^{18}F -FDG Uptake of Human Testis on PET/CT: Correlation with Age, Sex Hormones, and Vasectomy

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Abstract

Purpose The purpose of this study was to evaluate glucose metabolism of normal human testis on ^{18}F -FDG PET/CT and to assess possible correlations among age, the serum levels of sex hormones, and vasectomy.

Methods ^{18}F -FDG PET/CT was performed in 66 normal healthy men (50.8 ± 13.6 years, range 22–81), and mean standard uptake values (SUV) of ^{18}F -FDG in testis and adductor muscle were measured. Testis-muscle SUV ratios (T/M ratios) were calculated. Serum levels of total testosterone, free testosterone, estradiol, and of sex-hormone binding globulin (SHBG) were measured. We searched for correlations between T/M ratios and age and the serum concentrations of sex hormones. ^{18}F -FDG PET/CT was also performed in 32 vasectomized men (55.7 ± 7.8 years, range 38–71) and 52 nonvasectomized men (55.4 ± 11.6 years, range 37–72). Mean SUVs of testis and adductor muscle were measured, and T/M ratios were calculated.

Results A significant age-related decline was found in T/M ratio ($r = -0.509$, $p < 0.0001$). Serum levels of total testosterone and free testosterone were also found to be positively correlated with T/M ratio ($r = 0.427$, $p = 0.0003$; $r = 0.435$, $p = 0.0003$, respectively). The mean SUV and T/M ratio of vasectomized men were significantly lower than those of nonvasectomized men ($p < 0.0378$ and $p = 0.0001$, respectively).

Conclusions Glucose metabolism in the testis in an adult population was found to be correlated with age, serum sex hormone level, and vasectomy history. These results indicate that testicular ^{18}F -FDG uptake may have attributed to testicular function and testicular histology. Our findings may have important implications for the interpretation of testicular ^{18}F -FDG uptake in the normal adult population.

Keywords ^{18}F -FDG PET/CT · Testis · Glucose metabolism · SUV · Testosterone · Vasectomy

Introduction

The ability to assess glucose metabolism in a variety of tissues makes ^{18}F -fluoro-2-deoxyglucose (^{18}F -FDG) positron emission tomography (PET) a powerful diagnostic tool in the management of many cancers. ^{18}F -FDG accumulates in almost all cancer cells due to enhanced glycolysis, however it may also accumulate due to infection, inflammation, or physical activity, and it may be influenced by chemotherapy or high serum glucose level. ^{18}F -FDG also accumulates preferentially in the spleen, kidneys, liver, and brain.

The proper interpretation of ^{18}F -FDG PET/CT images requires knowledge of the normal physiological and variant distributions of ^{18}F -FDG. In women, it can accumulate in various regions, such as the ovary and endometrium [1], and it has been reported that in premenopausal patients, endometrial and ovarian ^{18}F -FDG uptake changes cyclically in concert with the menstrual cycle [2–4]. Furthermore, it has been suggested that ^{18}F -FDG uptake in female reproductive organs is affected by sex hormone levels.

In men, relatively high ^{18}F -FDG uptakes are frequently seen in normal testes, which indicates that testicular tissues

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metabolize glucose more actively than normal tissues. Moreover, a small number of studies have examined ^{18}F -FDG uptake in normal testes [5, 6] and concluded that ^{18}F -FDG uptake declines slightly with age. However, in these studies the number of healthy subjects examined was small, and almost all were cancer patients, and it is known that cancer can alter glucose metabolism in the testis. Furthermore, it has been well established that levels of total testosterone and free testosterone are diminished in elderly men. Estimated testicular metabolism by ^{18}F -FDG PET/CT could reflect hormonal status. However, the correlation between serum sex hormone levels and ^{18}F -FDG uptake has not been previously examined in healthy men.

It is known that human vasectomy induces a significant histological change in the testis, including reduction of spermatogenesis. Such a histological change of the testis will alter the findings on ^{18}F -FDG PET and suggest a clue about glucose metabolism. However, to our knowledge, there are also no studies that investigate the effect of human vasectomy on ^{18}F -FDG uptake of testis.

We hypothesized that ^{18}F -FDG uptake in the testis is likely to be correlated with serum sex hormone levels and that ^{18}F -FDG uptake probably reflects testicular function and testicular histology. We investigated ^{18}F -FDG uptake of testes with age and sex hormone levels in the healthy volunteers and compared ^{18}F -FDG uptake of testes in vasectomized men with that of nonvasectomized men.

Materials and Methods

Subjects

To investigate normal ^{18}F -FDG uptake of the testes and to search for a correlation with age and sex hormone level, a study was prospectively conducted in 66 consecutive healthy volunteers (50.8 ± 13.6 years) between November 2003 and November 2006 at Seoul National University Hospital. After explaining the study protocol to all volunteers, written informed consent was obtained. Ages ranged from 22 to 81 years, and by decade subject numbers were as follows; 20s ($n=4$), 30s ($n=10$), 40s ($n=19$), 50s ($n=13$), 60s ($n=14$), 70s ($n=5$), and 80s ($n=1$). Volunteers who had any known malignancy, diabetes mellitus, liver disease, other major organ disease, a history of chemotherapy, male organ prosthesis, or any abnormal CT findings in the testis were excluded. ^{18}F -FDG PET/CT was performed, and a blood sample was collected from each participant.

To compare the ^{18}F -FDG uptake of the testis between vasectomized men and nonvasectomized men, healthy

volunteers were enrolled among the patients who visited Seoul National University Hospital for routine check-up from November 2008 to June 2009. The same exclusion criteria were adopted as described above. Thirty-two vasectomized men (55.7 ± 7.8 years, range 38–71) who had a vasectomy >10 years previously and 52 nonvasectomized men (55.4 ± 11.6 years, range 37–72) participated, and ^{18}F -FDG PET/CT was performed.

^{18}F -FDG PET/CT Study

Image acquisition was performed using a dedicated PET/CT system (Gemini, Philips Medical System, Bothell, WA). The subjects were instructed to fast for at least 6 h prior to PET/CT, and blood sugar levels (90.9 ± 9.1 mg/dL) were checked to ensure the absence of hyperglycemia. One hour before imaging, subjects were injected with 5.2 MBq of ^{18}F -FDG per kilogram of body weight, and they sat quietly in a dimly lit room during the uptake phase and were asked to void just prior to imaging. For scanning, subjects lay supine with arms raised above the head. A fused PET-CT scanner was used with a single gantry and table. CT was performed prior to PET, and the data obtained were used to generate an attenuation correction map for PET. Sections 5 mm thick were obtained (Gemini: at 80 mA and 140kVp) from the skull base to the mid thigh. Images were reconstructed using a 512×512 matrix. PET was performed using a (Gemini: 5-min) emission acquisition per imaging level. Images were acquired in a caudocranial direction from mid-thigh to the skull base. The CT transmission map was used for attenuation correction, and PET images were reconstructed using a 128×128 matrix, an ordered subset expectation maximum iterative reconstruction algorithm (two iterations, 28 subsets), an 8-mm Gaussian filter, and a 50-cm field of view.

Image Analysis

PET/CT images were analyzed by two nuclear medicine physicians. Images were read on a Gemini workstation equipped with fusion software, which displayed PET, CT, and PET/CT fused images. Testes were identified as two discoid-shaped soft tissues on axial CT images. In slices containing testes, regions of interest were drawn to encompass whole testes. Maximum and mean standard uptake values (SUVs) were measured in regions of interest drawn on at least three successive trans-axial views (Fig. 1). As a reference [7], mean SUVs of adductor muscles were also determined from regions of interest drawn on at least 10 successive trans-axial views of adductor muscle. Testis-muscle SUV ratios (T/M ratios) were calculated using mean SUVs of testes and adductor muscles, and SUVs were calculated as the ratio of decay-corrected activity per cubic

Fig. 1 Transaxial view of PET and fused PET/CT images at the testicular level (a) and adductor muscle level (b) are shown. Regions of interest (ROI) were drawn by the experienced nuclear physicians. Maximum and mean SUV were obtained from the ROI

centimeter of tissue to the injected dosage divided by body weight.

Analysis of Serum Hormone Levels

Just before ^{18}F -FDG injection, 10–15 mL blood samples were drawn and serum hormone levels were analyzed by radioimmunoassay. All samples were assayed at the same time and run in duplicate. Total testosterone was measured using a commercially available Coat-A-Count Testosterone Kit (Siemens, Los Angeles, CA). The sensitivity of the total testosterone assay was 0.14 nmol/L [interassay coefficient of variation (CV) <12%]. Free testosterone was measured using a Coat-A-Count Free Testosterone Kit (Diagnostic Products, Los Angeles, CA). Its analytical sensitivity was 0.15 pg/mL and its CV was less than 8.5%. Sex-hormone binding globulin (SHBG) was measured using SHBG IRMA kits (Immunotech, Beckman Coulter, Prague, Czech), which had an analytical sensitivity of 0.2 nmol/L and inter- and intra-assay CVs of <8.6% and <6.1%, respectively. Serum estradiol was determined using E2-RIA-CT kits (BioSource Europe, Nivelles, Belgium), which had an analytical sensitivity of 2 pg/mL and inter- and intra-assay CVs of 10.1 and 5.9, respectively.

Statistical Analysis

The relationships between testis ^{18}F -FDG uptake and age and serum sex hormone levels were investigated using correlation analysis. Pearson's correlation coefficients were calculated, and p -values <0.05 were considered significant. Testis ^{18}F -FDG uptake of vasectomized men was compared with that of nonvasectomized men. Mann-Whitney U test was used, and p -values <0.05 were considered significant. Analysis was conducted using Medicalc version 1.9.

Results

Age and ^{18}F -FDG Testicular Uptake

A significant correlation was found between age and T/M ratio ($r=-0.509$, $p<0.0001$). Table 1 summarizes mean testicular SUVs, adductor muscle SUVs, and T/M ratios per decile. The mean±standard deviation of testicular SUV was 1.85 ± 0.33 (range 0.6–2.5). No significant correlation was found between age and mean testicular SUV. Mean muscle SUV was 0.79 ± 0.14 (range 0.40–1.40), and these were significantly and positively correlated ($r=0.42$, $p<0.0004$).

Table 1 ^{18}F -FDG uptake in normal human testis and adductor muscle

Age	Cases (n)	Mean SUV of testis		Mean SUV of muscle		Testis-to-muscle uptake ratio	
		Mean $\pm$ SD	Range	Mean $\pm$ SD	Range	Mean $\pm$ SD	Range
20–29	4	1.67 $\pm$ 0.2	1.4–1.9	0.54 $\pm$ 0.11	0.40–0.66	3.15 $\pm$ 0.41	2.57–3.50
30–39	10	1.86 $\pm$ 0.37	1.3–2.5	0.72 $\pm$ 0.14	0.50–0.90	2.59 $\pm$ 0.32	2.16–3.12
40–49	19	1.91 $\pm$ 0.18	1.6–2.2	0.82 $\pm$ 0.17	0.60–1.40	2.37 $\pm$ 0.38	1.50–3.00
50–59	13	1.92 $\pm$ 0.31	1.5–2.4	0.79 $\pm$ 0.06	0.69–0.90	2.40 $\pm$ 0.40	1.66–3.02
60–69	14	1.87 $\pm$ 0.38	1.3–2.5	0.81 $\pm$ 0.05	0.75–0.91	2.28 $\pm$ 0.43	1.64–3.10
70–81	6	1.61 $\pm$ 0.52	0.6–2.0	0.87 $\pm$ 0.08	0.78–0.95	1.80 $\pm$ 0.52	0.76–2.17
Total	66	1.85 $\pm$ 0.33	0.6–2.5	0.79 $\pm$ 0.14	0.40–1.40	2.39 $\pm$ 0.47	0.76–3.50

SUV Standardized uptake value

Serum Sex Hormones and ^{18}F -FDG Testicular Uptake

A significant correlation was found between serum sex hormone levels and normal testicular ^{18}F -FDG uptake (Fig. 2). The positive correlation found between T/M ratio and free testosterone level ($r=0.435$, $p=0.0003$), and between T/M ratio and total testosterone level ($r=0.427$, $p=0.0003$) were significant. However, no significant correlation was found between T/M ratio and estradiol level ($r=0.03$, $p=0.80$), and between T/M ratio and estradiol-to-testosterone ratio (E/T ratio) ($r=-0.08$, $p=0.50$).

A significant correlation was also found between serum sex hormone levels and age. Serum sex hormone levels, SHBG levels, and E/T ratios according to age groups are shown in Table 2. The negative correlations between age and total testosterone level ($r=-0.39$, $p=0.001$, Fig. 3) and between age and free testosterone level ($r=-0.534$, $p<0.0001$, Fig. 3) were significant. SHBG levels increased with age, however the correlation between age and SHBG ($r=0.308$, $p=0.011$) was weak. No significant correlations were found between age and serum estradiol levels or between age and E/T ratios.

^{18}F -FDG Testicular Uptake of Vasectomized Testis and Nonvasectomized Testis

A significant difference in mean SUV was found between vasectomized testis and nonvasectomized testis ($p<0.0378$, Fig. 4). The mean SUV of vasectomized testis was lower than that measured in nonvasectomized testis. The mean $\pm$ standard deviation of SUV ratio of vasectomized testis was 1.821 ± 0.257 (95% confidence interval for the difference: 1.7260–1.9403), and of nonvasectomized testis was 1.908 ± 0.315 (95% confidence interval for the difference: 1.8400–2.0124). In addition, a statistically significant difference was also found between the T/M ratios of vasectomized testis and those of nonvasectomized testis ($p<0.0001$, Fig. 4). The T/M ratios of vasectomized testis were lower than those measured in nonvasectomized testis. The mean $\pm$ standard deviation of T/M ratio of vasectomized testis was 2.44 ± 0.47 (95% confidence

interval for the difference: 2.14–2.74). The mean $\pm$ standard deviation of T/M ratio of nonvasectomized testis was 3.039 ± 0.59 (95% confidence interval for the difference: 2.78–3.33).

Fig. 2 Correlation between serum testosterone levels (free and total) and testis-to-adductor muscle ratio. Free testosterone level (a) and total testosterone level (b) were significantly correlated with testis-to-adductor muscle uptake ratio ($r=0.435$, $p=0.0003$; $r=0.427$, $p=0.0003$, respectively)

Table 2 Results (mean $\pm$ SD) of serum sex hormone levels and E/T ratio

Age	Cases (<i>n</i>)	Total testosterone (ng/ml)	Free testosterone (pg/ml)	SHBG (nmol/L)	Estradiol (pg/ml)	E/T ratio
20–29	4	6.81 $\pm$ 3.20	23.87 $\pm$ 7.00	27.95 $\pm$ 14.95	27.00 $\pm$ 20.96	7.64 $\pm$ 10.62
30–39	10	5.37 $\pm$ 2.32	19.03 $\pm$ 4.93	33.99 $\pm$ 17.22	36.80 $\pm$ 12.36	7.69 $\pm$ 3.79
40–49	19	5.04 $\pm$ 2.10	18.17 $\pm$ 4.04	33.28 $\pm$ 13.21	39.84 $\pm$ 15.69	9.56 $\pm$ 7.35
50–59	13	3.96 $\pm$ 1.21	14.33 $\pm$ 4.27	37.93 $\pm$ 11.24	33.53 $\pm$ 9.05	9.05 $\pm$ 3.27
60–69	14	4.00 $\pm$ 2.08	12.65 $\pm$ 8.41	41.88 $\pm$ 14.41	35.5 $\pm$ 14.35	9.66 $\pm$ 4.40
70–81	6	3.63 $\pm$ 0.48	12.05 $\pm$ 2.47	43.41 $\pm$ 11.15	36.16 $\pm$ 10.43	10.00 $\pm$ 2.69
Total	66	4.63 $\pm$ 2.07	16.16 $\pm$ 6.25	36.72 $\pm$ 13.92	36.10 $\pm$ 13.60	9.12 $\pm$ 5.40

SHBG Sex hormone-binding globulin, E/T estradiol-to-testosterone ratio

Discussion

This study was undertaken to evaluate glucose metabolism in human testis by ^{18}F -FDG PET/CT and to identify possible correlations with age and the serum levels of sex hormones. It was found that glucose metabolism declines in the testis with age and that it is correlated with serum testosterone and free testosterone levels. In addition, we found that vasectomized testes had much lower glucose metabolism than nonvasectomized. A histological change in the testis induced by vasectomy is postulated as the cause of reduced glucose metabolism. Our findings indicate that ^{18}F -FDG PET can be used to evaluate testicular function.

As far as we are aware three previous studies have previously examined normal ^{18}F -FDG uptake in human testes [5, 6, 8]. These studies demonstrated a significant correlation between normal testicular ^{18}F -FDG uptake and age. In the present study, ^{18}F -FDG PET/CT was performed in 66 normal healthy men, and a significant negative correlation was found between T/M ratio and age, which is consistent with the results of a previous study [6]. However, no significant correlation was found between mean testicular SUV and age, which does not concur with the findings of Kazuhiro et al., in which a weak, albeit significant negative correlation was found between the two [5]. There may have been other factors affecting testicular SUV such as testicular volume or sexual activity.

It is well known that the serum levels of some sex hormones are age-related. Serum levels of total testosterone and free testosterone decrease in elderly men, and SHBG levels increase [9–12]. Furthermore, the numbers of major cells in the testis, such as Sertoli cells, Leydig cells, and germ cells, decrease with age [13–18]. Decreases in serum testosterone are related to andropause, which is associated with sexual dysfunction, lack of energy, increased frailty, loss of balance, and cognitive impairments [19]. We found a significant negative correlation between age and the serum levels of sex hormones, and SHBG was also found to have a significant and positive correlation with age.

This is the first study to statistically evaluate the correlation between glucose metabolism in the normal testis and the serum levels of sex hormones. A positive correlation was found between normal testicular ^{18}F -FDG uptake and total testosterone and free testosterone levels. However, serum estradiol levels and E/T ratios were not found to be significantly correlated with testis-to-muscle uptake ratios, which suggests that testicular ^{18}F -FDG uptake reflects testis function and that ^{18}F -FDG PET/CT could be used to evaluate testicular function.

These correlations can be explained in terms of testicular structure and function. The major portions of testicular tissues are composed of Sertoli, Leydig, and germ cells. Leydig cells produce testosterone, and Sertoli cells support, protect, and provide nutrients to spermatids [20, 21]. Sertoli cells outnumber Leydig cells by a factor of three to four, and germ cells outnumber Sertoli cells by a factor of four to six [22, 23]. In view of these proportions, ^{18}F -FDG uptake by germ cells is probably greater than that of Leydig cells. Thus, we speculate that ^{18}F -FDG is accumulated mainly by germ cells, whereas testosterone is secreted by Leydig cells, which may be why ^{18}F -FDG accumulation was found to be only weakly correlated with serum testosterone. In this study, our speculation can be supported by comparison of glucose metabolism between vasectomized testes and nonvasectomized testes. The mean SUV and T/M ratio of vasectomized testes was much lower than those measured in the nonvasectomized testes. The previous studies reported that significant reduction in spermatids in vasectomized testis could explain this result. McVicar et al. [24] reported significant reduction in spermatids in the men who had a vasectomy at least 5 years previously compared with fertile men. However, there was no significant reduction in the numbers of Sertoli cells per unit area. They suggested that reduction of spermatogenesis caused by vasectomy is not a function of reduction in the number of Sertoli cells. Considering these findings, our results could suggest that the germ cell is a major cell of ^{18}F -FDG accumulation in the testis.

Fig. 3 Correlation between measures (testis-to-adductor muscle uptake ratio, serum total testosterone level, and serum free testosterone level) and age. **a** The testis-to-adductor muscle uptake ratio was significantly correlated with age ($r=-0.509$, $p<0.0001$). The **b** serum total testosterone and **c** serum free testosterone levels were significantly correlated with age ($r=-0.39$, $p=0.001$; $r=-0.534$, $p<0.0001$, respectively)

Fig. 4 The difference in the mean SUV (**a**) and testis-to-adductor muscle uptake ratio (**b**) between nonvasectomized testis and vasectomized testis was statistically significant ($p<0.0378$, $p<0.0001$, respectively)

Increased glucose metabolism in cells is due to the enhanced expressions of glucose transporters (GLUTs) and the increased activities of glycolytic enzymes, such as hexokinase. Some investigators have reported that glucose transporter levels are enhanced in human testes [25, 26], and Kim et al. [27] found that GLUT-8 and GLUT-9 are expressed by the majority of intraseminiferous tubular cells and Leydig cells, and that GLUT-8 predominantly localizes in sperm. Amrolia et al. [28] reported that Leydig cells can take up 2-deoxy-D- ^3H glucose via a transport system that appears to be similar to the facilitated-diffusion glucose uptake system and also found that hexose uptake is significantly stimulated by luteinizing hormone. In addition, Makamura et al. [29] found that variants of hexokinase 1 are expressed specifically in spermatogenic cells. Thus, glucose uptake is enhanced in the normal testis because of the energy requirements of steroidogenesis in Leydig cells and spermatogenesis in germ cells.

The limitation of this study is an uneven distribution of subjects' ages. Only four of the subjects were aged 20–29 years old and only six of the subjects were more than 70 years old. The other age groups had significantly more subjects. However, ages in this study were more evenly distributed than in previous studies. Kazuhiro et al. evaluated 203 cancer patients, however only 6 subjects were aged 30–39 years and no subjects were 20–29 years old [5]. Twenty-one percent of subjects were under 40 years old in our study, whereas only 2.95% of subjects were under 40 years old in Kazuhiro's study. Another limitation is the lack of data about testicular volume. SUV of testis may be affected by testicular volume. Age-associated atrophy and partial volume effect could affect the correlation between SUV and age [5].

Conclusions

Further studies, such as cell culture studies, immunohistochemical staining, autoradiography, and serum analysis are required to reveal the mechanisms that underlie glucose metabolism and ^{18}F -FDG uptake in the testis. Nevertheless, the present study shows that normal testicular ^{18}F -FDG uptake has a correlation with age in adult populations and with serum sex hormone levels and that there is a significantly decreased ^{18}F -FDG uptake in the testes of men who have had a vasectomy. These results indicate that testicular ^{18}F -FDG uptake may be related to testicular function and testicular histology. Our findings may have important implications for the interpretation of testicular ^{18}F -FDG uptake in a normal adult population.

Conflict of Interest The authors certify that no actual or potential conflict of interest in relation to this article exists.

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