Identification of current smokers among renal transplant recipients

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Abstract

Background. In renal transplant recipients, smoking is associated with a high burden of cardiovascular disease and a higher risk of graft loss. Surprisingly, the results of measurement of cotinine serum level, the gold standard for the detection of active smoking, have not been confronted with self-reported smoking history in this group.

The aim of our study was to identify and characterize the smoking group of renal transplant recipients.

Methods. Cotinine serum level was measured and all patients were asked to fill out an anonymized questionnaire on smoking history.

Results. Out of 233 renal transplant recipients, 106 (45%) reported to be lifetime and current non-smokers: cotinine serum level was below detection limit in all; among the 127 renal transplant recipients (55%) with a lifetime history of smoking, cotinine level was diagnostic of current smoking in 32 (25%). Only 21 of the current smokers (66%) declared to the nephrologist that they had continued smoking whereas 11 (34%) claimed to be non-smokers. Current smokers were younger \( (P=0.01) \) than former smokers.

Conclusion. The identification of current smokers among renal transplant recipients should start with questioning about lifetime history of smoking and if positive, measurement of cotinine serum level. Indeed up to 34% of current smokers do not acknowledge they are active smokers and would otherwise not offer to participate in programmes to stop smoking.

Keywords: current smoking; past smoking; renal transplantation; serum cotinine

Introduction

Smoking is a leading cause of cancer, cardiovascular and lung diseases in the general population [1].

The World Health Organization estimates that tobacco use will cause some 10 million deaths each year by 2020. In renal transplant recipients (RTR), smoking not only causes cardiovascular disease and cancer but also shortens patient and graft survival [2,3]. Surprisingly, little attention has been paid hitherto to the identification and characterization of smoking RTR despite the 1998 National Kidney Foundation Task Force recommendation of further research on the prevalence of tobacco use in Chronic Kidney Disease patients [4], a mandatory first step for successful interventions aiming at stopping smoking in these high risk patients. We therefore decided to study the prevalence of smoking in RTR returning to our clinic for a periodic follow-up. We relied not only on self-reported smoking but also on measurement of cotinine serum level, a highly sensitive (96%) and specific (100%) marker of smoking [5], used among others in high quality epidemiological studies such as the National Health and Nutrition Examination Survey (NHANES) 3 [6] and considered as the gold standard for the detection of active smoking [5]. The aims of our study were firstly, to identify all active smokers among RTR and compare the accuracy of self-reported smoking history with the gold standard (cotinine serum level), and secondly to better characterize the active smoking group of RTR.

Subjects and methods

Inclusion and exclusion criteria

In this cross-sectional study, we included consecutive RTR with a functioning kidney graft for at least 1 year, returning between 3 February 2004 and 5 October 2004 to our clinic for a periodic (annual or bi-annual) in-depth control. Patients with multiorgan grafts, younger than 18 years or not resident in Belgium were not included. Cotinine measurement was part of a larger study on the evaluation of cardiovascular risk factors in renal transplant recipients. Patients were unaware their blood samples would be used to measure cotinine level but they all gave written informed consent for the storage and use of serum samples for the study of CV risk factors in
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RTR. This study was approved by the Biomedical Ethics Committee.

**Smoking history**

Participating patients were asked to fill out a questionnaire about their current and past smoking history (ever smoked? yes/no; currently smoking? yes/no). Patients were also asked whether they were using nicotine substitutes (patches, chewing-gums, pills, etc.), in order to make the results of cotinine level measurement interpretable. Patients filled out the questionnaire before meeting the nephrologist. It was clearly mentioned on top of the questionnaire and repeated orally by the nephrology nurse sampling blood, that the results of the questionnaire would be anonymized by an external analyst and individual answers and results of patients, thus would not be known to the nephrologist. During the medical checkup, the nephrologist once again asked each patient whether he/she currently smoked and he calculated the number of pack-years when applicable.

**Other variables**

Body mass index (BMI) was calculated as weight/height (kg/m) [2]. Blood pressure (BP) was measured by a nurse, using an automatic validated device (Omron MI-5, Mannheim, Germany), according to the JNC VII recommendations [7]. Glomerular filtration rate was estimated by the abbreviated MDRD formula [8]. Information on demographic factors and medical history [such as age, gender, race, diabetes, date of transplantation, type of donor (cadaveric versus living), time spent on dialysis and history of cardiovascular event (CVE)] was obtained from the medical charts. A history of CVE was defined as having experienced at least one event among the following: myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, transient ischaemic attack, stroke, carotid endarterectomy, lower limb angioplasty, lower limb artery bypass graft, lower limb amputation and aortic surgery.

**Cotinine serum level**

Blood was obtained on the same day as the questionnaire was filled out, centrifuged and the serum immediately stored at −20°C. Cotinine serum level was measured using high performance liquid chromatography. A level >10 ng/ml was used as marker of current active smoking [9].

**Statistical analysis**

Continuous variables were expressed as mean ± SD or as median and range (depending on presence of a normal distribution). Discrete variables were reported as percentages. Standard tests such as chi-square, Mann–Whitney, one-way ANOVA or Kruskal–Wallis were used as indicated. Multiple linear stepwise regression and logistic regression were used when applicable. Statistical significance threshold was set at 0.05 and all analyses were performed with SPSS 12.0 for Windows (Chicago, IL, USA).

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**Table 1. Main characteristics of the 233 included patients**

<table>
<thead>
<tr>
<th>Variables</th>
<th>N and proportion (%)</th>
<th>Mean ± SD</th>
<th>[Range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>142 (61%)</td>
<td>53 ± 13</td>
<td>[18–78]</td>
</tr>
<tr>
<td>Age (years)</td>
<td>230 (99%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical parameters:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>27 ± 5</td>
<td>[18–44]</td>
<td></td>
</tr>
<tr>
<td>Systolic (BP) (mmHg)</td>
<td>137 ± 19</td>
<td>[101–214]</td>
<td></td>
</tr>
<tr>
<td>Diastolic (BP) (mmHg)</td>
<td>81 ± 12</td>
<td>[48–124]</td>
<td></td>
</tr>
<tr>
<td>Kidney function:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calculated GFR (ml/min/1.73 m²)</td>
<td>58.3 ± 24.7</td>
<td>[9.3–156.7]</td>
<td></td>
</tr>
<tr>
<td>Medical history and comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time after TP (years)</td>
<td>5.9</td>
<td>[1–33.5]</td>
<td></td>
</tr>
<tr>
<td>Time on dialysis (years)a</td>
<td>1.8</td>
<td>[0–16.3]</td>
<td></td>
</tr>
<tr>
<td>Living donor graft</td>
<td>31 (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>31 (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of CVE</td>
<td>67 (29%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aMedian.

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**Results**

Two hundred sixty-four patients were contacted. Twelve patients asked their periodic control to be postponed to a later time (5%) and 18 (7%) did not come for various reasons (refused n = 11, lost to follow-up n = 6, imprisoned n = 1). One autistic patient could not cooperate. Thus, 233 (88%) patients were included.

The main characteristics of the patients are shown in Table 1.

Figure 1 displays the breakdown of never smokers, former smokers and current smokers, from top to bottom, according to self-reporting (questionnaire), cotinine serum level and patient’s answer to the nephrologist. Overall, 127 patients had ever smoked before (55%). Cotinine level unequivocally pointed to active smoking in 32 patients (14% of the entire cohort). A positive cotinine level was detected only in patients who acknowledged a history of smoking. When comparing answers to the questionnaire and serum cotinine levels, 11 patients stated they were no longer active smokers while cotinine level was positive. By contrast, among the 24 self-reported current smokers, three of them reported to smoking very occasionally and had a negative cotinine level.

Among the current smokers (n = 32), 11 (34%) did not tell the nephrologist they were current smokers whereas cotinine serum level was positive. Mean cotinine level was 250 ± 160 ng/ml and did not correlate significantly in the 32 active smokers with age, gender, race, BMI, GFR, time on dialysis, time after TP, systolic and diastolic blood pressure, diabetes, history of CVE, or self-reported smoking or not (data not shown).

Using cotinine measurement as gold standard, the questionnaire had a sensitivity and specificity of...
Comparisons between cotinine-proven never smokers, ever smokers and current smokers

Current smokers were younger ($P = 0.01$) and had a significantly lower systolic BP than former smokers ($P = 0.02$, Table 2). Multiple linear regression showed that younger age ($P = 0.028$) and positive cotinine ($P = 0.045$) were independently associated with a lower systolic blood pressure.

In contrast, diastolic BP was similar across groups. The proportion of men was higher among former smokers than never smokers ($P < 0.01$). Patients who had never since smoked had a longer time transplantation than former smokers ($P = 0.04$). GFR, time on dialysis, BMI, history of diabetes or history of CVE were similar across groups. The proportion of patients with a living-donor kidney graft was higher in current smokers than never smokers ($9\%$ vs $25\%$ respectively, $P = 0.027$). As younger age was highly associated ($P < 0.01$) with having received a living donor graft, we performed a logistic regression. Then, the association between current smokers and living graft donors was no longer significant ($P = 0.071$).

The comparison of the 21 RTR current smokers acknowledging smoking and the 11 RTR denying smoking did not show any difference (data not shown); the pack-years did not show any significant difference ($P = 0.072$) between current and former smokers (Table 2).

Discussion

This is the first time cotinine serum level has been used to identify all current smokers in a large, representative cohort of RTR. This marker is the gold standard for that purpose, with a sensitivity and specificity of 96% and 100%, respectively [5], when the threshold of 10 ng/ml is taken to define current smoking. Thirty-four percent of current smokers in our cohort did not acknowledge active smoking and were unmasked by cotinine serum level measurement. Interestingly, mean cotinine level was $250 \pm 160$ ng/ml, suggesting a far from negligible exposure to smoking [6], in agreement...
with the average number of cigarettes smoked per day (9 ± 5), reported by our RTR who acknowledged active smoking.

In this study, the proportion of men among former smokers was higher than among never smokers. The same trend was observed for ever versus never smokers. This finding probably reflects the higher prevalence of smoking over the past decades in men than women. Current smokers were younger and had a lower systolic blood pressure than former smokers. The younger age of the active smokers may reflect the current increased prevalence of smoking in young adults. The lower systolic blood pressure in smokers should not be over-interpreted as after multivariate adjustment, we only found a marginal impact of a negative cotinine on systolic BP (P = 0.045), leaving open the possibility of other confounders. The shorter time after transplantation of the actively smoking group may reflect a more severe selection of transplant candidates in the earlier years of kidney transplantation than more recently, or alternatively the (expected) higher rate of death and graft loss in active smokers.

The relatively low prevalence of active smoking (14%) in our cohort is encouraging: it is lower than in the Belgian general adult population (24%) (CRIOC, edition 2006; http://www.oivo-crioc.org), in German heart transplant recipients (26%) [10] and in a large US study in RTR (25%) [2]. A recent US study relying on a telephone survey to assess smoking before and after liver transplantation [11] also reported 15% of current smokers. None of these studies used a biological marker such as cotinine serum level and most relied on oral interviews, a fact that further emphasizes the low prevalence of smoking in our population as detected by the current gold standard marker.

Some limitations of this study should be mentioned. This is a cross-sectional study, making the assessment of the past history of smoking retrospective and thus potentially subject to biases. Cotinine measurement is the best test to detect current smoking but no reliable marker is available to assess past exposure. Still, the negative cotinine serum level in all self-reporting never smokers conversely suggests that a history of past smoking is a valid starting point to identify current smoking. In the absence of nicotine replacement therapy, false positive cotinine levels are very rare as the minimal amount of cotinine present in food is not relevant and environmental (passive) smoking may at most elevate the cotinine level to 6 ng/ml [12]. Our results may not be generalizable to smoking black people, well known to have higher serum cotinine levels than white or hispanic people after adjustment for confounders [6].

Finally, whether the detection of active smoking by a positive cotinine measurement in RTR initially denying active smoking would improve the proportion of RTR succeeding in quitting smoking remains admittedly to be demonstrated.

In conclusion, this study focuses for the first time on the identification of all current smokers in a large group of renal transplant recipients. The identification of current smokers should start with questioning about lifetime history of smoking and if positive, measurement of cotinine serum level. This would make it possible to offer all active smokers the best test to detect current smoking but no reliable marker is available to assess past exposure. Still, the negative cotinine serum level in all self-reporting never smokers conversely suggests that a history of past smoking is a valid starting point to identify current smoking. In the absence of nicotine replacement therapy, false positive cotinine levels are very rare as the minimal amount of cotinine present in food is not relevant and environmental (passive) smoking may at most elevate the cotinine level to 6 ng/ml [12]. Our results may not be generalizable to smoking black people, well known to have higher serum cotinine levels than white or hispanic people after adjustment for confounders [6].

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Conflict of interest statement. None declared.

References


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