COMPARISON OF THE EFFECT OF THREE DIFFERENT DIETARY MODIFICATIONS ON MYOCARDIAL SUPPRESSION IN ^{18}F -FDG PET/CT EVALUATION OF PATIENTS FOR SUSPECTED CARDIAC SARCOIDOSIS

(DIET MYOCARDIAL SUPP PET/CT CAR SARCOID)

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ABSTRACT

Rationale: A definitive dietary preparation recommendation is not possible based on literature in achievement of myocardial suppression for diagnosis of cardiac sarcoidosis (CS) with ^{18}F -FDGPET/CT. Our goal is to compare three different dietary preparations in achievement of the best myocardial suppression and CS diagnosis.

Methods: We retrospectively reviewed and compared three dietary preparations used at our institution. Three different diets were applied from 03/2014 to 12/2019. 24-h ketogenic diet with overnight fasting (n=94); 18h-fasting (n=44); 72-h daytime ketogenic diet with 3-day overnight fasting (n=98). The interpretation of initial reports was recorded, and an independent radiologist (observer) retrospectively re-evaluated each case regarding CS diagnosis (Negative, Positive, Indeterminant) and myocardial suppression (Complete, Failed, Partial). Interobserver agreement was analyzed. We measured MaxSUV from bloodpool, liver, and the most suppressed normal myocardium.

Results: We identified superior myocardial suppression with the 72-h preparation indicated by a higher bloodpool/myocardium and liver/myocardium ratios ($P<0.001$). Myocardial suppression rates for 72-h ketogenic diet, 24-h ketogenic diet and 18-h fasting preparations are as follows; Complete myocardial suppression: 96.9%/68.1%/52.3%, Failed myocardial suppression: 0%/23.4%/25%, Partial myocardial suppression: 3.1%/8.5%/22.7%) ($P<0.001$). The 72-hour preparation had significantly fewer “indeterminant” and “positive” exams. CS diagnosis rates for 72-h ketogenic diet, 24-h ketogenic diet and 18-h fasting preparations are as follows; Negative:

82.7%/52.1%/27.3%, Indeterminant: 2.0%/24.5%/40.9%, Positive: 15.3%/23.4%/31.8% ($P<0.001$). High agreement was present with the observer and the report ($\kappa=0.88$)

Conclusion: A 72-h daytime ketogenic diet with 3-day overnight fasting, achieved substantially superior myocardial suppression versus 24-h ketogenic diet with overnight fasting and 18h-fasting using ^{18}F -FDG PET/CT. This 72-h preparation results in significantly fewer “indeterminant” and potentially “false positive” CS results.

Keywords: Cardiac sarcoidosis, PET/CT, myocardial suppression, ketogenic diet, fasting

INTRODUCTION

The diagnosis of cardiac sarcoidosis (CS) is challenging. Clinical presentation may vary from asymptomatic to ventricular tachycardia, high-grade atrioventricular block, or heart failure (1,2). The gold standard for diagnosis is endomyocardial biopsy. However, it is invasive, prone to false negatives from sampling errors, and has low sensitivity for CS when compared with autopsy (3). Therefore, non-invasive imaging methods, cardiac MRI and cardiac ^{18}F -FDGPET/CT (cPET/CT), are frequently used when screening or symptoms indicate cardiac involvement. While both modalities have limitations, they ultimately proved complementary as they measure different pathologic processes (3-8).

The major limitation of cPET/CT relates to the physiologic myocardial glucose metabolism. A normal healthy myocardium uses a combination of free fatty acids and glucose for energy in normal conditions. Thus, differentiation of myocardial inflammation from normal physiologic myocardial activity requires the suppression of physiologic myocardial uptake. This is achieved by switching the myocardial metabolism from glucose to free fatty acid consumption (9). Several different dietary and pharmacologic modifications have been proposed to achieve this goal. And yet, no standardized method exists with variation in protocols amongst institutions (3,4,7,9-16). Most recently, the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and American Society of Nuclear Cardiology (ASNC) jointly reported a consensus guideline for appropriate dietary modification to assess CS including two options (3). 1) Patient consumes at least two high-fat (>35 g), low-carbohydrate (<3 g) meals the day before the study and fast for at least 4–12h, 2) Patient fasts >18-h before the study. Despite these attempts, a recent large literature review concluded that “a definitive dietary preparation recommendation is not possible based on

current evidence; however, scan readability does seem to be improved when preparation includes a reduced carbohydrate intake” (10).

Since 2012, we utilized three different dietary modifications for patients with suspicion of CS, to suppress background myocardial ^{18}F -FDG metabolism. The first two methods were similar to above-mentioned consensus guideline. The new dietary protocol included a 72-h prolonged ketogenic diet with overnight fasting. Our purpose is to compare the effect of three different dietary modifications on cPET/CT in patients with suspicion of CS.

MATERIALS AND METHODS

Patients Selection and Diets

This Health Insurance Portability and Accountability Actcompliant retrospective study was approved by the institutional review board (STUDY00005814) and the need for written informed consent was waived. All dedicated cPET/CTs for CS from January/2012 to December/2019, obtained at the University of Minnesota, either for initial diagnosis or follow-up for assessing treatment response, have been collected in a picture archive and communication system folder. Three different dietary preparations were used during this time. Diet-A (24-h ketogenic diet) was applied from January/2012 to February/2018, Diet-B (18-h fasting) from March/2018 to September/2018 and Diet-C (72-h ketogenic diet with overnight fasting) from September/ 2018 to December/2019 (Table-1).

Our goal was to compare an equal number of exams for each diet. However, Diet-B was applied for a limited time, therefore there are less cPET/CTs in this group than Diet-A and Diet-C. We identified 98 studies for Diet-C. Therefore, the latest 98 studies using Diet-A going back from

February/2018, were selected. However, four were excluded later due to lack of image processing using the PET/CT viewer. In the end, a total of 236 cPET/CTs from 160 unique patients were included for analysis (Diet-A: 94 studies in 70 patients; Diet-B: 44 studies in 39 patients; Diet-C: 98 studies in 86 patients). Out of the 160 subjects, 128(80%) had only one unique diet and 32(20%) had more than one type of diet.

PET/CT Acquisition

Apart from the dietary modifications, smoking for 6-h and exercise for 24-h were restricted prior to cPET/CT. If patients had diabetes, blood glucose level should be under 200mg/dl and insulin was restricted for 6-h prior to the study. cPET/CT was rescheduled if above-mentioned criteria were not met.

All cPET/CTs were obtained with Siemens Biograph mCT 64 PET/CT scanners. All exams included ^{13}N -ammonia perfusion and ^{18}F -FDG metabolism studies, excluding follow-ups, as ^{13}N -ammonia study was not performed routinely for follow-ups. A 10-minute ^{13}N -ammonia study was performed using 740MBq of ^{13}N -ammonia with 128x128 resolution. Then, patients were taken to a separate room for ^{18}F -FDG injection and ^{18}F -FDG studies were performed 60mins after 555MBq of ^{18}F -FDG administration with 256x256 resolution.

Data Collection

A research fellow obtained the following information from the electronic medical records: exam date, patient age, sex, body-mass-index, the dose of administered ^{13}N -ammonia and ^{18}F -FDG, fingertip blood glucose level immediately before cPET/CT, diet type, dietary compliance and whether a repeat exam was performed due to dietary non-compliance. All cPET/CTs were initially

reported by two independent nuclear radiologists. The reports were retrospectively reviewed by the research fellow and categorized into three categories regarding the presence of CS; active inflammation from CS: “positive”, no active inflammation from CS: “negative”, “indeterminant”, and regarding the myocardial suppression; “complete suppression”, “partial suppression”, “failed suppression”.

Image analysis

All included cases were retrospectively evaluated by a separate nuclear radiologist (the observer). Qualitative and quantitative assessment was performed using SyngoVia “MMoncology” and “MIcardiology” applications. Each exam was reformatted in the oblique axial/coronal/sagittal planes according to the anatomic cardiac orientation (Figure-1) using the PET emission and CT images. Particularly, in those cases where myocardium heterogenous or completely suppressed, the anatomic orientation of the heart was adjusted based on CT appearance.(EDITOR)Quantitatively, “Bloodpool-MaxSUV” (from the mediastinal descending thoracic aorta), “Liver-MaxSUV” (from the right hepatic lobe), “Myocardium-MaxSUV” (from the most suppressed portion of the left ventricle), and “Lesion-MaxSUV” (from the most ^{18}F -FDG avid portion of the myocardium if active CS was suspected) were measured. “Bloodpool-MaxSUV/Myocardium-MaxSUV” and “Liver-MaxSUV/Myocardium-MaxSUV” ratios were calculated.

Qualitatively, the presence of myocardial suppression was visually categorized in three groups. If no physiologic uptake was perceived, categorized as “complete suppression”. If there was heterogenous uptake without typical mismatch pattern and appearance was not suggestive of early active disease (editor), categorized as “partial suppression”. If there was diffuse uptake,

categorized as “failed suppression”. The presence of CS was evaluated qualitatively according to two criteria based on literature. The first analysis consisted of six categories per SNMMI/ASNC guideline; 1:“Normal”, 2:“Diffuse non-specific”, 3:focal uptake without mismatch on ¹³N-ammonia representing “early active disease”, 4:focal uptake with mismatch pattern representing “active disease”, 5:focal uptake with mismatch pattern, mixed with non-FDG avid perfusion defects, representing “mixed scar and inflammation”, 6:non-FDG avid perfusion defect, representing “scar” (3). The second analysis consisted of four categories according to Lu et al; 1:“normal”, 2:ringlike diffuse uptake at the base, considered “negative for CS”, 3:Focal uptake considered “positive for CS”, 4:diffuse myocardial uptake considered “indeterminate” (7). To compare the interobserver variability between the radiology report and the observer, these analyses were recategorized; accordingly, SNMMI/ASNC classification: category 1+6=“negative”, category 2=“indeterminant”, category 3+4+5=“positive”. Lu classification: 1+2=“negative”, 3=“positive”, 4= “indeterminant”. The observer also evaluated the presence of systemic active sarcoidosis based on PET/CT, categorized in two groups, “negative”, and “positive”.

Statistical Evaluation

Descriptive statistics were used to compare the three diet groups on a number of clinical and demographic measures. All variables were summarized on a per-study, as opposed to a per subject basis. Chi-square tests were used to statistically compare the three groups on categorical measures, whereas one-way ANOVA tests were used for the continuous measures. Weighted Cohen’s Kappa was used to evaluate the inter-rater reliability of myocardial suppression and presence of active cardiac sarcoidosis between the report and the observer and recategorization of the SNMMI/ASNC and Lu classifications. Linear mixed-effect regression models were also used

to compare the myocardial glucose suppression between the diet groups, while accounting for the within-subject effects and repeated measurements. The myocardial suppression response variable was treated as an ordinal variable, where “failed”=0, “partially suppressed”=1, “completely-suppressed”=2. P-values <0.05 were used to determine statistical significance. “R” (Ver-3.6.0) was used for analyses.

RESULTS

Patients demonstrated high compliance with the applied diets without statistically significant difference [Diet-A: 89/94(94.7%), Diet-B: 41/44(93.2%), Diet-C: 96/98(99%), ($P=0.292$)]. Noncompliance led to repeat examination in 2/5 exams in the Diet-A, 3/3 in the Diet-B and 1/2 in the Diet-C groups. Below-mentioned analyses included the cases with dietary non-compliance. A repeat analysis excluding those with dietary non-compliance (not provided) did not show any meaningful difference (EDITOR).

Quantitative measurements are presented in Table-2. No difference was detected between the groups regarding sex, BMI, applied amount of ^{13}N -ammonia and ^{18}F -FDG. Regarding age, there was statistically significant but clinically insignificant difference between the groups. No difference was found between the groups regarding the liver uptake. Regarding the blood-pool uptake, there was statistically significant difference between the groups, although this difference was not clinically or radiologically significant. Most importantly, there was significantly lower myocardial uptake in the Diet-C group compared to other diets. Of equal importance, the Blood-pool/Myocardium and Liver/Myocardium MaxSUV ratios were significantly higher in the Diet-C group, indicating a better myocardial suppression relative to background references. It is

also noteworthy that lesion uptake was similar in all three. Mean fingertip glucose was also found significantly lower in the Diet-C group compared with the others. While there was no patient with a fingertip glucose <60mg/dl in the Diet-A and Diet-B groups, fingertip glucose was <60mg/dl in six patients using Diet-C at the time of ^{18}F -FDG injection with the lowest being 43. None of these patients demonstrated any clinical signs of hypoglycemia, thus it was decided to continue the PET/CT acquisition with attention to hypoglycemia symptoms. These patients well-tolerated the entire PET/CT with no complication related to hypoglycemia.

Table-3 shows qualitative comparison of the groups. Regarding the myocardial suppression, the observer found statistically superior myocardial suppression with the Diet-C where the complete suppression rate reached 96.9%, with 0% failed and 3.1% partial suppression. This included the cases with dietary non-compliance. These rates were similar for Diet-C according to the radiology report, however higher rates of complete myocardial suppression and lesser rates of partial and failed suppression were present in Diet-A and Diet-B in the radiology report. There was borderline statistical insignificance among the groups regarding myocardial suppression according to the original report ($P=0.052$). Mixed effects model per subject comparing each individual diet also showed significant myocardial suppression with Diet-C compared with Diet-A (*Effect:0.51, CI:0.32-0.69, $P=0.000$*) and Diet-B (*Effect:0.67, CI:0.44-0.90, $P=0.000$*). This was not significant when comparing Diet-A with Diet-B (*Effect:0.16, CI:-0.07-0.40, $P=0.169$*).

Regarding the assessment of myocardial suppression, there was moderate agreement between the observer and the radiology report (Table-4). This agreement was mostly valid in the

cases of complete suppression; however, the number of failed and partial suppression cases were less in the radiology reports than the observer's evaluation.

There was no statistical difference among the groups regarding the presence of systemic active sarcoidosis on whole-body PET-CT. The observer found more "normal" and "scar" in Diet-C group with markedly decreased amount of "diffuse non-specific" cases, compared with Diet-A and Diet-B using the SNMMI-ASNC assessment (Table-3). According to Lu assessment, the groups were also statistically different: Diet-C had more "normal" cases with decreased number of "positives" and "indeterminants" compared with Diet-A and Diet-B. After recategorization of these assessments into three categorizations as "positive", "negative" and "indeterminant", Diet-C group has significantly more "negative", less "positive" and less "indeterminant" active CS diagnosis compared with Diet-A and Diet-B (Table-3). Notably, this recategorization demonstrated near-complete agreement (Table-5). A similar observation was also found according to the radiology report, showing a high degree of agreement with the observer (Table-6). The numbers of the observer and the radiology report were remarkably similar for all diets when the diagnosis was negative (Table-3). The numbers of indeterminate and positive cases by the observer and the radiology report were also similar when Diet-C was used but remarkably different when Diet-A and Diet-B were used. Some examples are shown in Figures 1,2,3,4.

DISCUSSION

Since 2012, we used diets similar to the recommendations of SNMMI-ASNC guidelines. However, what we had called active inflammation was not correlating with either clinical findings or MRI in many cases during multidiscipline conferences. Therefore, we questioned our ability of myocardial suppression and decided to change the diet protocol. A new 72-h ketogenic diet

during the day with overnight fasting in three consecutive days (Diet-C), markedly improved myocardial suppression rates and this new protocol was quantitatively and qualitatively superior to the other previously used dietary modifications, including 24-h ketogenic diet with 6-h fasting (Diet-A) and 18-h fasting (Diet-B). The new regimen also resulted in better interobserver agreement. When we examined the radiology reports with the two older dietary regimens, there were higher rates of positive diagnoses, but the observer was not in agreement, calling most of these “positive” cases as “indeterminant”, due to the possibility of potential inadequate myocardial suppression and associated false positive results. It is possible that many of these cases with Diet-A and Diet-B, were overcalled as “positive” secondary to incomplete suppression, particularly, previously described “focal on diffuse” imaging pattern obtained with these diets were probably the reason why the radiologists had reported these exams as “positive”, which is a common problem in prior study designs (17,18)[REV2]. But that was not the case when Diet-C was used, excellent myocardial suppression was achieved with increased certainty in the diagnosis and increased agreement between the observer and report.

Our findings are supported by findings in the preclinical setting. Clement et al. demonstrated that marked myocardial background suppression was achieved with better determination of the myocarditis in ^{18}F -FDG PET/CT in mice with extension of ketogenic diet up to 7-days as opposed to 18-h fasting. Each mouse was given a standard diet with calculated calories and nutrients, and PET/CT findings were correlated with pathologic confirmation. This animal study proves that extension of ketogenic diet results in better myocardial suppression (13). However, 7-day dietary restriction could be hard for certain patients regarding dietary compliance and our three-day dietary restriction seems more pragmatic in clinical setting.

It is well-known that people often experience ketogenic flu in the first few days of ketogenic diet (19). The durations of these symptoms indicate that physiologic response to ketogenic diet takes several days. Based on our data, the body needs greater than 24-h to fully switch to ketogenic metabolism in the myocardium. When we first started this new dietary regimen, we were not aware of the study by Lu et al, which compared two groups (7). The first group contained PET/CTs from 12 patients with preparation using 24-h ketogenic diet with a ketogenic breakfast 4-h prior to PET/CT and the second group contained 193 PET/CTs from 185 patients with preparation using 72-h ketogenic diet with a ketogenic breakfast 4-h prior to PET/CT. According to their results, 7/193 (3.6%) “indeterminant”, 167/193 (86.6%) “negative” and 19/193 (9.8%) “positive” CS diagnosis was made with 72-h ketogenic diet, while 5/12 (41.7%) “indeterminant”, 6/12 (50%) “negative” and 1/12 (8.3%) “positive” CS diagnosis was made with 24-h ketogenic diet. Applying the same classification method, our diagnostic rates with 72-h ketogenic diet demonstrated similar rates while 24-h ketogenic diet group showed different results. Perhaps, our results could be more robust for 24-h ketogenic diet due to a larger sample size (94 vs. 12). However, there are differences in the 72-hour ketogenic diet method. A ketogenic breakfast 4-h before ^{18}F -FDG injection was used in Lu et al’s paper. On the contrary, we additionally applied the principles of intermittent fasting, including at least 12-h of overnight fasting for 3 consecutive days and fasting after 8pm until the ^{18}F -FDG injection for PET/CT exam (which is always after 8 am). Despite that difference, our findings are in-line with their results. It should also be emphasized that our dietary modification was very well-tolerated by our patients and the number of cases with non-compliance were the lowest with this diet, although not significantly different than other regimens. With the Diet-C, we observed low serum glucose

levels <60mg/dl in six patients. Despite that, none of these patients demonstrated any clinical signs of hypoglycemia and tolerated the entire PET/CT exam without any complication. However, diabetic patients can be challenging, and prolonged fasting could be omitted for diabetics to avoid potential hypoglycemia and exam can be performed in the afternoon after a ketogenic breakfast along with morning insulin administration, followed by 6-h of fasting.

There is no consistency in the diagnosis of cardiac sarcoidosis with PET/CT based on prior literature. We think the most reliable current classification is the SNMMI/ASNC consensus guideline (3). This allows a more standard and well-defined approach. That was the primary reason why we used this method for classification in our study. However, the largest diet study in this topic was performed by Lu et al, and they used a classification containing four groups based on prior literature (7). According to their study, the group with “ring-like diffuse uptake at the base” is not described in the SNMMI/ASNC consensus guideline. We think that pattern is more representative of partial myocardial suppression and in our entire cohort, we had 10 that type of observations without classical mismatch, which were more compatible with “diffuse nonspecific” according to SNMMI/ASNC classification and that is the main reason for the discrepancy shown in the Tables 3, 5. (Editor)

Our study has several strengths. To our knowledge, this is the first study that compares three different dietary modifications with relatively large and equal number of exams in each group. Two of these dietary modification strategies are mainly applied and recommended by current guidelines and the third one, which performs better, has not been used in the clinical setting despite preclinical evidence to support its use. The results of this new kind of diet are reported for the first time in the literature excluding the paper by Lu et al, which used a similar

but slightly different type of diet (7). Even though the paper by Lu et al has the largest study cohort (7,17), the compared groups did not contain comparably similar number of patients as our study (REV2, EDITOR). Interobserver variability regarding the myocardial suppression and CS diagnosis was made based on two different scoring systems, one is proposed by Blankstein et al and SNMMI-ASNC guideline and the other one is proposed by Lu et al (3,4,7). The agreement of these two scoring systems is also studied for the first time.

We acknowledge several limitations of our study. This is a retrospective study. However, our findings are valuable as existing strategies have limitations and our findings have the potential to change clinical practice and may improve the understanding of cardiac sarcoidosis and cardiac metabolism. Second, we did not give a standard calculated diet to each patient, this is practically possible for mice as demonstrated by Clement et al (13), but impractical for clinical usage and real-life scenario in humans. Third, the diagnosis made in current study is not confirmed by a gold standard, as there is no existing practical gold standard, or by clinical correlation, as clinical diagnosis was retrospectively diverted by initial PET/CT report. This could be only performed in a longitudinal prospective study. However, at our institution, all potential cardiac sarcoidosis cases are reviewed in a monthly multidisciplinary meeting comprising physicians with expertise in nuclear medicine, cardiology, cardiac electrophysiology, cardiac MRI, pulmonology and sarcoidosis.

CONCLUSION

It appears that the SNMMI-ASNC diet recommendations are inadequate to suppress the background myocardial glucose uptake, leading to many indeterminate and potentially false

positive results. A 72-h ketogenic diet with overnight fasting prior to cPET/CTs, is well-tolerated and superior to other dietary preparations, providing excellent physiologic myocardial glucose metabolism suppression, markedly decreasing the number of indeterminant results and potentially “false positive” results for active cardiac sarcoidosis diagnosis.

KEY POINTS

Question: Which dietary modification is better to suppress physiologic myocardial ^{18}F -FDG metabolism to diagnose active inflammation from cardiac sarcoidosis?

Pertinent Findings: Three dietary preparations, 24-h ketogenic diet with overnight fasting, 18h-fasting and 72-h ketogenic diet with 3-day overnight fasting, were retrospectively compared regarding their ability to suppress the physiologic myocardial ^{18}F -FDG uptake and diagnosis of cardiac sarcoidosis with PET/CT. The latter diet demonstrated markedly improved myocardial suppression, higher interobserver agreement and fewer indeterminant/positive cardiac sarcoidosis diagnosis.

Implications for Patient Care: 72-h ketogenic diet with overnight fasting can be applied instead of current SNMMI-ASNC dietary recommendations, as this new diet is well-tolerated and improves the cardiac sarcoidosis diagnosis by eliminating indeterminant and false positives.

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FIGURE-1: 62-year-old female with inferior wall motion abnormality, arrhythmia and an old outside PET/CT report raising suspicion of cardiac sarcoidosis. Prior endomyocardial biopsy was negative. No pathologic or imaging proof of sarcoidosis elsewhere in the body. Based on clinical findings, patient was considered as presumable cardiac sarcoidosis and referred for PET/CT. First PET/CT was obtained with Diet-B, (top row is ^{13}N -ammonia, middle row is ^{18}F -FDG /PET), which was reported as active cardiac sarcoidosis with complete myocardial suppression. However, the observer evaluated as indeterminant secondary to partial suppression. Patient subsequently received steroids and a follow-up study was performed with Diet-C (lower row). This time, both the report and observer agreed that there was complete suppression with no active cardiac sarcoidosis. While it is possible that this presumable cardiac sarcoidosis case might have responded treatment, it is also possible that the initial interpretation was wrong, and patient might have received unnecessary treatment.

FIGURE-2: 73-year-old male with chronic pericarditis and suspicion of cardiac sarcoidosis. First exam was obtained with Diet-B, (a)¹³N-ammonia and (b) ¹⁸F-FDG. Initially, this exam was interpreted as incomplete myocardial suppression and indeterminant cardiac sarcoidosis, agreed by the observer. Repeat ¹⁸F-FDG study with Diet-C(c), showed complete myocardial suppression with negative cardiac sarcoidosis, agreed by the observer and the report.

FIGURE-3: 35-year-old male. The first exam was obtained with Diet-A. Due to incomplete myocardial suppression, exam was repeated 2 days later with Diet-B . This showed partial myocardial suppression in the lateral wall with indeterminant result. Patient had a follow-up MRI (not shown here), which was negative for cardiac sarcoidosis at that time. A third follow-up with Diet-C showed complete myocardial suppression. Note the persistence of hypermetabolic mediastinal lymph nodes in all three exams.

FIGURE-4: 65-year-old male with new arrhythmia and a cardiac MRI (not shown), suspicious for sarcoidosis. Patient was referred for PET/CT obtained with Diet-C. Top row is ^{18}F -FDG and lower row is ^{13}N -ammonia. Both report and observer called this exam as active cardiac sarcoidosis with complete myocardial suppression. Note the mismatch pattern at the regions with active cardiac sarcoidosis (pink arrows) and how myocardium is well suppressed at normally perfused areas (blue arrows).

Graphical Abstract

Table-1. A simplified copy of dietary instruction given for each patient in a specific diet group.

Diet A	<p>-High fat low carbohydrate diet beginning 24 hours prior to the study.</p> <p>- Nothing by mouth, except water and oral pills, six hours before the exam.</p>	<p><u>Allowed foods</u></p> <p>-Beverages: club soda, black coffee, tea (without sugar), or water</p> <p>-Seasonings: Anything that does not contain sugar</p> <p>-Fats/Oils: butter, margarine, or vegetable oils</p> <p>-Eggs</p> <p>-Meat: Chicken, turkey, fish, beef, or pork (watch closely for sugars in processed meats), meat only sausages and non-sweetened bacon</p> <p>-Shellfish: Any non-processed shellfish</p> <p>Vegetables: alfalfa sprouts, artichokes, asparagus, bean sprouts, broccoli, Brussels sprouts, cabbage, celery, cucumber, eggplant, any lettuce</p>	<p><u>Forbidden Foods</u></p> <p>No carbohydrate or sugars</p> <p>- Anything with glucose, fructose, sucrose, or lactose</p> <p>- No artificial sweeteners</p> <p>- No fruit or fruit juices</p> <p>- No diet or regular sodas or sports drinks</p> <p>- No alcohol</p> <p>- No dairy products such as milk, cheese, cream or yogurt</p> <p>- No pastas, breads, cereals, rice, bagels, crackers, or muffins</p> <p>- No breadings on any food</p> <p>- No candy, cookies, or cake</p> <p>- No gum, mints, or cough drops</p> <p>- No condiments like ketchup and mustard with sugar in it.</p> <p>- No starchy vegetables such as corn, peas, carrots, most legumes, grains, and potatoes</p>
Diet B	<p>-18 hours of fasting prior to the study.</p> <p>- Nothing by mouth, except water and oral pills, for 18 hours prior to the study.</p>		
Diet C	<p>-High fat low carbohydrate ketogenic diet beginning 72 hours prior to the study.</p> <p>- Nothing by mouth, except water and oral pills, for three overnight fasts before the exam. First two nights from 08:00pm until at least 08:00 am the next morning. The night before the test from 08:00 pm until the time of the test.</p> <p>- For diabetics, consider avoiding prolonged fasting, preferably obtain the exam at noon hours after ketogenic breakfast + morning insulin, followed by 6-h fasting.</p>	<p><u>Allowed foods</u></p> <p>-Beverages: club soda, black coffee, tea (without sugar), or water</p> <p>-Seasonings: Anything that does not contain sugar</p> <p>-Fats/Oils: butter, margarine, or vegetable oils</p> <p>-Eggs</p> <p>-Meat: Chicken, turkey, fish, beef, or pork (watch closely for sugars in processed meats), meat only sausages and non-sweetened bacon</p> <p>-Shellfish: Any non-processed shellfish</p>	<p><u>Forbidden Foods</u></p> <p>No carbohydrate or sugars</p> <p>- Anything with glucose, fructose, sucrose, or lactose</p> <p>- No artificial sweeteners</p> <p>- No fruit or fruit juices</p> <p>- No diet or regular sodas or sports drinks</p> <p>- No alcohol</p> <p>- No dairy products such as milk, cheese, cream or yogurt</p> <p>- No pastas, breads, cereals, rice, bagels, crackers, or muffins</p> <p>- No breadings on any food</p> <p>- No candy, cookies, or cake</p> <p>- No gum, mints, or cough drops</p> <p>- No condiments like ketchup and mustard with sugar in it</p> <p>- Vegetables are not permitted. No beans or nuts.</p>

TABLE-2. Quantitative comparison of diets

	Diet-A(n=94)	Diet-B(n=44)	Diet-C(n=98)	Total(n=236)	P
Age					
Mean(SD)	55.9(11.4)	58.3(10.2)	60.6(11.6)	58.3(11.4)	0.018
Range	26-83	26-73	24-81	24-83	
Sex					
Male	29(30.9%)	14(31.8%)	37(37.8%)	80(33.9%)	0.570
Female	65(69.1%)	30(68.2%)	61(62.2%)	156(66.1%)	
Body-Mass-Index					
Missing	3	2	6	11	0.380
Mean(SD)	31.5(6.3)	30.1(6.1)	31.6(6.5)	31.3(6.3)	
Range	17.2-47.2	17.9-46.1	18.3-52	17.2-52	
¹³N-ammonia (MBq)					
Not present.	17	15	31	63	0.620
Mean(SD)	717.8(140.6)	740(103.6)	736.3(103.6)	728.9(122.1)	
Range	266.4-899.1	373.7-891.7	92.5-854.7	92.5-899.1	
¹⁸F-FDG (MBq)					
Mean(SD)	555(44.4)	558.7(37)	566.1(33.3)	562.4(40.7)	0.355
Range	388.5-658.6	469.9-610.5	451.4-636.4	388.5-658.6	
Blood glucose (mg/dl)					
Mean(SD)	99.5(21)	99.4(17.6)	91.6(25.7)	96.2(22.8)	0.032
Range	60-196	77-150	43-202	43-202	
Bloodpool-MaxSUV					
Mean(SD)	2.6(0.6)	2.6(0.5)	2.9(0.6)	2.7(0.6)	0.005
Range	1.3-3.9	1.4-3.6	1.5-4	1.3-4	
Liver-MaxSUV					
Mean(SD)	3.6(0.9)	3.7(0.8)	3.8(0.8)	3.7(0.8)	0.462
Range	1.3-6.7	2.1-5.8	1.9-6.5	1.3-6.7	
Myocardium-MaxSUV)					
Mean(SD)	3.5(3.5)	4.4(3.7)	2.0(0.8)	3(2.9)	<0.001
Range	1.2-22	0.9-16.2	0.8-7.4	0.8 – 22	
Bloodpool/myocardium					
Mean(SD)	1.1(0.5)	0.9(0.5)	1.6(0.4)	1.3(0.5)	<0.001
Range	0.1-2.2	0.1-2	0.4-3.1	0.1- 3.1	
Liver/myocardium					
Mean(SD)	1.6(0.8)	1.4(0.8)	2.1(0.6)	1.8(0.8)	<0.001
Range	0.2-3.9	0.2-3.9	0.5-4.1	0.2-4.1	
Lesion-MaxSUV					
Mean(SD)	7.4(4.1)	7(3.1)	7.8(3.5)	7.4(3.6)	0.858
Range	3.2-19	4.2-15.3	4-15.1	3.2-19	

TABLE-3. Qualitative comparison of diets regarding myocardial suppression and diagnosis according to the initial radiology report and the observer

	Diet-A(n=94)	Diet-B(n=44)	Diet-C(n=98)	Total(n=236)	P
Myocardial Suppression					
Radiology report					<i>0.052</i>
Failed suppression	9(9.6%)	7(15.9%)	3(3.1%)	19(8.1%)	
Partial suppression	2(2.1%)	2(4.5%)	1(1%)	5(2.1%)	
Complete suppression	83(88.3%)	35(79.5%)	94(95.9%)	212(89.8%)	
Observer					<i><0.001</i>
Failed suppression	22(23.4%)	11(25.0%)	0(0%)	33(14%)	
Partial suppression	8(8.5%)	10(22.7%)	3(3.1%)	21(8.9%)	
Complete suppression	64(68.1%)	23(52.3%)	95(96.9%)	182(77.1%)	
Diagnosis					
Radiology report					<i><0.001</i>
Negative	49(52.1%)	15(34.1%)	82(83.7%)	146(61.9%)	
Indeterminant	4(4.3%)	6(13.6%)	1(1%)	11(4.7%)	
Positive	41(43.6%)	23(52.3%)	15(15.3%)	79(33.5%)	
Observer (Recategorized according to SNMMI-ASNC)					<i><0.001</i>
Negative	49(52.1%)	12(27.3%)	81(82.7%)	142(60.2%)	
Indeterminant	23(24.5%)	18(40.9%)	2(2%)	43(18.2%)	
Positive	22(23.4%)	14(31.8%)	15(15.3%)	51(21.6%)	
Observer (Recategorized according to Lu)					<i><0.001</i>
Negative	53(56.4%)	18(40.9%)	81(82.7%)	152(64.4%)	
Indeterminant	19(20.2%)	12(27.3%)	2(2%)	33(14%)	
Positive	22(23.4%)	14(31.8%)	15(15.3%)	51(21.6%)	
Observer (SNMMI-ASNC)					<i><0.001</i>
Normal	40(42.6%)	10(22.7%)	62(63.3%)	112(47.5%)	
Diffuse non-specific	23(24.5%)	18(40.9%)	2(2%)	43(18.2%)	
Early active disease	8(8.5%)	2(4.5%)	4(4.1%)	14(5.9%)	
Active disease	6(6.4%)	9(20.5%)	5(5.1%)	20(8.5%)	
Mixed scar/active disease	8(8.5%)	3(6.8%)	6(6.1%)	17(7.2%)	
Scar	9(9.6%)	2(4.5%)	19(19.4%)	30(12.7%)	
Observer (Lu)					<i><0.001</i>
Normal	49(52.1%)	12(27.3%)	81(82.7%)	142(60.2%)	
Negative	4(4.3%)	6(13.6%)	0(0%)	10(4.2%)	
Positive	22(23.4%)	14(31.8%)	15(15.3%)	51(21.6%)	
Indeterminate	19(20.2%)	12(27.3%)	2(2%)	33(14.0%)	
Systemic sarcoidosis					<i>0.414</i>
Negative	55(58.5%)	30(68.2%)	65(66.3%)	150(63.6%)	
Positive	39(41.5%)	14(31.8%)	33(33.7%)	86(36.4%)	

TABLE-4. Correlation of the myocardial suppression according to the initial radiology report and the observer

	Observer			
	Failed (n=33)	Partial (n=21)	Complete (n=182)	Total (n=236)
Radiology report				
Failed	12(36.4%)	1(4.8%)	6(3.3%)	19(8.1%)
Partial	2(6.1%)	3(14.3%)	0(0%)	5(2.1%)
Complete	19(57.6%)	17(81%)	176(96.7%)	212(89.8%)

$\kappa=0.41$

TABLE-5. Correlation of observer's diagnosis according to recategorized SNMMI-ASNC and Lu classification

	Recategorization according to SNMMI-ASNC				
		Negative(n=142)	Indeterminant(n=43)	Positive(n=51)	Total(n=236)
Recategorization according to Lu					
	Negative	142(100%)	10(23.3%)	0(0%)	152(64.4%)
	Indeterminant	0(0%)	33(76.7%)	0(0%)	33(14.0%)
	Positive	0(0%)	0(0%)	51(100%)	51(21.6%)

$\kappa=0.97$

TABLE-6. Correlation of the initial radiology report with the observer according to the recategorized diagnosis based on SNMMI-ASNC and Lu classification

		Radiology report			
		Negative (n=146)	Indeterminant (n=11)	Positive (n=79)	Total (n=236)
Observer	Recategorization according to SNMMI-ASNC*				
	Negative	141(96.6%)	0(0%)	1(1.3%)	142(60.2%)
	Indeterminant	3(2.1%)	11(100%)	29(36.7%)	43(18.2%)
	Positive	2(1.4%)	0(0%)	49(62%)	51(21.6%)
	Recategorization according to Lu**				
	Negative	142(97.3%)	2(18.2)	8(10.1%)	152(64.4%)
	Indeterminant	2(1.4%)	9(81.8%)	22(27.8%)	33(14%)
	Positive	2(1.4%)	0(0%)	49(62%)	51(21.6%)

* $\kappa=0.88$

** $\kappa=0.82$