18F-FDG PET/CT use in functional assessment of the testes: A systematic review

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Abstract

Introduction: Our study analysed previous studies employing positron emission tomography with co-registered computer tomography (PET/CT) in andrological patient evaluation and assessed the differences in 2-[^18]F-fluoro-2′-deoxyglucose (FDG) uptake between three groups: healthy testes, benign and malignant testicular pathology.

Methods: Medline and Embase were systematically searched for studies involving FDG-PET/CT imaging of testes with results expressed as mean standardised uptake value (SUVmean). A one-way ANOVA was used to compare SUVmean between three groups. All papers assessing andrological parameters were pooled to compare fertility data.

Results: Seventeen studies, including three relating to fertility diagnosis, with a total of 830 patients, were included in the review. One-way ANOVA showed a statistical difference between mean values of tracer SUVmean in healthy and malignant testes (Dif. = −2.77, 95% CI = −4.32 to 1.21, p < 0.01) as well as benign and malignant (Dif. = −2.95, 95% CI = −4.33 to −1.21, p < 0.01) but no difference between healthy and benign (Dif. = 0.19, 95% CI = −0.96 to 1.33, p = 0.90). There is some evidence to suggest that FDG uptake and testicular volume are positively correlated to total sperm count, sperm concentration and sperm motility and that germ cells are likely to account for the majority of testicular FDG accumulation.

Conclusion: Our findings indicate that malignant testicular lesions demonstrate a significantly higher FDG uptake than benign testicular lesions or healthy testes. Some evidence also suggests that FDG-PET could visualise metabolic activity and thus spermatogenesis; however more studies are required to determine whether FDG-PET could also be used to diagnose infertility. Further studies should focus on correlating both sex hormone-serum levels and semen analysis results with imaging data.
1 | INTRODUCTION

2-\[^{18}\text{F}\]-fluoro-2'-deoxyglucose (FDG) is a well-established radiotracer for metabolic activity.\(^1\) \(^{18}\text{F}\) is a positron-emitting radioisotope and can be imaged within the human body by positron emission tomography (PET). PET is frequently paired with X-ray computed tomography (CT) to form a non-invasive hybrid diagnostic tool that provides metabolic activity information alongside anatomical insight. FDG uptake is substantially increased in most malignancies when compared to normal tissues, often allowing for cancer detection earlier than through anatomical imaging alone.\(^2\) However, FDG uptake is not cancer-specific and its uptake may be seen in numerous hypermetabolic processes such as inflammation, as well as in normal cardiac, lung and brain tissue.\(^3\)\(^-\)\(^8\)

PET/CT has been used extensively for the diagnosis and assessment of benign and malignant lesions in many organs.\(^9\)\(^,\)\(^10\) In urology, PET/CT plays a role in the management of prostate, kidney and bladder cancers; however, PET/CT is currently not the first-line investigation for diagnosis and staging of testicular cancers due to high sensitivity and diagnostic accuracy of other cross-sectional forms of imaging such as ultrasound or CT.\(^11\) Additionally, scrotal ultrasonography remains the most used imaging modality for the diagnosis of male infertility, primarily due to the lack of any ionising radiation being involved.\(^12\) Recent evidence has suggested links between specific testicular ultrasonography findings and impaired spermatogenesis,\(^13\)\(^,\)\(^14\) although the implication of these associations on clinical practice remains unclear.

Male infertility remains a debilitating condition, which currently lacks a single imaging modality enabling its diagnosis. Harvesting spermatozoa for further use in assisted reproduction techniques (ART) is an expensive, time-consuming, and invasive procedure which can ultimately have a detrimental effect on sperm quality. Testicular sperm extraction (TESE), which remains the last resort intervention for the most severe forms of male infertility, is successful only in 50%-54% of cases.\(^15\)\(^,\)\(^16\) FDG-PET/CT may enable better non-invasive characterisation of testicular viability prior to TESE and reflect overall fertility of male patients. Dierickx et al.\(^17\) were the first to suggest FDG-PET/CT could have the potential to become a first-line investigation allowing for non-invasive real-time assessment of testicular function, and also suggested prediction of success and the guidance of TESE as one of the investigation’s potential applications.

The accumulation of FDG in normal testicular tissue has been established to be significantly greater than in muscle as a result of higher glucose metabolism.\(^5\)\(^,\)\(^18\)\(^-\)\(^20\) FDG enters cells via the same transport mechanism as glucose and is phosphorylated by hexokinase to form FDG-6-phosphate which is not further metabolised.\(^21\) FDG uptake into testicular tissue is especially linked with the presence of GLUT-1 and GLUT-3 receptors.\(^22\) The latter has been found to be the predominant receptor in human testes due to its presence on Sertoli cells and early spermatocytes. Hence FDG-PET/CT may help to better characterise testicular function. Furthermore, estimation of testicular metabolism by FDG-PET/CT could visualise the ability of the testis to produce androgens and hence can be a reflection of the patient’s androgenic status.\(^23\)\(^,\)\(^24\)

Despite promising outcomes of multiple studies assessing the use of FDG-PET/CT in infertility, no study has explicitly been able to attribute FDG uptake to a specific testicular function, be it sperm or hormone production. Furthermore, no attempts to review and appraise the value of FDG-PET/CT in andrology have been reported.

This systematic review was undertaken to bridge the gap between testicular imaging and functional assessment of infertile patients, and to evaluate whether PET/CT can be a valid predictor of male fertility. Our aims were:

\begin{itemize}
\item to review the use of PET/CT for the differentiation of FDG uptake into healthy testes, benign testicular pathology and malignant testicular tumours.
\item to review the evidence base for using FDG-PET/CT to image testicular function, with emphasis on male fertility assessment.
\end{itemize}

2 | METHODS

2.1 | Selection criteria

This systematic review was conducted in conformity with the PRISMA guidelines for systematic reviews and a review protocol was established with PROSPERO (ID: CRD42018102668). A search of literature published between 1 January 1980 to 11 June 2020 was performed across two databases: Medline and Embase. References of relevant articles were also screened to reveal any omitted articles through database search. The search terms used to identify relevant papers were variations of the following terms: “tes*s”, “testes”, “testis”, “scrot”", “PET” and “position emission tomography”. Pre-determined inclusion and exclusion criteria were used to identify eligible studies.

Inclusion and exclusion criteria used are listed in Table 1: only full-text articles in English, including a male population, with results of FDG-PET/CT of the scrotal region expressed as mean or maximum standardised uptake value (SUV\(_{\text{mean}}\); SUV\(_{\text{max}}\)) were included. Studies utilising PET scanning only, but reporting SUV relevant to the scope of this review were also considered for inclusion. Articles using alternate PET tracers, assessing uptake primarily into non-testicular tissues or not reporting raw or mean SUV\(_{\text{mean}}\) or SUV\(_{\text{max}}\) were excluded from this review.
**TABLE 1** Inclusion and exclusion criteria of the applied search method

| Inclusion criteria          | Exclusion criteria                  |
|----------------------------|-------------------------------------|
| Full-text articles          | Alternate tracer to FDG used in PET imaging |
| English language            | Primary uptake into non-testicular tissue |
| Male population             | Lack of SUV<sub>mean</sub> or SUV<sub>max</sub> reported |
| FDG-PET/CT or PET modality used | Imaging results expressed as SUV<sub>mean</sub> or SUV<sub>max</sub> |

**Abbreviations:** FDG, 2-<sup>18</sup>Ffluoro-2'-deoxyglucose; PET, positron emission tomography; PET/CT, positron emission tomography with co-registered X-ray computed tomography; SUV<sub>max</sub>, maximal standardised uptake value; SUV<sub>mean</sub>, Mean standardised uptake value.

Standardised uptake value (SUV) which represents the proportion of radioactive tracer in a region of interest compared to the total injected radioactivity is the most widely used tracer uptake unit in human PET imaging.っ SUV<sub>mean</sub> is a measure of the mean relative uptake of radioactive tracer into an area of interest. SUV<sub>max</sub> or SUV<sub>peak</sub> are measures of relative uptake in an area within a region of interest (a voxel or a cubic centimetre spherical volume) which, on assessment of imaging, visually shows greatest uptake of tracer.

2.2 | Data extraction

The literature review, based on pre-defined selection criteria, was performed by two authors with the consultation of a third reviewer when needed. The following information was extracted from the reviewed studies: article title and authors, journal title, study period, country of study, study design, imaging modality, tracer, inclusion and exclusion criteria, population characteristics, intervention, subject number, age (mean, standard deviation and range), SUV<sub>mean</sub> (mean, standard deviation and range), SUV<sub>max</sub> (mean, standard deviation and range), testicular volume (mean, standard deviation and range) as well as fertility parameters and status subject to data availability in full-text. Testicular volume values were included in the data extraction process as it is a known predictor of male fertility.

The included cohorts were divided into three groups:

1. Healthy – no previous testicular malignancy and no testicular pathology found on CT scan.
2. Malignant – known primary testicular malignancy.
3. Benign – any remaining studies including non-malignant testicular pathology.

The extracted data were then compared with relevance to fertility to achieve our second aim — to determine whether current evidence is sufficient to support the use of PET/CT in assessment of the functional status of testes.

2.3 | Statistical analysis

The extracted mean SUV<sub>max</sub> and SUV<sub>mean</sub> for the three groups (see above) were then compared by using the one-way analysis of variance (one-way ANOVA) test with multiple comparisons using the Tukey’s range test. Further commentary on the findings was then provided by the authors.

2.4 | Critical appraisal

All included studies were graded via the Oxford Levels of Evidence tool. The assessment of quality was also performed by two reviewers, and a third reviewer was consulted in case of disagreements. Risk of bias for each included study was also assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tool, which was performed at the study level after full text review of all included articles.

3 | RESULTS

3.1 | Study characteristics

Through database search, 621 records were identified via Medline and 438 via Embase. Further review of references of relevant literature revealed five additional records giving a total of 1064 records. After duplicate removal, the records’ titles were screened for relevance to this review revealing 74 records for abstract screening review. Twenty-four records were full-text reviewed of which seven were excluded due to not reporting or measuring SUV (n = 3), usage of non-FDG tracer (n = 2) or reporting of imaging data of non-testicular lesions only (n = 2).

**FIGURE 1** PRISMA flow diagram of reviewed literature
### TABLE 2  
Summary of characteristics of studies which included a cohort with healthy testes (n = 701)

| Study | Journal | Study design | Imaging modality | Tracer | Patient number | Mean age ± SD (range)a | Testicular pathology |
|-------|---------|--------------|-----------------|--------|----------------|------------------------|---------------------|
| B Cavuçoğlu et al. 2011 | Mol Imaging Radionucl Ther | Retrospective, cross-sectional study | PET/CT | FDG | 22 | 25.0 ± 8.1 (5–37) | Healthy testes |
| L. Dierickx et al. 2012 | Eur J Nucl Med Mol Imaging | Retrospective, cross-sectional study | PET/CT | FDG | 20 | 22 ± 6.51 (14–35) | Healthy testes |
| I Goethals et al. 2009 | Ann Nucl Med | Retrospective, cross-sectional study | PET/CT | FDG | 22 | 14.3 ± 2.2 (9–17) | Healthy testes |
| K Kitajima et al. 2007 | Ann Nucl Med | Retrospective, cross-sectional study | PET/CT | FDG | 203 | 64.5 ± 13.7 (36–89) | Healthy testes |
| A Meij-de Vries et al. 2014 | World J Nucl Med | Retrospective, cross-sectional study | PET/CT | FDG | 20 | 26.5 ± 3.9 (19.3–31.2) | Healthy testes |
| A Meij-de Vries et al. 2015 | World J Nucl Med | Prospective, cross-sectional study | PET/CT | FDG | 11 | 24.1 ± 2.3 (20.6–28.0) | Healthy testes |
| Y Wang et al. 2007 | Mol Imaging Biol | Retrospective, cross-sectional study | PET/CT | FDG | 47 | (30–55) | Healthy testes |
| D Well et al. 2007 | Semin Nucl Med | Retrospective, cross-sectional study | PET | FDG | 48 | (56–80) | Healthy testes |
| S Zincirkeser et al. 2007 | J Int Med Res | Prospective, cross-sectional study | PET/CT | FDG | 38 | 55.5 ± 13 (28–75) | Healthy testes |
| SH Moon et al. 2011 | Nucl Med. Mol Imaging | Prospective, cross-sectional study | PET/CT | FDG | 66 | 50.8 ± 13.6 (22–81) | Healthy testes |
| S Kosuda et al. 1997 | Ann Nucl Med | Retrospective, cross-sectional study | PET | FDG | 7 | 60.8 (39–77) | Healthy testes |

Abbreviations: FDG, 2′-[18F]fluoro-2′-deoxyglucose; PET/CT, positron emission tomography with co-registered X-ray computed tomography; SD, standard deviation.

aData subject to availability in full text.
bCohort was split into two groups depending on age (see age range).
cStudy was divided into two parts and consisted of two independent cohorts of imaged patients with healthy testes.

Finally, 17 records met all inclusion criteria and were included in the qualitative synthesis (Figure 1).

### 3.2 Results for healthy tissue, benign and primary malignant lesions

#### 3.2.1 Patient characteristics

All included studies involved a combined cohort of 830 patients, which were classified into three groups as previously described: healthy, benign and malignant.

#### 3.2.2 Healthy tissue — study characteristics

The healthy testes group consisted of 11 studies and a total of 701 patients (Table 2). Out of the 11 studies, seven included an adult cohort, four included both adult and paediatric patients, while one involved a paediatric cohort only. One study had their patient cohort divided into two groups depending on age. Another study reported results from two separate healthy male cohorts. For these two papers, the cohorts were kept separated in presenting results. Presence of non-testicular malignancy in patient cohorts was not an exclusion criterion provided no lesions were present in the testes at the time of imaging and patients had no history of previous testicular cancer.

#### 3.2.3 Benign lesions — study characteristics

Benign testicular pathology was found in a cohort of 64 patients originating from data from three papers: One assessed uptake into testes in patients post-orchidopexy procedure; the second paper involved patients after a vasectomy; the third one analysed various benign testicular lesions including benign tumours, such as hemangiomas and teratomas, as well as testicular tuberculosis, abscesses, cryptorchidism and torsion. Study characteristics are outlined in Table 3. The study which involved a population of patients who underwent a previous unilateral orchidopexy reported uptake results also of the unaffected contralateral testis in all patients. Hence, imaging results from the affected testes were classified into the benign group, while results of their
TABLE 3  Summary of characteristics of studies which included a cohort with benign testicular pathology (n = 64)

| Study | Journal | Study design | Imaging modality | Tracer | Patient number | Mean age ± SD (range) | Testicular pathology |
|-------|---------|--------------|------------------|--------|----------------|----------------------|----------------------|
| A Meij-de Vries et al. 2015 | World J Nucl Med. | Prospective, cross-sectional study | PET/CT | FDG | 11 | 24.1 ± 2.3 (20.6–28.0) | Previous orchidopexy |
| D Shao et al. 2017 | Eur J Radiol | Prospective, Cohort study | PET/CT | FDG | 21 | 23° (15–45) | Benign testicular tumours (n = 8), non-neoplastic testicular lesions (n = 13) |
| SH Moon et al. 2011 | Nucl Med. Mol Imaging | Prospective, cross-sectional study | PET/CT | FDG | 32 | 55.7 ± 7.8 (38–71) | Vasectomy |

Abbreviations: FDG, 2′-[18F]fluoro-2′-deoxyglucose; PET/CT, positron emission tomography with co-registered X-ray computed tomography; SD, standard deviation.

aData subject to availability in full text.

bMedian instead of average age given in full text.

TABLE 4  Summary of characteristics of studies which included a cohort with malignant testicular pathology (n = 76)

| Study | Journal | Study design | Imaging modality | Tracer | Patient number | Mean Age ± SD (range) | Testicular pathology |
|-------|---------|--------------|------------------|--------|----------------|----------------------|----------------------|
| K Okuyucu et al. 2016 | Radiol Oncol | Retrospective, cohort study | PET/CT | FDG | 8 | 49 ± 24.4 (2–68) | Malignant testicular lesions: lymphoma |
| K Okuyucu et al. 2018 | Mol Imaging Radionucl Ther | Retrospective, cohort study | PET/CT | FDG | 12 | 57 ± 15 (21–77) | Malignant testicular lesions: testicular lymphoma (DLBCL) |
| D Shao et al. 2017 | Eur J Radiol | Prospective, cohort study | PET/CT | FDG | 32 | 40° (1–74) | Malignant testicular lesions: various malignant tumours |
| P Sidhu et al. 2014 | Br J Radiol | Retrospective, cohort study | PET/CT | FDG | 7 | 63 (37–82) | Malignant testicular lesions: lymphoma (focal, multifocal and asymmetric diffuse FDG uptake) |
| J Yang et al. 2018 | Contrast Media Mol Imaging | Retrospective, cohort study | PET/CT | FDG | 6 | 58° (37–73) | Malignant testicular lesion: testicular lymphoma (DLBCL) |

Abbreviations: DLBCL, diffuse large B-cell lymphoma, FDG, 2′-[18F]fluoro-2′-deoxyglucose; PET/CT, positron emission tomography with co-registered X-ray computed tomography; SD, standard deviation.

aData subject to availability in full text.

bType of testicular pathology outlined after colon or in brackets.

Median instead of average age given in full text.

Study was subdivided into two cohorts depending on visual assessment of tracer uptake into testicular tissues. See “testicular pathology” column for more detailed inclusion criteria.

Contralateral testes were pooled into the healthy group. The study by Shao et al.23 compared data of patients with malignant testicular disease against those with benign testicular pathology. The data were split into the malignant and benign groups and are included in Tables 3 and 4 accordingly. The study also included a mixed adult and paediatric cohort.

3.2.4 Malignant lesions — study characteristics

Primary malignant testicular pathology was found in six studies involving a total of 76 patients. Two studies included a cohort with diffuse large B-cell lymphoma, two with other types of lymphoma, one with a variety of different malignant tumours and one with
TABLE 5  Maximum and mean SUV for cohorts with no testicular pathology (n = 701)

| Study                                  | SUV max | SD  | SUV data range | SUV mean | SD  | SUV data range | Testicular pathology |
|----------------------------------------|---------|-----|----------------|----------|-----|----------------|----------------------|
| B Cavusoglu et al. 2011                | 3.2     | 0.9 | –              | 2.6      | 0.9 | –              | Healthy testes       |
| L. Dierickx et al. 2012                | 3.73    | 0.99| 2–5.7          | 2.67     | 0.71| 1.47–4.38      | Healthy testes       |
| I Goethals et al. 2009                 | –       | –   | –              | 0.6      | 0.3 | 0.1–1.4        | Healthy testes       |
| K Kitajima et al. 2007                 | –       | –   | –              | 2.44     | 0.45| 1.23–3.85      | Healthy testes       |
| A Meij-de Vries et al. 2014            | 3.42    | 0.61| 2.07–4.82      | 2.44     | 0.44| 1.40–3.37      | Healthy testes       |
| A Meij-de Vries et al. 2015            | 3.04    | 0.53| 2.34–3.82      | 2.2      | 0.35| 1.76–2.8       | Healthy testes       |
| Y Wang et al. 2007                     | –       | –   | –              | 2.39     | 0.51| –              | Healthy testes       |
| D Well et al. 2007                     | 1.9     | 0.5 | –              | –        | –   | –              | Healthy testes       |
| S Zincirkeser et al. 2007              | –       | –   | –              | 2.6      | 0.7 | 1.3–3.6        | Healthy testes: R testis |
| SH Moon et al. 2011                    | –       | –   | –              | 1.82     | 0.33| 0.6–2.5        | Healthy testes: L testis |
| S Kosuda et al. 1997                   | –       | –   | –              | 2.44     | 0.53| 1.9–3.34       | Healthy testes       |

Abbreviations: L, left; R, right; SD, standard deviation; SUV max, maximal standardised uptake value; SUV mean, mean standardised uptake value.
Notes: All data was subject to availability in full text; aWang et al. 2007 listed only ranges of SUV max and provided SUV mean ± SD for their cohort.

TABLE 6  Maximum and mean SUV for cohorts with benign testicular pathology (n = 64)

| Study                                  | SUV max | SD  | Range       | SUV mean | SD  | Range       | Testicular pathology |
|----------------------------------------|---------|-----|-------------|----------|-----|-------------|----------------------|
| A Meij-de Vries et al. 2015            | 3.26    | 0.44| 2.43–3.81   | 2.37     | 0.28| 1.85–2.74   | Benign testicular pathology: previous orchidopexy |
| Dan Shao et al. 2017                   | 2²      | –   | 1–15.3      | –        | –   | –           | Benign testicular lesions: various       |
| SH Moon et al. 2011                    | –       | –   | –           | 1.82     | 0.26| –           | Benign testicular pathology: vasectomy  |

Abbreviations: SD, standard deviation; SUV max, maximal standardised uptake value; SUV mean, mean standardised uptake value.
Notes: All data was subject to availability in full text; amedian instead of average age given in full text.

non-seminomatous testicular germ cell tumours. Of these, three studies involved a mixed adult and paediatric population. One study differentiated patients into two groups depending on the type of uptake seen in the testis, so the results of the respective cohorts were also kept separate in Table 4. Uptake into testicular tissue expressed as either SUV max or SUV mean was extracted from each study and summarised in Tables 5–7.

3.2.5  | PET uptake into testes — healthy testes

One of 11 studies did not report mean SUV mean values and their standard deviations for their cohorts. Five of the 11 studies reported mean SUV max values (Table 5).

3.2.6  | PET uptake into testes — benign testicular lesions

Both SUV max and SUV mean have been utilised in only one of the three included studies devoted to the assessment of benign testicular lesions (Table 6). Vasectomised testes were found to have the smallest SUV mean out of all the studies in this review.

3.2.7  | PET uptake into testes — malignant testicular lesions

All six included papers adhered to assessment via SUV max; however, only one of these reported SUV mean as well (Table 7). Maximum SUV allows for a more accurate uptake measurement in a lesion, which will show a markedly higher uptake than surrounding tissues.

3.2.8  | Statistical analysis of patient groups

All uptake data was pooled, and average values were calculated for both SUV max and SUV mean within all three cohort groups. Malignant testicular lesions showed higher mean values of both SUV max (9.81 ± 4.62) and SUV mean (5.05 ± 1.52) than benign lesions (SUV max: 2.63 ± 0.44; SUV mean: 2.10 ± 0.27) and healthy testes (SUV max: 3.01 ± 0.71; SUV mean: 2.28 ± 0.53). The full results are shown in Table 8.
TABLE 7 Maximum and mean SUV for cohorts with malignant testicular pathology ($n = 76$)

| Study                          | SUV$_{\text{max}}$ | SD | Range      | SUV$_{\text{mean}}$ | SD | Range      | Testicular pathology                           |
|-------------------------------|--------------------|----|------------|----------------------|----|------------|-----------------------------------------------|
| K Okuyucu et al. 2016         | 8.6                | 2.68 | 6.5–14.8   | 5.05                 | 1.52 | 3.8–8.1    | Malignant testicular lesions; lymphoma         |
| K Okuyucu et al. 2018         | 18.5               | 7   | 9.8–30.8   | –                    | –   | –          | Malignant testicular lesions; testicular lymphoma (DLBCL) |
| Dan Shao et al. 2017          | 7.9$^a$            | –   | 2.5–23.4   | –                    | –   | –          | Malignant testicular lesions; various malignant tumours |
| P Sidhu et al. 2014           | 8.1                | –   | 3.2–17.5   | –                    | –   | –          | Malignant testicular lesions; lymphoma (focal, multifocal and asymmetric diffuse FDG uptake) |
|                               | 8.1                | –   | 2.6–16.4   | –                    | –   | –          | Malignant testicular lesions; lymphoma (benign testicular uptake) |
| J Spermon et al. 2002         | 6.37               | 4.17 | 3.8–14.8   | –                    | –   | –          | Malignant testicular lesions; non-seminomatous testicular germ cell tumour |
| J Yang et al. 2018            | 11.09              | –   | 7.2–19.75  | –                    | –   | –          | Malignant testicular lesion; testicular lymphoma (DLBCL) |

Abbreviations: SD, standard deviation; DLBCL, diffuse large B-cell lymphoma.; SUV$_{\text{max}}$, maximal standardised uptake value; SUV$_{\text{mean}}$, mean standardised uptake value.

Notes: All data was subject to availability in full text; $^a$Median instead of average age given in full text.

TABLE 8 Average values of maximum and mean SUV and their respective standard deviations (SD) for all three testicular pathology groups ($n = 841$)

|                        | Mean SUV$_{\text{max}}$ | Mean SD | Mean SUV$_{\text{mean}}$ | Mean SD |
|------------------------|--------------------------|---------|--------------------------|---------|
| Healthy testes ($N = 11$) | 3.01                     | 0.71    | 2.28                     | 0.53    |
| Benign testicular lesions ($N = 3$) | 2.63                     | 0.44    | 2.10                     | 0.27    |
| Malignant testicular lesions ($N = 6$) | 9.81                     | 4.62    | 5.05                     | 1.52    |

Notes: All data was subject to availability in full text. For ranges of given values please see Tables 4–6.

A one-way ANOVA test was performed to compare the mean SUV$_{\text{max}}$ and SUV$_{\text{mean}}$ values of the three groups separately and the results are shown in Table 9 and Figure 2. A p-value of < 0.05 was considered statistically significant. There was no meaningful difference between healthy and benign group uptake regardless of whether SUV$_{\text{mean}}$ ($p = 0.89$) or SUV$_{\text{max}}$ ($p = 0.99$) was utilised. SUV$_{\text{mean}}$ in the malignant group was statistically greater than that of either healthy or benign groups ($p < 0.01$ in both). For SUV$_{\text{max}}$, there was a statistical difference between malignant and healthy groups ($p < 0.01$), although the difference between malignant and benign groups was statistically insignificant ($p = 0.06$).

3.3 Results — PET/CT for functional assessment of testes

Out of all the 17 included studies in this review, only three papers referred to fertility in any way. They included a cohort of 149 patients with their age ranging between 14 and 81. The results are shown in Table 10.

Two included studies measured testicular volume (TV) on imaging, of which one also measured semen parameters such as sperm count per millilitre, motility, vitality and total sperm count per ejaculate. One study provided data of patient serum sex hormone levels (total testosterone, free testosterone, oestradiol, sex-hormone binding globulin). Quantitative comparison of data was not viable.
**TABLE 9**  Results of the one-way ANOVA test comparing mean \( \text{SUV}_{\text{max}} \) values of the healthy, benign and malignant groups (top) and mean \( \text{SUV}_{\text{mean}} \) of the same groups (bottom)

| \( \text{SUV}_{\text{max}} \)        | Mean diff. | 95.00\% CI of diff. | Adjusted \( p \) value | Significant? |
|-----------------------------------|------------|---------------------|--------------------------|--------------|
| Healthy vs. benign                | 0.428      | −6.476 to 7.332     | 0.9847                  | No           |
| Healthy vs. malignant             | −6.751     | −11.58 to −1.919    | 0.008                    | Yes          |
| Benign vs. malignant              | −7.179     | −13.79 to −0.562    | 0.0338                   | Yes          |

| \( \text{SUV}_{\text{mean}} \) | Mean diff. | 95.00\% CI of diff. | Adjusted \( p \) value | Significant? |
|---------------------------------|------------|---------------------|--------------------------|--------------|
| Healthy vs. benign              | 0.1873     | −0.9554 to 1.330    | 0.9027                   | No           |
| Healthy vs. malignant           | −2.768     | −4.329 to −1.206    | 0.0012                   | Yes          |
| Benign vs. malignant            | −2.955     | −4.798 to −1.112    | 0.0026                   | Yes          |

Abbreviations: CI, confidence intervals; Dif., difference; \( p \), probability value. \( p < 0.05 \) was considered statistically significant.

**TABLE 10**  Summary of characteristics of studies which involved assessment of fertility (\( n = 149 \))

| Study                     | Age range | \( \text{SUV}_{\text{max}} \) | SD  | Range | \( \text{SUV}_{\text{mean}} \) | SD  | Range | Mean TV (mL) ± SD (range) | Mean total testosterone (ng/mL) ± SD | Mean free testosterone (pg/mL) ± SD |
|---------------------------|-----------|------------------------------|-----|-------|-------------------------------|-----|-------|---------------------------|--------------------------------------|--------------------------------------|
| L. Dierickx et al. 2012   | 14–35     | 3.73                         | 0.99| 2–5.7 | 2.67                          | 0.71| 1.47–4.38 | 24.50 ± 10.70 (4.8–51) | –                                    | –                                    |
| A Meij-de Vries et al. 2015 | 20.6–28.0 | 3.04                         | 0.53| 2.34–3.82 | 2.2                           | 0.35| 1.76–2.8 | 20.0 ± 11.3 (11.2–52.4) | –                                    | –                                    |
| SH Moon et al. 2011       | 22–81     | –                            | –   | –     | 1.85                          | 0.33| 0.6–2.5 | –                         | 4.63 ± 2.07                         | 16.16 ± 6.25                         |

Abbreviations: SD, standard deviation; \( \text{SUV}_{\text{max}} \), maximal standardised uptake value; \( \text{SUV}_{\text{mean}} \), mean standardised uptake value; TV, testicular volume.

\*Study was divided into two parts and consisted of two independent cohorts of imaged patients with healthy testes.

due to incomplete reporting of andrological data across all three studies.

Moon et al.\(^{31}\) found a positive correlation between normal testicular FDG uptake and both total and free testosterone levels, but no correlation to serum oestradiol levels or oestradiol-to-testosterone ratios. The majority of testicular tissue is composed of Leydig, Sertoli and germ cells, with the former two being respectively responsible for testosterone production and spermatid support, and the latter constituting spermatid precursors.\(^{35}\) Since germ cells vastly outnumber Leydig or Sertoli cells, Moon et al. concluded that they are likely to be responsible for the majority of testicular FDG uptake, explaining at the same time why uptake was weakly correlated to testosterone levels produced by the rarer Leydig cells. This idea was further supported by demonstrating that FDG uptake was significantly reduced in vasectomised men when compared to a non-vasectomised control group. As vasectomies are known to produce a decrease in spermatid numbers but do not influence Sertoli cell concentration in the testis,\(^{36}\) the authors concluded that germ cells are likely to account for the majority of testicular FDG accumulation. Testicular volume was not assessed in this study, which limits the ability to draw conclusions regarding fertility of the patients involved.

Dierickx et al.\(^{17}\) correlated testicular FDG uptake data of 20 patients with their semen analysis parameters. They found that patients with a sperm cell concentration of less than \( 20 \times 10^6 \)/mL on semen analysis had lower mean testicular volumes and a larger difference in tracer uptake between their two testes. Overall patients with fewer than \( 39 \times 10^6 \) sperm cells per ejaculate were found to have lower mean \( \text{SUV}_{\text{mean}} \) and mean testicular volume. The study showed that both intensity of FDG uptake and testicular volume measured using PET/CT scanning were positively correlated to total sperm count, sperm concentration and sperm motility. The authors observed that sperm concentration was much less strongly correlated to intensity of uptake and testicular volume than the total sperm count. They explained that because concentration is dependent on the function of not only testes but also prostate and seminal vesicles, while total sperm count relies only on testicular function, FDG uptake may be a marker of fertility. Correlation to motility was explained by increased glucose consumption of the sperm cells. Within their cohort, the difference in uptake of tracer between a patient’s two testes was negatively correlated with sperm cell concentration. Furthermore, statistical differences in mean \( \text{SUV}_{\text{mean}} \), mean testicular volume and uptake intensity were found between normospermic and oligospermic men.

Lastly, Meij-de Vries et al.\(^{32}\) reported that post-orchidopexy testes showed a statistically lower tracer uptake than the contralateral healthy testis. As it is known that testes post-orchidopexy show very low metabolic activity, the study findings suggested that the surgical procedure allows for some return of function into the affected testis. However, no separate assessment was performed in parallel to assess the andrological function of the investigated subjects.
TABLE 11 Study design according to Oxford Levels of Evidence

| Level of evidence | Number of studies included in review |
|-------------------|-------------------------------------|
| 1                 | 0                                   |
| 2                 | 0                                   |
| 3                 | 0                                   |
| 4                 | 17                                  |
| 5                 | 0                                   |

Notes:
Level 1: systematic review of randomised trials or n-of-1 trials.
Level 2: randomised trials or observational studies with dramatic effects.
Level 3: nonrandomised controlled cohort/follow up studies.
Level 4: case series, case-control studies, or historically controlled studies.
Level 5: mechanism-based reasoning.

3.4 Quality assessment

All of the 17 included studies were critically appraised using the Oxford Levels of Evidence tool. Six of the studies had a cohort study design while the remaining 11 were cross-sectional studies (Table 11).

Critical appraisal was performed for each study using the JBI Critical Appraisal Tool. Through the use of this tool, all studies were deemed of sufficient study design quality to be included in this review and had no obvious shortcomings in their methodology (Appendix 2 in the Supporting Information).

4 DISCUSSION

4.1 SUV in healthy testes, benign and malignant testicular lesions

Studies included in the benign and healthy groups showed a preference for the use of SUV\textsubscript{mean} as a measure of PET/CT tracer uptake while primary malignant lesion uptake was most commonly expressed using SUV\textsubscript{max}. While SUV\textsubscript{max} remains the most commonly reported value in primary malignant testicular lesion imaging studies, our results show that SUV\textsubscript{mean} is a more accurate method of differentiation between malignant, benign and healthy groups. However, it has to be taken into account that only one study of the malignant group reported SUV\textsubscript{mean} values.

Our review of current literature suggests that PET/CT can be an accurate tool to diagnose or confirm primary malignant lesions of the testes, which is in line with the findings of Shao et al.\textsuperscript{33} who proposed SUV\textsubscript{max} of 3.75 as an optimal cut-off point between benign and malignant testicular lesions. Further well-designed studies, focusing on FDG-PET/CT imaging of healthy testes as well as benign and malignant lesions of testicular tissue reporting both SUV\textsubscript{mean} and SUV\textsubscript{max} are required to establish more accurately the superiority of either value in testicular lesion diagnosis.

4.2 Value of PET as an investigation of testicular function

The first study to measure FDG uptake into healthy testes was performed by Kosuda et al.\textsuperscript{19} who found an inverse correlation with age. This was confirmed in a later study by Kitajima et al. who showed a weak inverse correlation between FDG uptake and both age and testicular volume, which is known to decrease with age.\textsuperscript{18} The authors attributed the decrease in FDG uptake over time to testicular atrophy, hypothesising that Leydig cells, which utilise glucose in the production of testosterone and lose their productive potential over time, may be responsible, hence establishing the first connection between PET and functional activity of the testes. Furthermore, a similar study performed on a paediatric population\textsuperscript{37} revealed that both FDG uptake and testicular volume are positively correlated with age in this group.

All these results were confirmed in a study by Yang et al.\textsuperscript{38} who established that testicular metabolism, reflected by FDG uptake and testicular volume, increase sharply with the onset of puberty, reach a plateau between the age of 40 and 60 after which they begin to decline. Despite establishing that glycolytic metabolism in the testis and testicular volume decrease over a male’s life, no evidence was obtained to prove whether glycolytic activity is correlated with spermatogenesis, sperm metabolism or hormone production, hypothesised to be the most likely factors.\textsuperscript{17,31,39} Nevertheless, Yang et al. made an important observation regarding any possible correlation. Their results showed that testicular metabolism declines at a slower pace than testicular volume after 60 years of age. It is known at the same time that during this period male sex hormone production decreases significantly without impacting the testes’ fertilising capacity,\textsuperscript{40} which itself remains relatively stable. The authors postulated that as reproductive function consumes more energy than hormonal production in the testes, glycolytic activity in that organ may be more correlated to the former.

Despite the above conclusions, the applicability of PET/CT andrological investigation remains unclear. Further well-designed prospective studies on both rats and humans should be considered to assess the potential of this imaging modality in andrology. Rats have been shown to be valid models of testicular function due to anatomical and physiological similarities.\textsuperscript{19,41} Some of the potential applications of PET/CT in andrology have been described by Dierickx et al.\textsuperscript{17} and mentioned in the introduction of this review. The ability to map areas of high spermatogenesis or sperm storage within the testis pre-operatively could benefit TESE procedures in three ways: First, as discussed earlier, TESE and micro-TESE procedures fail to extract sufficient amounts or even any spermatozoa in half of the cases. An imaging modality mapping the presence of mature spermatozoa could be implemented in a standard pre-operative assessment in non-obstructive azoospermia (NOA) patients. In patients shown to have minimal or no testicular function at all, TESE could be deemed pointless. The patient would then not have to undergo a surgical procedure and subsequently risk suffering any post-operative complications. The cost of the operation, incurred by
the healthcare service, or the patient if performed privately, would be averted as well.

Second, in patients who have spermatozoa for extraction, metabolic imaging of the testes could provide the surgeon with valuable preoperative information, allowing guidance to the exact area within the testis suitable for harvest. This is especially useful in atrophic testis and in borderline hypogonadal men, as testicular tissue trauma could be minimised. Currently, andrological surgeons identify which seminiferous microtubules to harvest for further use in ART based on the visual assessment of the testes under a microscope during a micro-TESE procedure. Even though the PET image resolution of 3–4 mm is around 30–40 times greater than the diameter of seminiferous tubules, localised uptake in a particular region of the testis would allow for some surgical guidance which theoretically could be more accurate than visual assessment alone.

Lastly, such an investigation could provide an alternative to periodical semen analysis in patients who are assessed for potential return of sperm production in the testis after irradiation or chemotherapy, especially in cases of azoospermia.

Given the limitations of currently available investigations and the evident need for a non-invasive testicular function investigation, PET/CT needs further attention in the context of andrology and ART.

This review aimed to systematically appraise current evidence on the use of PET/CT in the functional imaging of testes, its value for the assessment of male fertility, and to qualitatively evaluate the uptake of radioactive PET tracer into healthy testes and testes affected by several testicular pathologies. However, current literature lacks well-designed studies of higher levels of evidence to determine whether PET/CT may be used clinically to assess the functional status of testes.

4.3 Limitations of current literature

Current studies involving PET/CT imaging of healthy testicular tissue have shown a preference towards SUV_{mean} as a preferred tracer uptake unit while malignant testicular tissue studies were more likely to use solely SUV_{max}. This hindered a more robust statistical analysis of the data. Except for the studies mentioned in the discussion, no other studies in relevant current literature included data on fertility such as correlation with sperm parameters or sex-hormone serum levels of assessed patients. There are no current studies correlating PET/CT imaging with histopathological results of testicular tissue.

4.4 Limitations of review

The limitations of this review were as follows: inclusion of all age cohorts despite it being known that SUV increases rapidly throughout adolescence and then slowly declines after 60 years old. Also, inclusion of patients with previous pelvic irradiation or disease outside of testes (especially in healthy testes cohort) could have had an uncontrolled impact on fertility. It was also assumed that all benign and malignant conditions would show similar uptake despite involving different pathology, hence allowing the pooling of the included studies into the three groups.

5 CONCLUSION

Current literature suggests that PET/CT tracer uptake into malignant lesions of testes is significantly higher than the tissues of healthy testes or testicles with benign pathology. Although available studies suggest that PET tracer uptake into testicular tissue could correspond to spermatogenesis, more robust studies are required to establish whether a different process might be responsible. Further studies involving PET/CT imaging of the testes should focus on correlating tracer uptake with fertility parameters such as sperm cell count, sperm viability and sex-hormone serum levels. Histopathology and/or immunohistochemistry data should also be evaluated to determine whether this modality is appropriate to assess testicular function in andrological patients.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTION

Study concept and design: Tet Yap and Antoni Bochiński. Data collection: Antoni Bochiński, Mohamed Al-Hussini and Arunan Sujenthiran. Contributed data or analysis tools: Antoni Bochiński, Arunan Sujenthiran, Mohamed Al-Hussini, Gilbert O. Fruhwirth and Tet Yap. Performed analysis: Antoni Bochiński and Gilbert O. Fruhwirth. Writing — Original Draft: Antoni Bochiński. Writing — Review and Editing: All Authors.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

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