Can PET/CT Imaging Replace Adrenal Vein Sampling as the Gold Standard for Lateralizing Aldosterone Hypersecretions?

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Abstract

Objectives: To investigate the potential of PET/CT imaging, using either ^{11}C-metomidate (CMTO) or ^{18}F-flurodeoxyglucose (FDG), to replace adrenal vein sampling as a widely-used lateralization procedure for primary hyperaldosteronism.

Hypothesis: PET/CT imaging using a special radiotracer will prove to be an effective lateralization method that can potentially act as a substitute for AVS.

Methods: Publications for this review were obtained using relevant MeSH terms in PubMed. Literature searches were done separately between the two radiotracers investigated in this review. Articles from the MeSH searches were then screened using inclusion/exclusion criteria in order to gain a final set of publications to be reviewed.

Results: A final total of thirteen articles were found from the literature search. Three of them were literature review studies, while the remaining articles were comparative effectiveness research studies. The publications that measured standardized uptake values showed that CMTO had a greater uptake in unilateral aldosterone-producing adenomas than FDG. All articles that compared AVS against CMTO concluded by supporting the use of CMTO as a lateralization method.

Conclusion: The literature shows that the radiotracer CMTO demonstrates a high uptake in unilateral APAs similar to those found in primary hyperaldosteronism. These findings suggest that CMTO PET/CT would be an effective lateralization procedure and does have the potential to act as an alternative to AVS. The literature on FDG showed that it had a relatively low uptake in adrenocortical tumors. Hence, FDG PET/CT does not have the potential to be an effective lateralization procedure and cannot replace AVS.

Introduction

Conn's Syndrome, also called primary hyperaldosteronism (PA), is a condition characterized by elevated serum aldosterone levels and is associated with a variety of characteristic symptoms, including hypertension. It is estimated that more than 25% of Americans have hypertension, 15% of which as a result of primary hyperaldosteronism (1). The two main causes of PA are either bilateral adrenal hyperplasia (BAH) or the presence of a unilateral aldosterone-producing adenoma (APA). Distinguishing between these two causes is crucial in the treatment and management of PA. PA caused by bilateral adrenal hyperplasia is managed with anti-hypertensive medications, while unilateral APAs can be resected via surgery commonly leading to a full cure of hypertension in PA patients (2). The process of subtyping

primary hyperaldosteronism as being caused by either BAH or APAs is called lateralization. Adrenal vein sampling (AVS) is considered the gold standard procedure for lateralizing aldosterone hypersecretions. The procedure involves gauging the position of each adrenal vein using high-quality CT scanning, followed by the insertion of catheters into the adrenal veins in order to obtain serum values that will lead to the subsequent subtyping of a patient's PA.

The Endocrine Society, the world's oldest and largest organization dedicated to advancing hormone research and clinical endocrinology, recognizes only adrenal vein sampling as a reliable way to correctly subtype primary hyperaldosteronism (3). Despite this, however, AVS as a lateralization procedure has critical shortcomings. One such shortcoming is the inherent difficultly in performing the procedure accurately. Specifically, AVS requires the cannulation of both adrenal veins, which has proven to be a challenging step in the procedure. The left adrenal vein, in particular, is difficult to cannulate due to its small diameter, typically ranging from 3.5-5.0 mm (4). Another shortcoming of AVS is the lack of general consensus on the technique of the procedure (i.e. with or without ACTH stimulation) and the interpretation of the results (i.e. lateralization index criteria and adrenal/peripheral vein cortisol ratio). The absence of procedural agreement prevents all PA patients from receiving consistent optimal care (5).

During the many years that AVS has existed as the gold standard for lateralizing aldosterone hypersecretions, interest toward the potential utility of PET/CT has grown. Many believe that PET/CT imaging and specific radiotracers, like ^{18}F-fluorodeoxyglucose and ^{11}C-metomidate, can be used to effectively identify unilateral APAs in PA patients, thus establishing a lateralization procedure that circumvents the shortcomings associated with AVS. ^{18}F-fluorodeoxyglucose (FDG) is a radiolabeled glucose analog used as a marker for the uptake of

glucose by tissues, which in turn can be used to correlate the level of metabolism in certain tissues. ^{11}C-metomidate (CMTO) is a radiolabeled derivative for metomidate, a potent inhibitor of CYP11B1 (11β-hydroxylase) and CYP11B2 (aldosterone synthase) enzymes, which are important enzymes for cortisol and aldosterone synthesis in the adrenal cortex (6). The goal of this review is to assess whether PET/CT imaging using FDG or CMTO can effectively identifying APAs, thereby replacing AVS as a method of lateralizing aldosterone hypersecretions. It is hypothesized that PET/CT imaging using a special radiotracer will prove to be an effective lateralization method that can potentially act as a substitute for AVS.

Methods

The review was conducted using publications obtained through the use of relevant Medical Subject Heading (MeSH) terms established within the PubMed database. The search for publications in PubMed and the use of related MeSH terms were done individually between the two lateralization methods discussed in this review: ^{18}F-flurodeoxyglucose PET/CT imaging and ^{11}C-metomidate PET/CT imaging.

^{18}F-flurodeoxyglucose PET/CT imaging

Publications regarding FDG PET/CT were obtained by first using the MeSH terms “Fluorodeoxyglucose F18” and “Adenoma” coupled with its subheading “diagnostic imaging” *("Fluorodeoxyglucose F18"[Mesh]) AND "Adenoma/diagnostic imaging"[Mesh]*). The related entry terms in the MeSH database under the term “Fluorodeoxyglucose F18” included its abbreviations (“18F-FDG” and “18FDG”) as well as its full chemical name (“2-Fluoro-2-deoxy-D-glucose”). The resulting amount of publications from the MeSH search were further screened using inclusion and exclusion criteria. The applied inclusion criteria were as follows: (I) articles

discussing tumors of specifically the adrenal gland, (II) articles discussing primary hyperaldosteronism, (III) articles discussing the use of FDG as a PET/CT radiotracer, and (IV) articles comparing FDG to AVS. The applied exclusion criteria were as follows: (I) studies on non-humans (i.e. mice and rats), (II) articles with a published date older than 20 years, and (III) case report/series and cross-sectional studies. Related publications listed as citations to the screened articles were also considered. The final remaining articles were deemed relevant and subsequently examined.

^{11}C-metomidate PET/CT imaging

Publications for CMTO PET/CT were obtained using the MeSH term “Metomidate”. The related entry terms established in the MeSH database under the term “Metomidate” its radiolabeled derivative, “C-11 metomidate”. The resulting amount of publications from the MeSH search were further screened using inclusion and exclusion criteria. The applied inclusion criteria were as follows: (I) articles discussing tumors of specifically the adrenal gland, (II) articles discussing primary hyperaldosteronism, (III) articles comparing CMTO to AVS. The applied exclusion criteria were as follows: (I) studies on non-humans (i.e. frogs and fish), (II) studies discussing CMTO as a hypnotic agent or anesthetic, (III) articles with a published date older than 20 years, and (IV) case report/series and cross-sectional studies. Additional publications listed as citations to the screened articles were also considered. The final remaining articles were deemed relevant and subsequently examined.

Data Analysis

In this review, standardized uptake values (SUVs) were used to gauge the effectiveness of a radiotracer to identify an aldosterone-producing adenoma. Specifically, the measured

difference between the SUVs in adrenocortical tumors and normal glands were used for each radiotracer as a way to compare the success of each radiotracer across multiple research studies. This measure was used based on the fact that the greater the difference in SUVs between the unilateral APA and the normal adrenal tissue, the more apparent the presence of the APA in a particular PA patient. The clear identification of a unilateral adenoma in a PA patient will facilitate their guidance into adrenal gland surgery and subsequent cure or significant lessening of their hypertension. The measured difference of normal and abnormal SUVs was taken across the studies examined in this review and compared in order to estimate the effectiveness of each radiotracer.

Results

A final total of thirteen publications were considered as a result of the search process, six of which focused primarily on FDG and the remaining seven focused primarily on CMTO. Of the final thirteen articles, three of them were literature review studies that compared AVS to CMTO. No articles were found that directly compared FDG to AVS. The remaining ten were comparative effectiveness research studies that tested the effects of PET/CT and a certain radiotracer on a patient population. Figure 1. displays the flowchart detailing the search process for FDG-related publications. As seen in Figure 1, the MeSH search produced two hundred eighty-two articles, which were narrowed down to the final six articles by the inclusion/exclusion criteria screening.

Figure 1. Literature Search Process for FDG-Related Articles

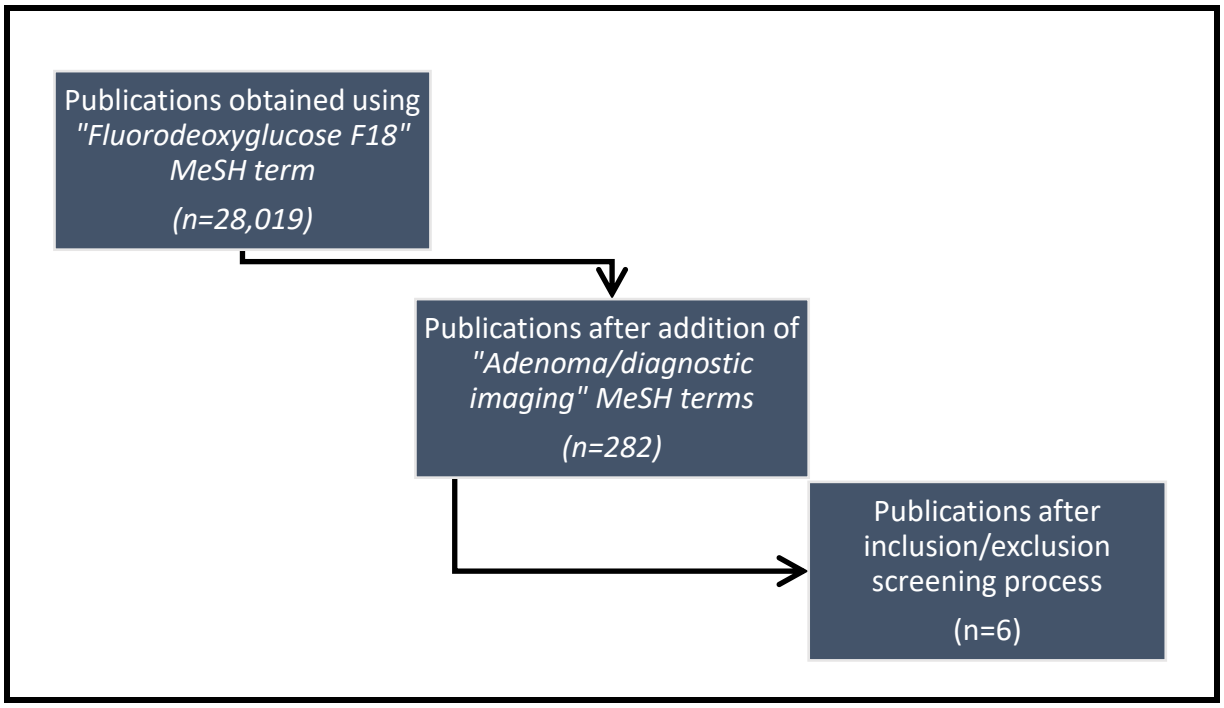

Figure 1. *Flowchart outlining the steps of the literature search process for FDG-related articles and the number of articles obtained after each step, denoted as "n=x".*

The literature search process for CMTO-related articles is displayed in Figure 2. As seen in the Figure 2, the MeSH search produced forty-four articles that reduced to seven after being screened using inclusion/exclusion criteria.

Figure 2. Literature Search Process for CMTO-Related Articles

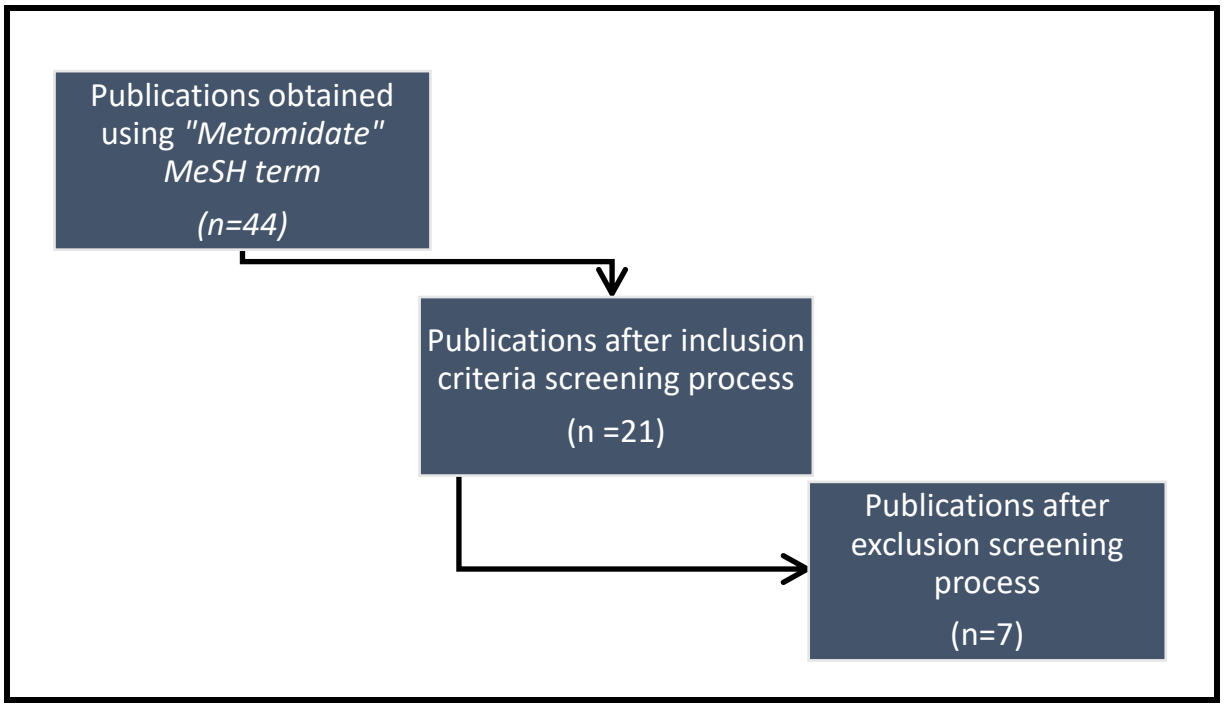

Figure 2*. Flowchart outlining the steps of the literature search process for CMTO-related articles and the number of articles obtained after each step, denoted as "n=x".*

Many publications regarding the CMTO radiotracer highlighted its ability to identify adrenocortical tumors. Zettining et all, in particular, examined eleven patients with functioning adrenal tumors, five of which were diagnosed with Conn's Syndrome. They found that CMTO PET/CT clearly distinguished between cortical and non-cortical adrenal tumors with median standardized uptake values of 18.6 and 1.9 respectively ($p<0.01$) (**7**). Burton et al similarly found that CMTO clearly distinguishes between unilateral adrenocortical adenomas and normal functioning adrenal glands. SUVs in unilateral adenomas measured 21.7 ± 1.6 and were

significantly higher than in the examined normal adrenals, with SUVs of 13.8 ± 0.6 (*P* = 0.00003) (8). These studies suggest that CMTO has a consistent uptake in adrenocortical tumors.

Comparatively, publications regarding FDG revealed that it is not as effective in identifying unilateral adrenal adenomas. In particular, Minn et al conducted a comparative study between CMTO PET/CT and FDG PET/CT that evaluated each's ability to identify various tumors of the adrenal gland. They found that adrenocortical tumors had a relatively low uptake of FDG ($SUV_{average}$ = 2.9) compared to CMTO ($SUV_{average}$ = 28.0), suggesting that CMTO is better suited for identifying tumors of adrenocortical origin than FDG (9). The study performed by Akkus et al, where one hundred nine patients were screened using FDG PET/CT, found that certain functioning adrenal adenomas only produced mild FDG uptake values (10). Publications regarding FDG PET/CT instead highlighted its ability to distinguish between benign and malignant adrenal tumors. Launay et al, for instance, found that FDG had a significantly higher uptake in malignant adrenal carcinomas (SUV_{max} = 11.1) than in benign adrenal adenomas (SUV_{max} = 3.24) ($P<0.05$) (11). This finding is consistent with the review conducted by Hahner et al., which investigated the use of radiotracers in identifying adrenal masses. The review concluded that FDG PET/CT does indeed help in distinguishing between malignant and benign adrenal lesions, but does not differentiate cortical and non-cortical lesions (12). In addition, the review also echoed the previous findings regarding CMTO PET/CT by concluding that CMTO is a useful radiotracer for identifying cortical adenomas because of its highly specific uptake in adrenocortical cells. However, one clinical study highlighted a potential limitation of CMTO as a radiotracer. Khan et al investigated the effect of medications containing adrenal steroid inhibitors and chemotherapy on the uptake of CMTO (13). They found that both steroid inhibitor

medications and chemotherapy lead to a decrease in measured SUV, which could possibly prevent a clear distinction between adenomas and normal adrenal tissue.

Multiple publications were found that directly compared AVS against CMTO PET/CT as a lateralization procedure for subtyping primary hyperaldosteronism. O'Shea conducted a clinical study which evaluated the use of CMTO PET/CT in fifteen patients already diagnosed with primary hyperaldosteronism via CT scanning (14). They found that CMTO PET/CT provided useful information when AVS gave inconclusive results that helped inform clinical decisions that guided patients toward surgery and subsequent cure or lessening of PA symptoms. The review concluded by suggesting that CMTO could serve as a useful supplement alongside AVS. Similarly, the review by Powlson et al, which investigated the recent clinical use of CMTO, concluded by categorizing CMTO PET/CT as a "rapid, non-invasive alternative to AVS" for localizing unilateral aldosterone-producing adenomas (15). Mendichovszky et al explored the use of CMTO as a radiotracer for the treatment and management of adrenal disease (16). Their study described CMTO as a welcomed addition to the diagnostic options for primary hyperaldosteronism that could remove the roadblocks seen in AVS, thus leading to more potential patients with confirmed unilateral adenomas undergoing curative surgery.

Discussion

Overall, the reviewed publications support the initial hypothesis, which stated that PET/CT imaging using a specific radiotracer would prove to be an effective lateralization procedure. All of the reviewed articles that measured the standardized uptake values of CTMO in PA patients with unilateral APAs demonstrated a clear and significant difference between the APAs and normal adrenal tissue. This clear difference in SUVs makes the presence of unilateral APAs very apparent, making them easy to spot in PA patients. This is important because once

unilateral APAs are identified, PA patients can be readily directed to surgery for resection of the unilateral APA and subsequently become cured of their hypertension. The ability of CMTO PET/CT to consistently produce clear and significant differences in SUVs between the adenomas and normal tissue is what suggests that CTMO PET/CT is an effective lateralization procedure. One aspect that suggests that CMTO PET/CT can replace AVS as a widely-used lateralization procedure is the fact that it avoids the shortcomings associated with AVS. Two important shortcomings of AVS include difficulty in cannulating the left adrenal vein and the lack of consensus in the technique of AVS or the interpretation of the results. However, CMTO PET/CT does not require the cannulation of adrenal veins and uses a completely separate set of techniques and measures. As a result, CMTO PET/CT provides a potential lateralization method that circumvents the two important shortcomings of AVS.

This literature review, however, did discover potential limitations of CMTO PET/CT. The study by Khan et al found that patients taking adrenal steroid inhibitors or patients on chemotherapy showed a decrease in uptake on CMTO. The reduced uptake of CMTO in adrenocortical tumors would make it relatively harder to distinguish them from normal functioning adrenal glands and would ultimately reduce the reliability of CTMO PET/CT in PA patients who are also taking adrenal corticosteroids and/or on chemotherapy regimens. This finding suggests that there is a limit to the number of PA patients that could possibly benefit from CMTO PET/CT. In addition, the review by Mendichovszky et al also mentioned that CMTO has a relatively short half-life of 20 minutes, which requires the presence of an on-site cyclotron in order to generate the radiotracer. This requirement could possibly limit the clinical application of CMTO PET/CT in certain locations that can not accommodate the necessary machinery.

The results regarding FDG, on the other hand, do not suggest that it would be a good radiotracer for lateralizing aldosterone hypersecretions. All publications that measured the SUV of FDG found that it had a relatively low uptake in adrenocortical tumors. This prevents the clear differentiation between abnormal and normal tissue and, thus, does not facilitate the clear-cut identification of unilateral APAs.

The limitations of this literature review include the small quantity of publications used. The use of CTMO PET/CT as a lateralization method is relatively new, which resulted in the total publications obtained being less than ideal. This literature review also included some clinical studies with small patient sample sizes ($n<30$). In addition, no randomized control trials were available to be investigated because none were found during the literature search process. RCT would have been optimal for the comparison AVS and PET/CT with specific radiotracers.

Conclusion

The current literature shows that CMTO has a relatively high uptake in unilateral APAs, which suggest that it can be used with PET/CT imaging as a radiotracer to identify them. This supports the initial hypothesis stating that CMTO PET/CT can in fact be used as a lateralization procedure to replace AVS, mainly because it sidesteps the shortcomings associated with AVS while still proving to be effective. The literature does not support the use of FDG PET/CT as a procedure to replace AVS because of its relatively low uptake in unilateral APAs. Future research regarding this topic will include investigating other radiotracers that were not included in this review. For instance, certain norcholesterol-based radiotracers like ^{131}I-iodomethyl-norcholesterol and ^{75}Se-selenomethyl-19 -norcholesterol have been used historically in adrenal scintigraphy for the detection of adrenal masses. These norcholesterol-based radiotracers could be investigated to gauge their ability to identify APAs and then subsequently compared with

CMTO to determine which radiotracer serves as the most effective lateralization tool. Another avenue for future research is to investigate the possible techniques used to increase the uptake of CMTO into adrenal tissue, which would help improve its use as a lateralization method.

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