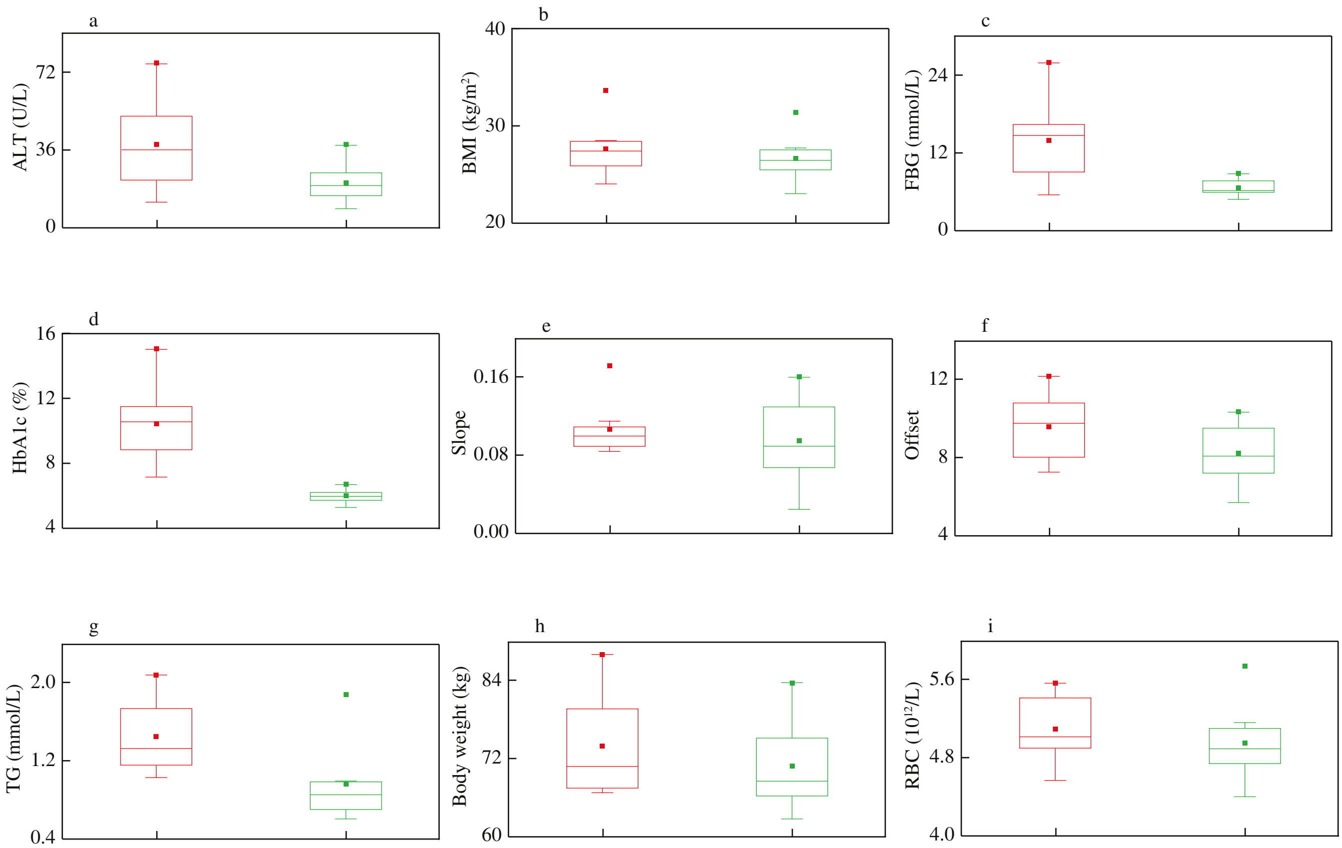

Fig. 3 The box plot of Physiological parameter. a-i represent the boxplot of participants with different physiological parameters. Red and green represent the physiological parameters before and after the ketogenic diet respectively.

3.3 Ketogenic diet improves the symptoms of diabetes

The difference in critical physiological parameters for all participants shows reducing trend towards healthy state after 3-months ketogenic diet treatment, especially ALT, FBG, HbA1c, and TG (Fig. 3). It is known that HbA1c level is positively correlated with diabetes severity [44]. Patients with type 2 diabetes have a higher risk of elevated ALT with increasing body mass index. Elevated ALT and TG increase the risk of diabetes, reflecting the severity of diabetes. The P-value of these parameters is less than 0.05 withone sided t-test.

3.4 Abdominal MRI dataset and adipose tissue segmentation

We build the first abdominal MRI dataset for algorithm development. FCN, UNet, PSPNet, and Deeplabv3 are used for MRI image segmentation. The UNet uses Adaptive Moment Estimation (Adam) to optimize the hyperparameters. Adam algorithm can automatically optimize the learning rate during the training stage. The hyperparameters of FCN, PSPNet, and Deeplabv3 networks are set as epoch = 50, batch size = 4, and learning rate = 0.01. The segmentation results showed that PSPNet and Deeplabv3 perform better than FCN and UNet (Fig. 4). Mean intersection over union (Miou) and Pixel accuracy (PA) are commonly used to evaluate segmentation performance. The results show that the PSPNet scores higher in Miou (95.292%) and PA (98.672%) than other networks (Table 1). Therefore, the PSPNet is chosen for adipose tissue segmentation. The correlation between the number of segmented fat pixels with other physiological parameters are analyzed further.

Table 1
The performance of different deep learning methods for MRI image segmentation.

Name	PA (%)	Miou (%)
UNet	98.606	90.235
FCN	95.635	85.313
PSPNet	98.672	95.292
Deeplabv3	98.426	94.996

3.5 Efficacy of the ketogenic diet on diabetes shown by comprehensive analysis all physiological parameters

We perform the paired t-test on the available parameters for all participants to obtain t-values and P-values. In particular, we summarize the GLU data in OGTT of 7 participants and preprocess the data by randomly deleting one participant at a time. We fit the curve of OGTT for seven participants and get slopes and offsets for the paired *t*-test. Table 2 and Table 3 summarize HbA1c, TG, ALT, FBG, BMI, Weight, and other parameters for all participants and shows significant decrease after ketogenic diet interference ($P < 0.05$). Slope and offset of the OGTT curve show a strong correlation with other diabetes parameters. Moreover, the Spearman correlation shows strong associations between segmented pixel numbers of abdominal fat MRI and other physiological parameters such as Albumin/Urine Creatinine Ratio (ACR, $\rho = 0.85$), BMI ($\rho = 0.81$), Hemoglobin ($\rho = 0.81$), Testosterone (TT, $\rho = -0.64$) (Fig. 5). The ketogenic diet affects the physiological parameters of the participants by reducing the content of adipose tissue, thereby alleviating T2D symptoms.

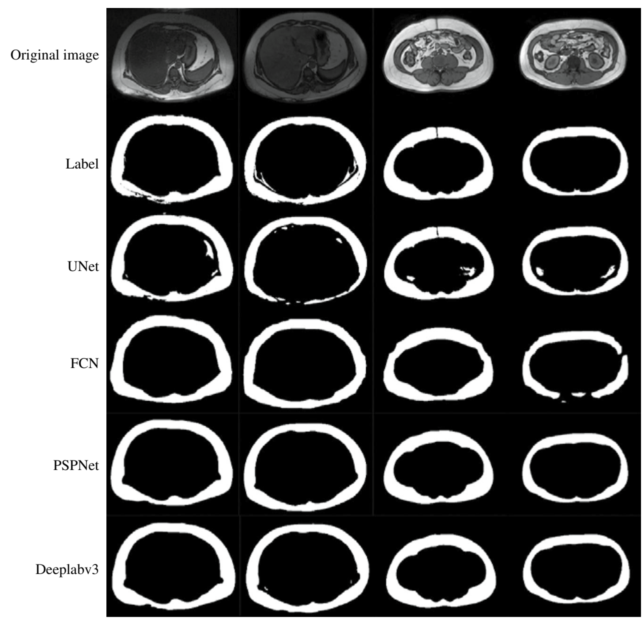

Fig. 4 MRI image segmentation with deep learning network. The horizontal axis represents abdominal fat images at different locations. The first row is the original MRI image and the second line is doctor's label. The rest rows are the segmented fat tissue by different network model.

Table 2
The critical physiological parameters for participants before and after 3-months ketogenic diet treatment.

Parameter	Sample size (*n*)	Mean value (before)	Mean value (after)	*P* value
slope	8	0.10	0.084	< 0.001
offset	8	9.70	8.46	< 0.001
HbA1c (%)	8	10.5	5.99	0.001
ALT (U/L)	8	38.38	20.88	0.010
FBG (mmol/L)	8	13.99	6.63	0.021
Body Mass Index (kg/m^2)	8	27.55	26.59	0.039
Body Weight (kg)	8	73.85	70.86	0.044
TG (mmol/L)	8	1.45	0.96	0.003
Hemoglobin (g/L)	8	150.75	144.75	0.080
FT4 (pmol/L)	8	13.24	11.76	0.082
Red Blood Cell (10^{12}/L)	8	5.10	4.95	0.156
Glutamyl Transpeptidase (U/L)	8	43.13	27	0.174
FT3 (pmol/L)	8	5.05	5.44	0.176
Aspartate Aminotransferase (U/L)	8	26.13	17.25	0.181
C Reaction Protein (mg/L)	8	3.31	6.75	0.296
White Blood Cell (10^9/L)	8	7.28	6.86	0.297
K^+ (mmol/L)	8	3.94	4.11	0.298
Lymphocyte (%)	8	29.84	29.84	0.313
Uric Acid (μmol/L)	8	331.38	357.00	0.417
Cl^- (mmol/L)	8	103.00	103.88	0.443
Blood Urea Nitrogen (mmol/L)	8	4.54	4.79	0.466

Table 3
The physiological parameters for participants before and after 3-months ketogenic diet treatment.

Parameter	Sample size (*n*)	Mean value (before)	Mean value (after)	*P* value
Neutrophil (mmol/L)	8	59.85	57.69	0.513
Na^+ (mmol/L)	8	136.25	136.88	0.603
Blood Platelet (10^9/L)	8	249.13	253.38	0.689
Thyroid Stimulating Hormone (mU/L)	8	1.83	2.11	0.696
Total Bilirubin (μmol/L)	8	16.83	17.13	0.886
Mg^{2+} (mmol/L)	7	0.80	1.00	0.118
Estradiol (pmol/L)	7	246.43	127.00	0.175
Urine Creatinine (mmol/d)	7	9.94	13.50	0.174
Total Cholesterol (mmol/L)	7	5.07	4.61	0.098
LH (mU/mL)	7	5.14	3.64	0.237
Liver Fat (%)	7	8.41	6.61	0.552
Low Density Lipoprotein (mU/L)	7	3.32	3.07	0.259
Ca^{2+} (mmol/L)	7	2.31	2.34	0.430
Total Protein (g/L)	7	71.10	73.61	0.559
P (mmol/L)	7	1.15	1.11	0.535
Follicle-stimulating Hormone (mIU/mL)	7	4.25	4.58	0.619
Pancreatic Fat (%)	7	5.21	5.43	0.774
Total Testosterone (nmol/L)	7	9.83	10.56	0.522
High-density Lipoprotein (mmol/L)	7	1.12	1.14	0.733
Urinary albumin / Urine Creatinine (%)	7	2.69	2.71	0.981

4. Conclusion and discussion

The ketogenic diet, as an important non-drug and surgery treatment, has high-fat, adequate-protein, and low-carbohydrate. Ketogenic diet has shown good efficacy in the treatment of epilepsy, tumors, diabetes, and other diseases [45-49]. Although ketogenic diet has a positive effect on some diseases, it could induce cardiovascular diseases by increasing blood lipid and glucose metabolism disorder due to high fat with low carbohydrates [42]. Ketogenic diet treatment requires strict self-discipline, which is a difficult challenge for most patients. The subjects in this study follow our therapeutic guidelines and minimize the side effect of ketogenic diet treatment. We exclude patients with other complications, which makes our analysis more reliable.

The effect of ketogenic diet on adipose tissue in patients with T2D is analyzed by deep learning to segment and evaluate the subcutaneous adipose tissue from the patients' abdominal MRI images. The results show a significant decrease in physiological parameters and the segmented volume of adipose tissue after a 3-months treatment. We propose a new parameter that is the slope and offset derived from OGTT assay and use this parameter to evaluate the diabetes symptoms after ketogenic diet treatment. Combining this new parameter with other physiological indicators, we demonstrate that ketogenic diet treatment can improve diabetes. Most physiological factors indicate that patients are in more health conditions and ketogenic diet shows positive treating efficacy.

We collect and build abdominal MRI dataset for subcutaneous fat segmentation to evaluate the segmentation accuracy for different frameworks. In our study, we collect 315 MRI images from 8 diabetes patients, which can be analyzed manually on small dataset without deep learning. However, we utilize deep learning to segment subcutaneous fat automatically in case we have more data in the future study. We compare four different deep learning

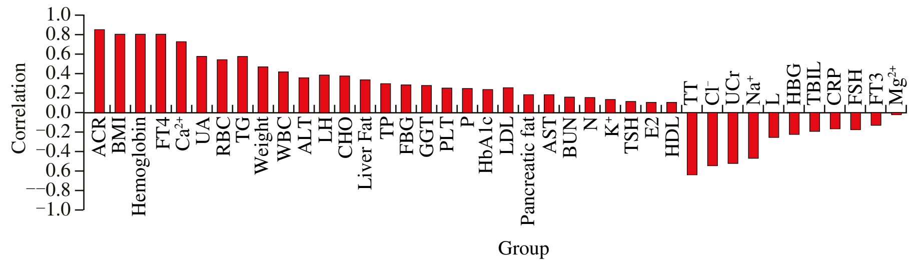

Fig. 5 The correlation between the number of abdominal fat pixels and physiological parameters. The correlation coefficients are arranged in descending order. The *X*-axis represents physiological parameter and the *Y*-axis represents correlation coeffiecient. Greater than zero means positive correlation, less than zero means negative correlation.

models and demonstrate that PSPNet predicts adipose tissue closer to the experienced doctor's label. The segmented subcutaneous fat together with various physiological parameters demonstrate the therapeutic effect of ketogenic diet. In the future, we will recruit more subjects to participate in the study and collect large dataset to increase the prediction accuracy of deep learning network. With more multimodality data collected, we can expand the dataset and elucidate the relationship between the ketogenic diet and T2D more accurately.

Conflict of interest

The authors declare that they have no financial or commercial conflict of interest.

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