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Can a urine dipstick test be used to assess smoking status in patients undergoing planned orthopaedic surgery? A prospective cohort study

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3 **Can a urine dipstick test be used to assess smoking status in patients**
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6 **undergoing planned orthopaedic surgery? A prospective cohort study**
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11 **Abstract**
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13 Smoking is associated with post-surgical complications but smokers often under-report their
14 smoking. Our objective was to determine whether a urine dipstick test could be used as a substitute
15 for quantitative cotinine assays to determine smoking status in patients. We conducted a
16 prospective cohort study over a 10 month period in which 127 consecutive patients undergoing
17 planned foot and ankle arthrodesis or osteotomy were included. Patients self-reported their
18 smoking status and were classified as: 'never smoked' (61 patients), 'ex-smoker' (46 patients), or
19 'current smoker' (20 patients). Urine samples were analysed with cotinine assays and cotinine
20 dipstick tests. There was a high degree of concordance between dipstick and assay results (Kappa
21 coefficient = 0.842, $p < 0.001$). Compared to the quantitative assay, dipstick had a sensitivity of
22 88.9% and a specificity of 97.3%. Patients claiming to have stopped smoking just prior to surgery had
23 the highest rate of disagreement between reported smoking status and urine testing. Urine cotinine
24 dipstick testing is cheap, fast, reliable, and easy to use. It may be used in place of quantitative assays
25 as a screening tool for detecting patients who may be smoking. A positive test may be used as a
26 trigger for further assessment and counselling.
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46 **Introduction:**
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48 Smokers are at increased risk of post-surgical complications.¹⁻⁴ Nicotine causes peripheral
49 vasoconstriction through its adrenergic effects and this is exacerbated by the carbon monoxide
50 present in cigarette smoke. This results in reduced blood flow and decreased oxygen perfusion of
51 subcutaneous tissues,⁵ which increases the risk of poor wound healing and infection.⁶ Nicotine also
52 reduces the expression of bone morphogenic proteins (BMP-2) in osteoblasts which, combined with
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3 reduced blood flow, impairs bone healing.^{7,8} Abstinence from smoking for a period of 4 to 8 weeks
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5 prior to surgery has been shown to reduce these risks.⁹⁻¹² Smoking status is therefore particularly
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7 pertinent in planned surgery, where there is the opportunity for pre-operative counselling and
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9 cessation.¹³ Patients are often not aware of the potential adverse impact of smoking on surgical
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11 outcomes¹⁴ and following appropriate counselling a significant proportion of patients will stop or
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13 reduce smoking prior to surgery.^{13,15}
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18 However, many patients under-report tobacco consumption.¹⁶⁻¹⁸ These are often patients with low
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20 to intermediate levels of education¹⁹ who may fear their surgery will be postponed if they admit to
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22 smoking. Self-reporting is therefore not an accurate means of assessing smoking status¹⁶ and various
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24 biochemical tests may be employed to confirm smoking status objectively. Serum cotinine is one
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26 such test and raised serum cotinine levels have been associated with post-surgical wound
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28 complications.²⁰ Other well validated tests include urinary and salivary cotinine assays which are
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30 highly sensitive and specific when appropriate cut-off values are used for analysis.^{21,22} However,
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32 these tests require specialised equipment and are not widely available. Salivary and urinary dipstick
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34 tests are a cheaper, more accessible alternative to cotinine assays which may also be used in
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36 screening of smoking status.^{23,24}
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42 Our primary research question was to determine whether a simple point of care urine dipstick test
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44 could be used as a substitute for quantitative urine cotinine assays to determine smoking status in
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46 patients undergoing planned orthopaedic surgery.
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49 50 51 **Patients and Methods:**

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53 This was a single-centre prospective cohort study on all adult patients undergoing planned
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55 osteotomies or arthrodesis procedures in our tertiary Foot and Ankle unit. The protocol for this
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3 study was approved by the National Health Service (NHS) Research Ethics Committee (ref:
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5 13/LO/0670, date: 14/05/2013).²⁵ All data was collected in a study specific database.
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10 Over a 10 month period, between September 2013 and July 2014, 515 patients were admitted for
11 planned surgery and all were assessed for inclusion in our study. All patients were given verbal
12 advice to stop smoking at their outpatient and pre-assessment clinic attendances, although the trust
13 did not offer smoking cessation programmes.
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20 Inclusion criteria consisted of sequential patients booked for arthrodesis or osteotomy of the foot
21 and/or ankle, who were under the care of one of three named consultant orthopaedic surgeons.
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23 Patients were excluded if they were under 16 years of age, if they were unable to provide informed
24 consent, or if their operation did not involve an arthrodesis or osteotomy. Of the 515 admissions
25 during the study period, 197 patients were deemed eligible for the study. On the morning of
26 admission, eligible patients were approached with an information sheet and invited to participate in
27 the study; 45 patients were not approached either because of time constraints or because the main
28 investigator was unavailable. Nine patients declined to participate. Patients were further excluded if
29 they were unable to provide a urine specimen or there was a change to the planned procedure.
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39 (Figure 1)
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44 Once informed consent was obtained, patients were asked to complete a short questionnaire
45 regarding their smoking status. (Table 1) Based on their responses patients were assigned to one of
46 the following groups: 'never smoked', 'ex-smoker', or 'current smoker'. A urine sample was also
47 obtained and collected in a specimen pot, labelled with the patient number and study identification.
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55 Two cotinine level testing methods were performed for each sample: a urine dipstick test and a
56 urine laboratory assay. The dipstick test used was the COT One Step Cotinine Test Device which has
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3 a positive reading for cotinine concentrations above 200 ng/ml.²⁶ The test yields a positive / negative
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5 result within three minutes of administration. This test was performed on the ward within two hours
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7 of sample collection and the result recorded. The remainder of the urine sample was frozen onsite
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9 and stored at -20 degrees Celsius prior to transport to an offsite laboratory for direct quantitative
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11 measurements of the cotinine levels. Urinary cotinine concentrations were determined using the
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13 Dynex DS2[®] analyser (DYNEX Technologies Ltd, Worthington, UK), and an Alere™ Toxicology
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15 (Abingdon, UK, formerly Concateno) urine cotinine assay which is an enzyme-linked immunosorbent
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17 assay (ELISA). Samples were analysed twice and the mean recorded.
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22 There is no well-defined cut-off for urinary cotinine (as measured by ELISA) to distinguish smokers
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24 from non-smokers. Active smokers may have urinary cotinine levels >1000 ng/ml whereas non-
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26 smokers may have levels <50 ng/ml.^{16,27} These numbers vary with populations studied and exposure
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28 to passive smoke. In this study we have used an ELISA assay cut-off of 500 ng/ml to distinguish active
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30 smokers from non-smokers and passive smokers.^{28,29} A quantitative value of > 500 ng/ml is therefore
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32 taken to represent a positive test.
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37 The hospital number, gender, age, co-morbidities and operative procedure were recorded for each
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39 patient. Patients were followed up post operatively at weeks 2, 6, 12, 24 and 52, or until union, with
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41 extra appointments for those with clinical concerns. At each follow-up appointment any
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43 complications and progress toward union was recorded. This was the routine follow-up for all
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45 patients having the same type of surgery within our department. Non-union was diagnosed when
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47 there was no radiographic evidence of progression toward union over a three month period and at
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49 least 6 months had elapsed since surgery. Infections were managed according to the National
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51 Institute of Health and Care Excellence (NICE) guidelines.³⁰
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57 **Statistical analysis and sample size estimation:**
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3 Statistical analysis was performed using SPSS 22.0 (IBM, New York, USA). Shapiro-Wilks test for
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5 normality was performed which confirmed all continuous data was parametric ($p < 0.001$).
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7 Significance of the observed difference in means of continuous data between patient subgroups was
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9 calculated using an independent samples t-test. An ANOVA test was performed to analyse
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11 differences in age and assay levels between subgroups of patients (smokers, non-smokers and ex-
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13 smokers). Independent categorical data were analysed using a Chi-squared test. Correlations were
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15 analysed using Pearson's product moment correlation. Means are presented with a standard
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17 deviation. The Kappa coefficient was calculated for agreement between the results of the
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19 quantitative assay and the dipstick test. A 2-tailed p-value of less than 0.05 was considered
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21 statistically significant.
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26 A *a priori* power calculation was performed using G*Power© v3.1.7 (Universität Kiel, Germany).
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28 Previous literature detailing under-reporting of smoking suggests under-reporting of 7-25%.^{18,19,31}.
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30 This data suggested an effect size of $w=0.34$ to 0.63 . Using a 2-tailed alpha of 0.05 and a Power (1-
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32 beta) of 0.8 the total sample size required was calculated as 114 to 32 patients respectively. We
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34 therefore estimated 120 patients would be sufficient to adequately assess our study question. Based
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36 on previous local audits we felt 10 months of data collection would be sufficient.
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43 **Results:**

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45 One hundred and twenty-seven patients were included over the 10 month period. No patients
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47 withdrew and no patients were lost to follow-up. The mean age of participants was 55.68 ± 13.72
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49 years (range: 20 to 82 years). Seventy-nine patients were female and 48 were male. Forefoot
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51 osteotomy or fusion was performed in 58 patients, midfoot surgery in 10 patients, and hindfoot
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53 surgery in 59 patients. Mean follow-up for all patients was 52.09 ± 17.18 weeks (range: 12 to 104
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55 weeks).
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5 Sixty one patients (48.0%) stated they never smoked, 20 patients (15.8%) admitted to being current
6 smokers, and 46 patients (36.2%) stated they were not currently smoking although they had smoked
7 in the past. Of those who claimed to be ex-smokers, 15 (32.6%) stated they stopped smoking over 10
8 years ago, 22 (47.8%) stated they had stopped over a year ago, and 9 (19.6%) stated they had
9 stopped in the few weeks / months preceding their surgery. (Table 2) Amongst current smokers, the
10 mean reported cigarettes smoked was 9.2 ± 10.16 cigarettes / day (range: <1 to 40 cigarettes / day).
11 There was no difference in gender distribution or region operated on between smokers, non-
12 smokers and ex-smokers. Smokers were significantly younger (mean age: 47.75 ± 13.56 years) than
13 self-reported non-smokers (mean age: 56.57 ± 14.71 years) and ex-smokers (mean age: $57.93 \pm$
14 11.26 years, $p = 0.016$). There was no difference in complication or union rate between groups.
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29 An ANOVA test revealed a significant difference in mean cotinine assay levels between smokers
30 ($5486.30 \pm 10,238.43$ ng/ml), non-smokers (94.89 ± 103.52 ng/ml) and ex-smokers (254.02 ± 720.39
31 ng/ml, $p < 0.001$). A positive dipstick was obtained in 19 (15.0%) patients, and these patients had a
32 mean cotinine assay of 6086 ± 10310 ng/ml. This was significantly higher than patients with a
33 negative dipstick (mean of 107 ± 155 ng/ml, $p < 0.001$). There was a significant correlation between
34 assay level and reported number of cigarettes smoked per day: Pearson product moment correlation
35 coefficient of $r=0.719$, $p < 0.001$.
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46 All reported non-smokers had a negative dipstick result, and only 1 (1.6%) had a positive assay (580
47 ng/ml). No reported ex-smoker who claimed to have stopped smoking over a year prior tested
48 positive on dipstick or assay. Of the 9 (19.6%) patients who claimed to have stopped smoking in the
49 weeks preceding surgery, 4 had a positive dipstick test and 3 had a positive assay test. None of these
50 patients reported passive smoking. Five reported current smokers (26.3%) had a negative dipstick
51 and 6 (31.6%) had a negative assay test. Five of these patients reported themselves as current
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3 smokers, but said they only smoked occasionally / socially. The other 2 patients reported smoking 1
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5 to 5 cigarettes a day. These results are summarised in Table 3 and Figure 2.
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10 There was a high degree of agreement between the results of the urine dipstick test and the
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12 quantitative ELISA assessment (Kappa coefficient = 0.842, $p < 0.001$). In total there were only 5
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14 (3.93%) cases where the dipstick and assay results differed. (Table 3) Table 4 demonstrates our
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16 achieved sensitivity/specificity, and positive/negative predictive values for the urine dipstick test as
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18 compared to the quantitative assay.
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20 21 22 **Discussion:**

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25 Our research objective was to establish whether a point of care urine dipstick test could be used in
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27 place of a quantitative urine assay to detect patients who smoke. We performed both urine dipstick
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29 and assay tests on all patients. There was a very high correlation between the results of both tests
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31 indicating that the urine dipstick is as effective as the assay.
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36 Cotinine is a tobacco specific nicotine metabolite and has a longer half-life than nicotine and may
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38 therefore be detectable up to 2-3 days after nicotine consumption.³²⁻³⁴ Cotinine levels may also be
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40 raised by passive smoking, environmental pollution and certain foods.^{35,36} We took these factors into
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42 account when choosing our cut-off values. Although the dipstick uses a different cut-off point than
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44 the quantitative assay (200 ng/ml vs 500 ng/ml), the methods of detection differ and the results in
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46 both groups were found to be comparable. Urinary cotinine was used as many units routinely
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48 acquire a urine sample as part of pre-assessment for planned orthopaedic surgery. Semi-quantitative
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50 urine dipsticks have previously been validated against assays^{23,37}, however, to our knowledge there
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52 have been no comparisons between assays and a 'Positive/Negative' urine dipstick test such as
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54 employed in this study.
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3 A point of care dipstick test is easy to administer, provides a result within a matter of 3-5 minutes,
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5 and a single test cost us £1.50. A single quantitative assay, by contrast, cost £7.00 plus the costs of
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7 refrigeration and transport to an offsite laboratory. A urine dipstick test is therefore a quick, easy,
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9 accurate and cost-effective screening tool for detecting raised levels of urinary cotinine.
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14 The adverse of effects of smoking for patients undergoing surgery are well documented. Sorensen
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16 performed a meta-analysis on almost 500,000 patients across surgical specialities and demonstrated
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18 odds ratios of 3.6 for wound necrosis, 2.07 for delayed wound healing, 2.27 for other wound
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20 complications, and 1.79 for surgical site infection.¹ This also holds true in foot and ankle surgery.³⁸⁻⁴⁰
21
22 Raised serum cotinine concentration has been shown to predict wound complications in head and
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24 neck surgery,²⁰ however, there is no other literature exploring the link between urinary cotinine
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26 concentration and complications. In our series, as expected, urinary cotinine concentration
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28 increased with number of cigarettes smoked but we did not observe an increased complication or
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30 non-union rate amongst smokers or those with high cotinine assays. However, the proportion of
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32 smokers in our cohort was very low and we did not assess for confounding factors such as co-
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34 morbidities which would impact on complication rate. This study cannot therefore assess the
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36 relationship between urinary cotinine concentration and complications. Nevertheless, routine
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38 monitoring of assay levels prior to surgery is probably not cost effective, and should be reserved for
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40 higher risk patients identified by screening (those with a positive urine dipstick result).
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46 Smoking cessation can reduce the risks of complications^{1,9} and pre-operative counselling has been
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48 shown to reduce smoking both prior to, and after surgery.¹³ All patients who smoke should therefore
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50 be counselled to stop smoking prior to surgery, and in some cases surgery may be delayed until this
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52 is achieved. However, patients often under-report their tobacco consumption.^{17-19,31} In particular,
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54 patients who describe themselves as ex-smokers have a higher incidence of under-reporting.⁴¹ Our
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56 findings concur with the literature. No non-smokers had a positive dipstick test and patients
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3 admitting to being current smokers had a positive dipstick result in most cases. The few patients
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5 with negative results were only occasional smokers and the negative test may be due to
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7 coincidentally not having smoked prior to assessment. Majority of reported ex-smokers had only
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9 ever smoked in their youth, or had given up smoking a number of years previously. None of these
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11 patients tested positive. However, amongst the 9 patients who stated they had given up smoking for
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13 the surgery, 4 (44%) tested positive for smoking.
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18 Patients claiming they had only recently given up smoking therefore had the highest proportion of
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20 contradictory cotinine assays and this is the patient group of greatest interest to the orthopaedic
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22 surgeon. It is likely that this group may be larger in normal practice as in this study, patients were
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24 aware their answers would be validated with a biochemical test.
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29 This study has limitations. Patients are categorised by self-reported smoking status which may be
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31 inaccurate. Validity of the urine dipstick is compared to a quantitative cotinine assay, but it is not
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33 possible to confirm patients with a positive assay were under-reporting their smoking, as cotinine
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35 levels can be raised for other reasons as discussed. Although there was a good correlation between
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37 our dipstick and assay results, there may have been an error in choosing our assay cut-off point. We
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39 aimed to minimise this by using values previously reported as reliable, but consensus in the
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41 literature is poor. It is also likely that as patients were enrolled in a study, they were more honest
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43 with their answers than would be seen in normal practice. Strengths of our study include a
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45 prospective study design with a *priori* power calculation to determine number of patients required,
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47 which was achieved. We used validated assessment tools, the results of which strongly correlated.
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49 We repeated each assay twice to improve accuracy and tested for confounding demographic factors.
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54 In conclusion, dipstick testing for urinary cotinine is cheap, fast, reliable, and easy to use. It may be
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56 used in place of quantitative assays as a screening tool for detecting patients suspected of under-
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3 reporting their smoking. It has a high specificity and negative predictive value and therefore a
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5 negative result strongly suggests the patient is not currently smoking. A positive test does not
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7 equate to proof of smoking but may be used as a trigger for further assessment and counselling.
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10 11 **Funding Received:**

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14 A grant for this study was received from British Orthopaedic Foot and Ankle Society (BOFAS).
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17 18 **Conflict of Interest:**

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21 No benefits in any form have been received or will be received from a commercial party related
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23 directly or indirectly to the subject of this article. There are no conflicts of interest to declare.
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26 27 **Figure Captions:**

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33 **Figure 1:** Flow chart demonstrating the recruitment of participants. No patients were lost to
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35 follow-up
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41 **Figure 2:** Results of ELISA urine assay and urine dipstick tests by smoking status. A positive
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43 quantitative cotinine assay was taken as greater than 500 ng/ml. For all groups, there was good
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45 correlation between the results of the dipstick test and assays ($\text{Kappa} = 0.842, p < 0.001$).
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Table 1:

Questionnaire patients were asked to complete regarding their smoking behaviour / status.

Question	Response
Have you ever smoked cigarettes / tobacco?	Yes / No
If 'Yes', do you currently smoke?	Yes / No
How many cigarettes do you smoke per day?	_____
How many years have you smoked for?	_____
If you no longer smoke, how long ago did you stop smoking?	_____
Are you exposed to smoking in your home / work environment?	Yes / No

Table 2:

Patient reported smoking status. Duration since cessation listed for reported ex-smokers and number of cigarettes smoked per day listed for reported current smokers.

	Never Smoked	Ex-Smoker	Current Smoker
Number (Percentage)	61 (48.0%)	46 (36.2%)	20 (15.8%)
Report Stopping: > 10 years ago	-	15 (32.6%)	-
Report Stopping: 1 – 10 years ago	-	22 (47.8%)	-
Report Stopping: Weeks prior to surgery	-	9 (19.6%)	-
Report smoking: < 1 / day	-	-	4 (20.0%)
Report smoking: 1-10 / day	-	-	10 (50.0%)
Report smoking: 11-20 / day	-	-	4 (20.0%)
Report smoking: > 20 / day	-	-	2 (10.0%)

Table 3:

Results of urine assay and dipstick per category of patients. Where annotated '*' assay and dipstick results are not in agreement.

Assay Result	Dipstick Result	Non-Smoker	Ex-Smoker (> 1 year)	Ex-Smoker (< 1 year)	Current Smoker
< 500 ng/ml	-ve dipstick	60	37	5	4
	+ve dipstick	-	-	1*	2*
> 500 ng/ml	-ve dipstick	1*	-	-	1*
	+ve dipstick	-	-	3	13

Table 4:

Results of urine dipstick tests compared to patient reported smoking status and smoking status as determined by urine cotinine assay. The urine cotinine assay was considered positive if the value was > 500 ng/ml. The data in this table assumes patients' description of themselves as 'ex-smokers' was accurate.

Urine Dipstick Result versus Reported Smoking Status				Urine Dipstick Result versus Urine Cotinine Assay			
	Smoker	Non-Smoker	Total		>500ng/ml	<500ng/ml	Total
+ve test	15	4	19	+ve test	16	3	19
-ve test	5	103	108	-ve test	2	106	108
Total	20	107	127	Total	18	109	127

<i>Sensitivity:</i>	75.00%	<i>Sensitivity:</i>	88.89%
<i>Specificity:</i>	96.26%	<i>Specificity:</i>	97.25%
<i>Positive Predictive Value:</i>	78.95%	<i>Positive Predictive Value:</i>	84.21%
<i>Negative Predictive Value:</i>	95.37%	<i>Negative Predictive Value:</i>	98.15%

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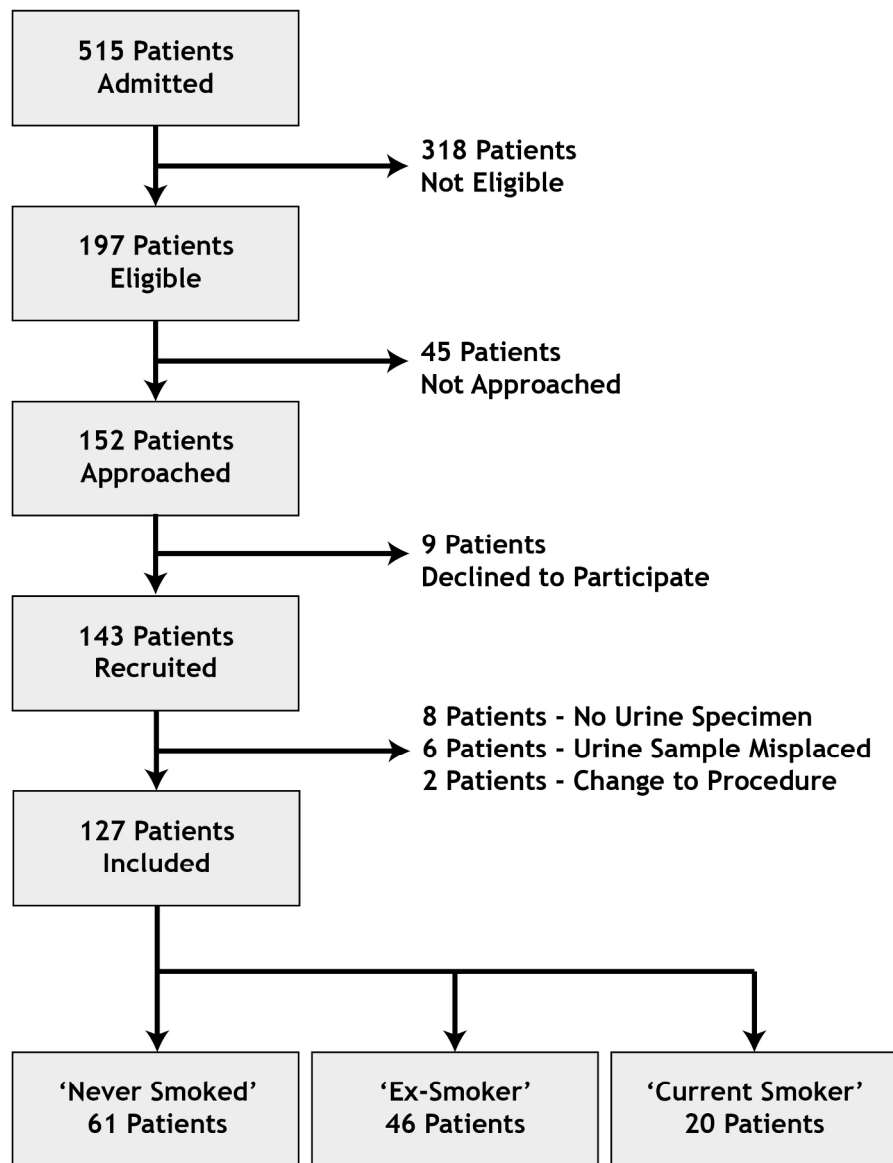


Figure 1: Flow chart demonstrating the recruitment of participants. No patients were lost to follow-up
192x251mm (300 x 300 DPI)

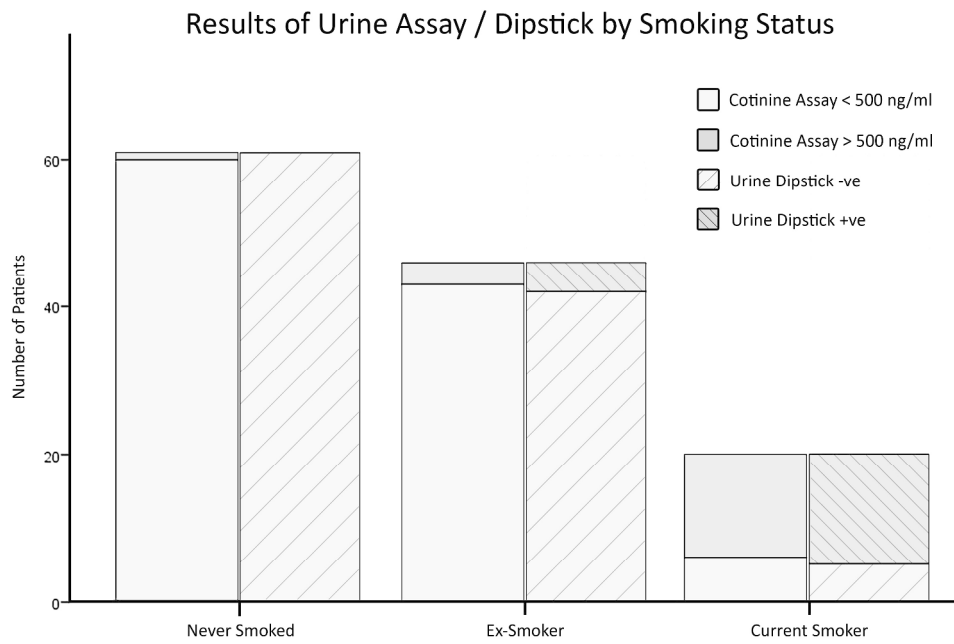


Figure 2: Results of ELISA urine assay and urine dipstick tests by smoking status. A positive quantitative cotinine assay was taken as greater than 500 ng/ml. For all groups, there was good correlation between the results of the dipstick test and assays (Kappa = 0.842, p < 0.001).
268x177mm (300 x 300 DPI)

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