Diagnostic utility of ^{18}F-FDG PET/CT in fever of unknown origin among patients with end-stage renal disease treated with renal replacement therapy

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Abstract

Objective: To evaluate the role of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in identifying the cause of fever of unknown origin (FUO) in patients on renal replacement therapy (RRT) for end-stage renal disease (ESRD). **Subjects and Methods:** We retrospectively reviewed the ^{18}F-FDG PET/CT scans of 46 patients with a mean age of 39.28±12.50 years on RRT for ESRD. All patients with abnormal scans had histopathologic examination and microbial cultures of tissue samples from areas with increased standardized uptake value maximum (SUVmax) suggesting the cause of FUO in the ^{18}F-FDG PET/CT scan. Fluorine-18-FDG PET/CT was considered helpful if it led to the diagnosis of the cause of FUO after histopathologic and microbiologic examinations. **Results:** Fluorine-18-FDG PET/CT was helpful in identifying the cause of FUO in 22/46 patients (47.83%). Infection was the cause of fever in all these 22 patients. C-reactive protein (CRP) (P=0.003) and procalcitonin levels (P=0.021) were higher in patients with helpful ^{18}F-FDG PET/CT. No significant difference was found in blood sugar levels and leucocytes counts between patients with helpful ^{18}F-FDG PET/CT outcome and those without. By multiple regression analysis, the odds of a helpful ^{18}F-FDG PET/CT increased with every unit increase in CRP level (OR: 1.009; 95% CI: 1.003-1.016; P=0.005). **Conclusion:** About half of the ^{18}F-FDG-PET/CT scans (22/46) identified the cause of FUO in patients on RRT for ESRD. The clinical utility of ^{18}F-FDG PET/CT in this group of patients is comparable to its average performance in the unselected patients' population evaluated for FUO. A higher CRP level was predictive of a positive ^{18}F-FDG PET/CT outcome.

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Introduction

Despite advances in serologic, immunologic, and imaging techniques available for clinical workup of patients, fever of unknown origin (FUO) remains a significant cause of morbidity and mortality in medical practice. After a rigorous diagnostic workup, about one third to a half of these patients will remain without a known cause for their prolonged fever [1]. Fever of unknown origin is defined as temperature ≥38.3°C (101°F) measured on at least two occasions during an illness lasting ≥three weeks or during multiple febrile episodes occurring over ≥ three weeks [2]. In patients with FUO, the cause of fever must remain uncertain despite thorough history-taking, physical examination and many other diagnostic tests, usually performed.

Several molecular imaging probes are available for imaging inflammation and infection [3]. Positron emission tomography/computed tomography imaging (PET/CT) with fluorine-18 labeled fluorodeoxyglucose (^{18}F-FDG) is by far the most common nuclear medicine technique used as an adjunct in the overall diagnosis of patients with FUO. Fluorine-18-FDG PET/CT has been found useful in identifying the cause of fever in about a half of patients with FUO in whom the cause of fever remained unknown after standard diagnostic workup [4, 5]. Only one study with 20 patients has evaluated before the utility of ^{18}F-FDG PET/CT imaging in diagnosing the cause of FUO among patients treated with peritoneal dialysis [6].

Previous studies evaluating the role of ^{18}F-FDG PET/CT in FUO were mostly done in unselected groups of patients.

In ESRD cases, there is an impaired renal clearance of ^{18}F-FDG, which may contribute to poor signal-to-noise ratio that may be encountered in ^{18}F-FDG PET/CT imaging. Furthermore, CT component of the ^{18}F-FDG PET/CT is less efficient as is performed without intravenous contrast administration in cases of ESRD in RRT [7]. It is currently unknown if the image quality seen in patients with ESRD impacts on the usefulness of ^{18}F-FDG PET/CT to

identify in ESRD on RRT patients the cause of FUO. The aim of this study was, therefore, to determine the usefulness of ^{18}F-FDG PET/CT in the determination of the cause of FUO among patients on RRT for ESRD. Our study is unique in that it presents the first evaluation of the utility of ^{18}F-FDG PET/CT done in a mixed population of patients with end-stage renal failure imaged to unravel the cause of prolonged fever the source of which remained unknown after standard diagnostic work-up.

Subjects and Methods

Patients

The ^{18}F-FDG PET/CT scans of patients with ESRD on RRT were retrospectively studied in our institution in order to identify the site and suggest the cause of long standing FUO. All patients included had been febrile for more than three weeks or had multiple febrile episodes over three or more weeks. The cause of fever remained unknown after patients had a thorough history-taking, physical examination and after the following investigations were done: CRP, hemoglobin level, total and differential blood cells count, serum electrolytes, urea and creatinine, protein electrophoresis, liver function tests, creatinine kinase, ferritin, antinuclear antibodies, rheumatoid factor, urine microscopy and culture, at least three blood cultures at the peak of fever, chest X-rays and abdominopelvic ultrasound scan. We excluded orthopedic or vascular grafts patients. For all patients included, we assessed their medical records to extract the following information: Empirical antibiotic use, use of anti-inflammatory medications, fasting blood sugar on the day of ^{18}F-FDG PET/ CT, CRP level, leucocyte count, procalcitonin level, and type of RRT. In our institution patients who are willing to allow their ^{18}F-FDG PET/CT imaging data to be used anonymously for research purpose sign a consent form. Only data from patients who had previously signed this consent form were used in this study. Out of 53 patients with ESRD and RRT who were imaged with ^{18}F-FDG PET/CT to determine the cause of prolonged fever, 46 patients met our inclusion criteria and were included in this retrospective review. Our institutional review board approved this study.

^{18}F-FDG PET/CT imaging

The ^{18}F-FDG-PET/CT scans were acquired on a Biograph 40 Truepoint hybrid PET/CT scanner (Siemens Medical Solution, Illinois, USA). The standard patient preparation was observed including a minimum of six hours of fasting. Fasting blood sugar was less than 11.0mmol/L in all patients before intravenous administration of ^{18}F-FDG. In patients already on antibiotics or steroids, these medications were not discontinued before ^{18}F-FDG PET/CT imaging. The activity of ^{18}F-FDG administered was weight-based using the formula: [(body weight÷10)+1]x37MBq. Vertex to mid-thigh CT followed by PET imaging was commenced 60 minutes after tracer injection Positron emission tomography imaging was acquired in 3D mode at 3 minutes per bed position.

Image analysis

Two experienced nuclear medicine physicians interpreted the ^{18}F-FDG PET/CT scans by consensus. Image analysis was done on a dedicated workstation equipped with Syngo Via software (Siemens Medical Solution, Illinois, USA). The maximum intensity projection image (MIP) and the reconstructed axial, coronal and sagittal PET, CT and fused PET/CT scans were used for image analysis. Areas of abnormally increased ^{18}F-FDG uptake that could not be explained otherwise were considered abnormal and suggestive of the cause of FUO. The maximum standardized uptake value (SUVmax) of such lesion was measured. Where multiple areas of increased ^{18}F-FDG uptake were seen, the SUVmax of the most intense of them was recorded.

Standard of reference and interpretation of ^{18}F-FDG PET/CT findings

All patients had tissue biopsy/ fluid aspirate at the site of abnormal ^{18}F-FDG accumulation for histological examination and/or microbial microscopy and culture. Fluorine-18-FDG PET/CT scan was considered useful if either biopsy /aspirate taken from these sites revealed the cause of fever. Fluorine-18-FDG PET/CT scan was considered not useful if no abnormality suggestive of the cause of fever was seen or if findings on the ^{18}F-FDG PET/CT scan did not lead to the identification of the cause of fever.

Statistical analysis

Data are expressed as the mean±standard deviation (SD) when they are normally distributed or as median interquartile range (IQR) when they are skewed. Categorical data are presented as proportions (percentages). We used the chi-square test to compare categorical data and the Mann Whitney U test and independent samples Student's t-test for continuous variables. We used multiple logistic regression analysis to evaluate for the predictors of helpful ^{18}F-FDG PET/CT in identifying the cause of fever. The statistical significance was set at a P value of less than 0.05. We performed statistical analysis using IBM SPSS Statistics 21.0 (IBM Corp, Armonk, New York USA).

Results

A total of 46 patients with ESRD were included in this study, males 26, females 20. Mean age distribution: 39.28±12.50 years. Regarding RRT, 21/46 patients were on hemodialysis, 17/46 had received renal transplant and 8/41 were on peritoneal dialysis (PD). Table 1 shows the clinical characteristics of the study population.

In most patients 29/46, at least a single focus of increased ^{18}F-FDG uptake was seen on the PET/CT images while no abnormal uptake was noted in 17/46. Following confirmation by biopsy and microbial culture, the cause of fever was diagnosed at the site of abnormal ^{18}F-FDG uptake in 22 patients with a mean SUVmax of 9.26±4.65. In the remaining 7 patients with positive findings on ^{18}F-FDG PET/CT, no abnorma-

lity was confirmed at the site of ^{18}F-FDG accumulation after biopsy and microbial culture (false positive: FP). The cause of FUO in the 22 patients in whom ^{18}F-FDG PET/CT was helpful was infection due to: klebsiella spp. (n=4), mycobacterium tuberculosis (n=4), staphylococcus aureus (n=4) and other microorganisms (n=10). Figure 1 shows the site of infection causing FUO in the study population. Figures 2-4 show typical images of patients in whom PET was helpful in identifying the site of the cause of FUO.

Table 1. *Clinical characteristics of the study population.*

Variable	Frequency
Age (years)	
Mean±SD	39.28±12.50
Range	16-69
Gender	
Male	26
Female	20
Renal replacement therapy	
Hemodialysis	21
Peritoneal dialysis	8
Transplant	17

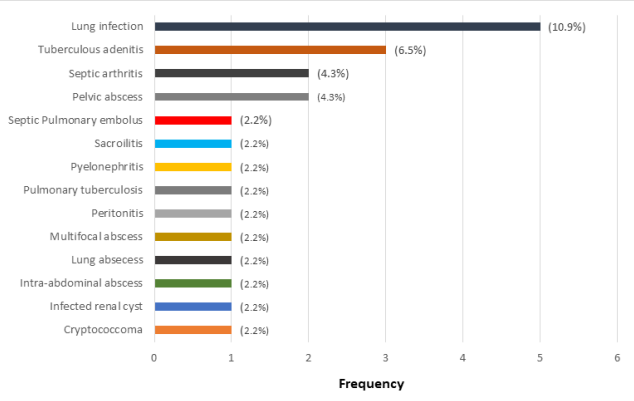

Figure 1. The sites of infection causing FUO in the 22 patients in whom ^{18}F-FDG PET/CT was truly positive.

The helpful group of ^{18}F-FDG PET/CT included older and more male patients (P=0.295 and P=0.34, respectively). The type of RRT the patient was undergoing had no impact on the PET outcome (P=0.782). Both procalcitonin and the CRP levels were significantly higher in the PET helpful group compared with PET unhelpful group, P=0.021 and P=0.003, respectively. Table 2 shows the comparison between the PET helpful group and the PET unhelpful group.

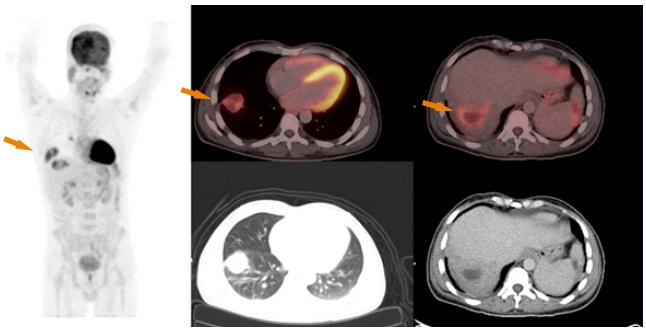

Figure 2. A 47 years old male with end-stage renal disease secondary to membranous glomerulonephropathy. He developed retroperitoneal bleeding with organizing hematoma complicating peritoneal dialysis. He was subsequently switched to hemodialysis. He developed a prolonged fever which did not resolve despite standard diagnostic workup and empirical antibiotic therapy. Fluorine-18-FDG PET/CT was obtained at day 32 following the onset of fever. Images showed multifocal abscesses involving the right lung, liver and the spleen. These abscesses were confirmed to be caused by Enterococcus spp. (arrows)

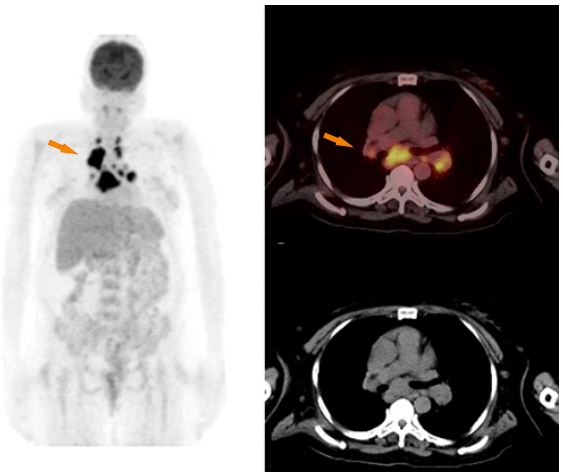

Figure 3. A 47 years old female on peritoneal dialysis for end-stage renal disease. Prolonged fever persisted despite standard diagnostic workup and antibiotic use. Fluorine-18-FDG PET/CT showed multiple chest foci with intense avidity for ^{18}F-FDG. Histological examination of lymph node biopsy revealed tuberculous lymphadenitis. (arrows)

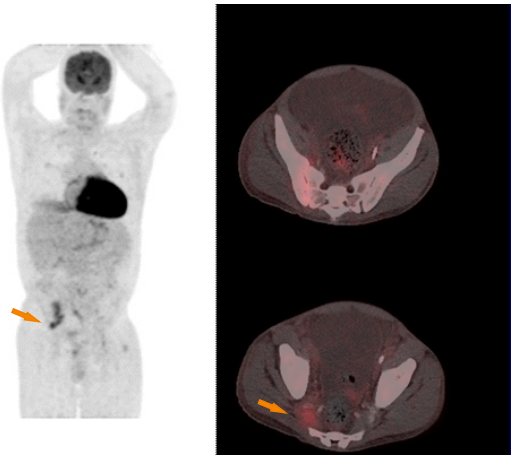

Figure 4. A 25 years old male on hemodialysis for ESRD. Fluorine-18-FDG-PET/CT showed tracer accumulation in the right sacroiliac joint which was later confirmed to be due to Staphylococcus aureus-causing sacroilitis and a right peri-anal abscess. (arrows)

Table 2. *Comparison between Patients in whom ^{18}F-FDG-PET/CT was helpful versus patients in whom it was unhelpful in identifying the cause of prolonged FUO.*

Variable	PET Helpful Yes n (%)	No n (%)	χ^2	P value
Age (years)				
Mean±SD	41.32± 12.56	37.42± 12.41	1.059t	0.295
Gender				
Male	16 (61.5)	10 (38.5)	4.506	0.034*
Female	6 (30.0)	14 (70.0)		
Renal replacement therapy				
Hemodialysis	11 (52.4)	10 (47.6)	0.491	0.782
PD	4 (50.0)	4 (50.0)		
Transplant	7 (41.2)	10 (58.8)		
FBS (mmol/L)				
Mean±SD	6.46± 1.57	6.63± 1.56	-0.349t	0.729
CRP (mg/L)				
Median (IQR)	184.00 (95.00-247.00)	34.50 (16.50-159.00)	131.000U	0.003*
WBC (X 10^9/L)				
Median (IQR)	8.25 (4.97-11.35)	6.86 (4.90-11.59)	240.000U	0.598
Procalcitonin (µg/L)				
Median (IQR)	3.20 (1.58-6.30)	0.75 (0.23-5.38)	159.500U	0.021*

*χ^2: Chi square; t: Independent Samples T test; U: Mann Whitney U test; *: P value <0.05; PD: Peritoneal Dialysis; FBS: Fasting blood Sugar; CRP: C-Reactive Protein; WBC: White Blood Cell Count*

We performed a multivariate logistic regression to determine if gender, CRP level or procalcitonin level separately or in combination, could suggest a helpful outcome as suggested by PET and found both CRP level and male gender to be a significant predictor of a helpful PET outcome. Male patients have about six times increase in the odds of having a helpful PET outcome compared with females (OR: 5.780; 95% CI: 1.280-26.092). The statistics for CRP and procalcitonin are found in Table 3.

Table 3. *Predictors of the 22 helpful PET using multivariate logistic regression.*

Variable	B	P value	OR (95% CI)
Male	1.754	0.023*	5.780 (1.280-26.092)
CRP (mg/L)	0.009	0.005*	1.009 (1.003-1.016)
Procalcitonin (µg/L)	-0.011	0.351	0.989 (0.967-1.012)

*B: Coefficient of logistic regression; OR: Odds ratio; 95% CI: 95% Confidence Interval; *: P value <0.05, R^2: 0.377; Predictive value: 71.7%; χ^2: 15.255; P value: 0.002*

Discussion

Our study indicates that ^{18}F-FDG PET/CT in about half of selected group of ESRD patients on RRT with FUO showed the site of cause of FUO. As a functional modality ^{18}F-FDG PET is better than stand-alone morphologic imaging such as CT [8].

The kidneys play vital roles in both innate and adaptive immunity [9]. Renal failure is characterized by impaired functioning of the inflammatory cells with higher levels of, but ineffective, serum inflammatory cytokines [10, 11]. Immunosuppressive therapy in patients who received renal transplant is an added risk for infection. Therefore, patients with end-stage renal disease on renal replacement therapy represent a group with an increased risk for infection. Besides, they are at increased risk of malignancies including lymphomas [12, 13]. Fluorine-18-FDG PET/CT can show lesions due to infectious, inflammatory and/or neoplastic diseases [7]. The poor renal clearance of ^{18}F-FDG and the use steroid for immunosuppression in transplant patients may reduce the contrast between sites of lesions and the background tracer activity. Nevertheless, our study showed adequate imaging results that is comparable to the average performance of ^{18}F-FDG PET/CT in evaluating unselected groups of patients with FUO imaged to unravel the cause of prolonged fever [4]. There is wide variability in the usefulness of ^{18}F-FDG PET/CT in identifying the cause of FUO reported in the literature. This variability ranged between 23% to 81% [14-20]. There are several factors responsible for this wide variation including non-standardized cases selection and diffe-

rences in the diagnostic evaluation undertaken before patients were submitted to ^{18}F-FDG PET/CT scan [4].

In all patients in whom ^{18}F-FDG PET/CT was useful in our study, infection was confirmed as the cause of FUO. This is a unique difference from the usual reports in the literature. While infection is the more common cause of FUO in general, inflammatory non-infectious conditions, as well as neoplastic disorders are two big groups contributing significantly to the causes of FUO [21].

We found mycobacterium tuberculosis as the causative organism for infection in 4 patients; three with tuberculous lymphadenitis and one patient with pulmonary tuberculosis. End stage renal disease is a potent risk factor for acquiring new tuberculous infection or reactivating old ones because among other reasons, as said before, it is associated with impairment in the cellular immunity responsible for curtailing infections [10]. Tuberculous infections in ESRD and RRT patients are atypical-mostly extra-pulmonary and more likely to be associated with treatment failure [22, 23]. In the setting of ESRD, tuberculous infection presents with FUO in about 77.4% of patients in general [23].

To our knowledge, the only study that has evaluated the usefulness of ^{18}F-FDG PET/CT in ESRD patients was that by Tek Chand et al. (2017) who studied 20 patients on (hemo and peritoneal) dialysis with ^{18}F-FDG PET/CT for FUO [6]. They found ^{18}F-FDG-avid lesions in 15 patients, 10 of which were confirmed to be a tuberculous infection, mostly tuberculous lymphadenitis. Our study is different from this study in that we also included patients who had received renal transplant for ESRD [6]. In our study, 29 patients were on dialysis (21 patients on hemodialysis and 8 patients on peritoneal dialysis), PET was useful in identifying the cause of FUO in 15 patients (hemodialysis=11, peritoneal dialysis=4). The definition of PET usefulness was stricter compared with the study by Tek Chand and colleagues (2017). For PET to be regarded as useful in our study, a focus of abnormal ^{18}F-FDG must be confirmed by biopsy/aspirate and must grow the offending organism on microbial culture.

All patients included in this study were already on empirical antibiotic treatment at the time of imaging. Data are emerging to show that antibiotic use may not impact on the outcome of ^{18}F-FDG PET/CT imaging for infection [24]. Empirical antibiotic treatment is based on the epidemiology of microbial organisms causing infection in a particular region of the body in a given environment. Patients are unlikely to be referred for ^{18}F-FDG PET/CT if empirical antibiotic treatment is effective. Therefore, patients undergoing imaging probably still have an active ongoing infection. Kagna et al. (2017) in a recent large study showed that, indeed, prior antibiotic treatment does not impact on the outcome of ^{18}F-FDG PET/CT imaging of infection [25].

C-reactive protein is a cheap and widely available test for infection/inflammation. In our study population, we found significantly higher CRP levels in those patients in whom PET was helpful versus patients in whom PET was not helpful (values of 184.00 versus 34.50, P=0.003). In a multiple logistic regression analysis, CRP remained a significant predictor of a helpful PET scan. This finding is similar to the results reported by Balink and colleagues (2015) who found a better performance of ^{18}F-FDG PET/CT when the images were interpreted using the CRP level [26]. Similar to our findings, Crouzet et al. (2012) also reported CRP level to be a significant predictor of a helpful ^{18}F-FDG PET/CT scan among 79 patients with FUO [27]. Higher levels of CRP may, therefore, increase the odds of identifying an infection or inflammation cause of FUO on ^{18}F-FDG PET/CT imaging.

The results from our study must, however, be interpreted bearing in mind the limitations therein especially regarding its retrospective design and its modest study population. A significant proportion of patients with FUO will remain undiagnosed until fever resolves or their disease may be fatal [17]. A negative ^{18}F-FDG PET/CT is therefore not synonymous with the absence of pathology. Large prospective multi-centered studies to validate our findings are warranted.

In conclusion, ^{18}F-FDG PET/CT in about half of patients with FUO on RRT for ESRD studied, helped to identify the cause of FUO. All these patients had infection as the cause of FUO. Higher CRP levels were predictive of a helpful ^{18}F-FDG PET/CT outcome in such cases.

Ethical approval

This study was performed in accordance with the ethical standard of our institutions and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

All patients included in this study provided written informed consenting agreeing to anonymous publication of their disease-related information. A formal consent form was, therefore, not required at this time of reporting.

The authors declare that they have no conflicts of interest.

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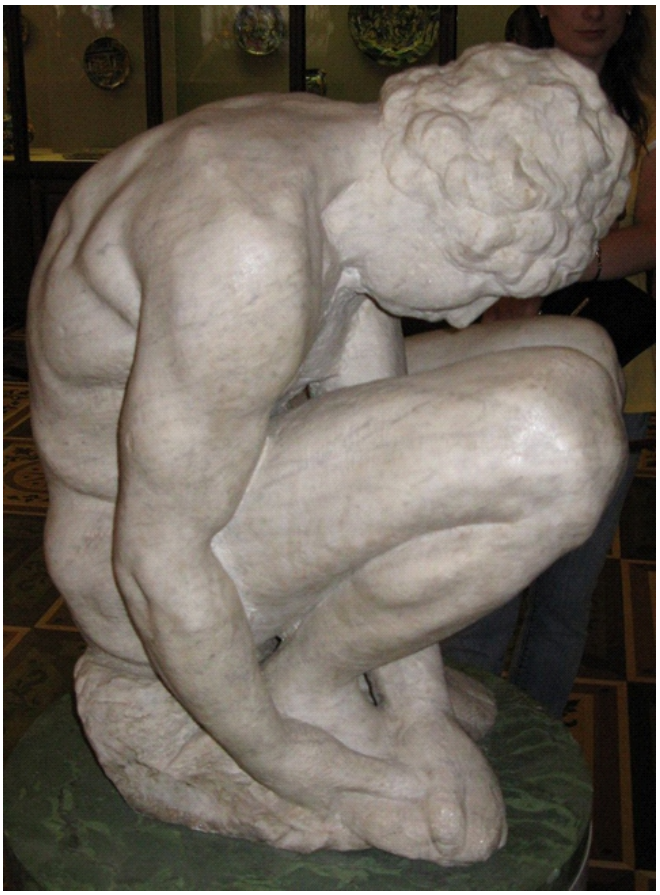

Michelangelo, 1475-1564, Italy. Crouching boy, 1530s.