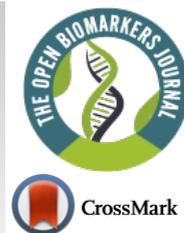




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REVIEW ARTICLE

Urinary Cotinine as a Biomarker of Cigarette Smoke Exposure: A Method to Differentiate Among Active, Second-Hand, and Non-Smoker Circumstances

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Abstract:

Objective:

To review the literature on the use of urinary cotinine as a biological marker of cigarette smoke exposure.

Methods:

Narrative review of original and review articles on the topic of interest, published in Portuguese or English by June 2018, and selected in the following online databases: PubMed and Virtual Health Library (VHL).

Results:

Urinary cotinine is usually the recommended biomarker to estimate exposure to cigarette smoke, and can be used alone or, preferably, in association with questionnaires. Different analytical techniques can be used to quantify urinary cotinine and are differently performed because of urine sample interfering factors.

Conclusion:

The precise classification of smoking status is essential. It is advisable to use objective measurements regarding smoking habits since self-reported smoking may not always represent the true smoking status of the individual, particularly in groups that are more vulnerable to omitting the information of questionnaires, in addition, it has possible biases of memory. The accurate assessment of smoking is crucial to improve clinical management and counseling for different diseases as well as the establishment of preventive strategies. So, the use of urinary cotinine as a biomarker of cigarette smoke exposure seems to be a suitable assay to distinguish non-smokers from passive and active smokers.

Keywords: Biomarkers, Cotinine, Smoking, Exposure, Tobacco Smoke Pollution, Environmental Biomarkers.

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1. INTRODUCTION

Cigarette smoke exposure is one of the main risk factors associated with a marked increase in the risk of developing

noncommunicable diseases, cardiovascular diseases, respiratory diseases and cancers [1]. It also translates into economic costs for patients, companies, and society as a whole. These may be direct, health care-related costs, or indirect, associated with a loss of productivity [2]. The prevalence of smoking has reduced in Brazil, going from 15 to 13% between 2011 and 2013 [3, 4]. According to data from the Surveillance System for Risk and Protective Factors for Chronic Diseases by Telephone Survey (VIGITEL), in 27 Brazilian capitals, the

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percentage of adult smokers in the year 2017 ranged from 4.1 in Salvador to 15.6% in Curitiba [5].

Cigarette smoke is a heterogeneous mixture of gases and particulate matter composed of more than 7000 substances, although nicotine (*i.e.* a tertiary amine composed of a pyridine and a pyrrolidine) stands out as the main compound present in the tobacco leaf [6, 7], it has a relatively short half-life when compared to the cotinine [8]. Cotinine is the main metabolite of nicotine biotransformation [9]. In brief, the CYP 2A6 transforms nicotine into a nicotine- δ -iminium ion, followed by the enzyme aldehyde oxidase action to produce cotinine, and possibly four other cotinine metabolites, such as cotinine *n*'-oxide, trans-3'-hydroxy-cotinine, 5'-hydroxy-cotinine, and norcotinine [9].

Cotinine concentration is proportional to the degree of exposure to nicotine and can be measured in different body fluids, such as blood, urine, and saliva, as well as in nails and hair [10]. Among these, urine is the most suitable biological fluid to detect current and secondhand smoke exposure through the quantification of cotinine. Even in situations of low exposure, the use of urine proves appropriate due to the possibility of estimating recent exposure and of showing higher concentrations, thus facilitating the use of different analytical techniques [10, 11]. The ideal time for measurement is 4 to 8 hours after exposure, at which point the maximum levels of this biomarker can be observed [12].

In addition, cotinine concentration can be calculated directly or corrected by urinary creatinine concentration to make this biomarker method even more accurate by normalizing the results through urine dilution [11]. Although multiple measurements reduce the incidence of classification errors, a single measurement of this biomarker can accurately determine the level of exposure to tobacco smoke [13].

Determining urinary cotinine concentration has been recommended in several situations, such as monitoring of cigarette smoke exposure, even during pregnancy and in some risk groups [7, 14]; impact assessment of smoking cessation programs [15]; occupational exposure assessment [16] and; exposure to environmental pollutants [17]. Therefore, this study aimed to review the literature on the use of urinary cotinine as a biomarker of cigarette smoke exposure and the methods used for its quantification.

2. METHODS

A narrative review of the literature was carried out by using the following online databases: PUBMED and Virtual Health Library (VHL), which includes LILACS, IBECs, MEDLINE, Cochrane Library and SciELO. The search was conducted between April and June 2018, based on the combination of selected keywords and the Boolean Operators "AND" and "OR".

Original and review articles on the subject, in Portuguese and in English, available in full version and published by June 2018, were selected by using the following keywords: biomarkers, cotinine, smoking, and exposure. The references of the articles were also checked in order to locate those that could not be found in the databases.

3. RESULTS AND DISCUSSION

3.1. Assessment of Tobacco Exposure: Urinary Cotinine Versus Self-Report

Self-reported smoking using questionnaires has been the most widely used tool to assess exposure to cigarette smoke, however, this strategy may underestimate smoking habits. Some authors suggest that self-reporting should be associated with the analysis of specific biomarkers, especially in groups which are more likely to omit information [18, 19].

Markers of tobacco smoke exposure allow an estimation of the degree of exposure to cigarette smoke. In this scenario, cotinine is the main metabolite of nicotine and, therefore, largely used as a biological marker of exposure. However, the analysis of biomarkers, including urinary cotinine, depends on information obtained through self-report, which is used as a reference for the estimation of cutoff values that help define smoking status [20]. Although some cutoff values for urinary cotinine are more commonly adopted in the literature (Table 1), there is no consensus and some authors suggest that these values should be specific for each population [21].

In fact, active smokers show high levels of urinary cotinine, and the cutoff points described in the literature would be adequate for their identification. On the other hand, the differences between the other groups (*i.e.* exposure to secondhand smoke and non-smokers) are less clear and require different strategies to estimate cutoff points based on the data obtained by self-report and, therefore, to define more appropriate values to such populations [22, 23].

Self-report questionnaires are the main form of smoking assessment among pregnant women, however, confirmation by laboratory analysis allows correct and reliable classification [24]. In addition, double-monitoring strategies using questionnaires and urinary cotinine quantification have been used to obtain information on the smoking status and the exposure to cigarette smoke from different sources among various population groups, such as pregnant women, university students and renal transplant recipients [21, 25, 26].

In pregnant women, smoking concealment is frequent due to the influence of social factors. The same is true for patients suffering from diseases with a strong correlation with smoking, such as chronic obstructive pulmonary disease, and head and neck cancer. In these cases, self-reported smoking had no correlation with the concentration of carcinogenic metabolites, unlike urinary cotinine [18, 27, 28]. In children, secondhand smoke exposure estimates are usually obtained through the self-report of their parents or caregivers, who are likely to be the source of exposure. Therefore, accurate and objective measurements are crucial, with the use of urinary cotinine concentration being a noninvasive option widely described in the literature for this age group [29].

Also, assessing cigarette smoke exposure using both urinary cotinine quantification and questionnaires in early life allows us to estimate the risk of recurrent wheezing and asthma in childhood. In addition, smoke exposure is closely related to the greater presence of daily symptoms of asthma and its assessment helps in the identification of children at higher risk

of experiencing an asthma crisis aggravation [29 - 31].

It is recognized that cotinine is the better predictor of birth weight than self-reported per-day tobacco use [32]. Most studies of reproductive consequences that were based on cotinine body fluid levels such as urine of mother or neonate demonstrate a better correlation between higher cotinine level and poor neonatal outcome [33, 34].

In all of these cases, the analysis of tobacco biomarkers is an indispensable tool that can be used independently to measure the exposure to cigarette smoke or, preferably, together with questionnaires.

3.2. Urinary Cotinine for Measuring Exposure to Secondhand Smoke

Exposure to secondhand smoke is defined as the exposure to the smoke that comes from the direct burning of cigarettes or other tobacco products, usually in combination with the smoke exhaled by the smoker, with harmful effects on the health of the exposed individual. The exposure of non-smokers to cigarette smoke depends on some factors, such as the room ventilation rate, the proximity of smokers to non-smokers, number of cigarettes smoked, among others [2]. For example, in seamen volunteers recruited from submarines, it was observed that the urinary cotinine levels of non-smoker on board were 2.1 times higher than at the seaport [35].

Cotinine is also the biomarker of choice for the quantification of exposure to secondhand smoke. It is possible to establish a dose-response relationship between the intensity and duration of exposure and the amount of cotinine excreted in the urine [36] since urinary cotinine is highly correlated with active and passive smoking [37]. Some authors believe that urinary cotinine concentration is a useful biomarker to distinguish non-smokers from current smokers. However, a careful interpretation of the cotinine concentration is necessary to estimate passive exposure to cigarette smoke [14].

The effects of secondhand smoke on children can be seen through respiratory diseases, infections, reduced school performance, and neurobehavioral problems [38]. Therefore, more effective strategies should be implemented towards protecting this population, which represents the most susceptible group to the harmful effects of environmental tobacco smoke exposure [38]. Urinary cotinine levels in children tend to vary depending on the number of household smokers or involved in their daily activities, the parents' perception of the tobacco exposure effects on children, the family members number of cigarettes smoked per day, and the exposure duration at home [39 - 41].

Just as it is the case for children, bar and restaurant staff are also a vulnerable population when it comes to secondhand smoke exposure. Promoting smoking cessation programs and occupational rules regarding smoking prohibition can have a significant impact on public health, and the measurement of urinary cotinine can be a valuable form of biological monitoring. In an experimental study with bar staff after the implementation of anti-smoking laws, there was a significant reduction in mean urinary cotinine concentration, from 35.9 ng / mL to below the limit of quantification (5 ng / mL), as well as

in self-reported respiratory symptoms [42]. Therefore, it is clear that measures focused on occupational health such as the implementation of policies for smoke-free places are extremely relevant.

3.3. Analytical Methodologies for Determination of Urinary Cotinine

Urinary cotinine can be quantified by several analytical techniques, such as High- Performance Liquid Chromatography (HPLC); Gas Chromatography (GC); thin-layer chromatography; Enzyme-Linked Immunosorbent Assay (ELISA); chemiluminescent immunoassay; radioimmunoassay. Mass spectrometry or ultraviolet absorption detectors have been widely applied for the detection of cotinine in chromatographic techniques (Table 1).

Despite their high sensitivity, the immunoassays specificity is low for cotinine quantification due to cross-reactions with other nicotine metabolites, such as 3-hydroxycotinine and 3-hydroxycotinine glucuronide; on the other hand, their acquisition and operating costs are lower and they can be very useful as a *screening* assay, especially when used in new *high throughput* systems, which can be highly efficient [25, 43]. In addition, immunoassays can also be complementary to the analyses conducted with chromatographic techniques, helping achieve greater selectivity when required [26].

Chromatographic techniques are primarily separation methods with high analytical specificity as they are able to separate structurally related metabolites from nicotine. In addition, their high sensitivity allows the limit of quantification for cotinine to be as low as 0.05 ng / mL when using liquid chromatography-mass spectrometry [12]. Chromatography-based methods can selectively quantitate free cotinine in urine. Some authors have also been performing cotinine-N-glucuronide hydrolysis using alkaline or enzymatic hydrolysis in order to determine total cotinine (*i.e.* free and conjugated) [29, 37].

However, different chromatographic techniques such as thin-layer chromatography, liquid chromatography, and gas chromatography can be used to detect cotinine; as a limitation, to detect cotinine these methods are more expensive and time-consuming. Usually, such techniques require urine samples prior to treatment to cotinine quantification, which may be done by purification through previous chromatography, solid-phase extraction or liquid-liquid extraction [21, 23, 44].

3.4. Variability in Urinary Cotinine Concentration

Urine cotinine levels tend to be influenced by environmental factors related to the intensity and duration of exposure to tobacco smoke, the amount of nicotine in the cigarette, the size and ventilation of the place of exposure.

Several factors influence the metabolism of nicotine, such as ethnic differences, Black and Asian individuals have a lower nicotine metabolism rate when compared to White people [45]; dietary habits, because some types of food have nicotine in their composition, which may increase the cotinine metabolite levels [46]; age, newborns have prolonged elimination of nicotine, but similar elimination of cotinine and other

conjugated metabolites. This may be caused by the difference in the action of the CYP2A6 enzyme, which is responsible for the metabolism of these substances [47]. Moreover, the elderly tend to have reduced renal clearance of cotinine compared to adults [48], and during pregnancy, metabolic clearance of

cotinine is markedly accelerated, resulting in a shorter half-life when compared to non-pregnant women [49]. On the other hand, individuals with severe renal impairment have reduced metabolic clearance of nicotine by about 50% when compared to healthy subjects [50].

Table 1. Studies using urinary cotinine as a biomarker of tobacco smoke exposure, published in the last five years.

Author, (year)	Study Design	Study Population	Level of Exposure	Analytical Method	Urinary Cotinine Concentration
Paci, et al., 2018	Cross-sectional study	1,075 individuals	Smokers: 27.5%	HPLC-MS	Cutoff point: 100 µg/g creat. Median - smokers: 1,504.7 ug/g creat. Median - non-smokers: 5.6 ug/g creat.
Perry et al., 2018	Case-control study	295 individuals	Urinary cotinine was detected in 60 children subject to exposure at home (parents' self-report) and 14 children whose parents denied exposure.	MS	Cutoff point: > 5 µg/L.
Moon et al., 2017	Cross-sectional study	276 employees at tobacco and hookah smoking places	Median creatinine concentration (interquartile): 1.1 (0.2 - 40.9) µg / g.	Enzyme-linked immunosorbent assay kit.	Limit of detection: 2 mg/dL.
Kim et al., 2018.	Cross-sectional study	96,806 medical records of asymptomatic individuals subjected to colonoscopy	Active smokers: 23% Non-smokers: 77%	DRI cotinine assay using a modular P800 chemistry analyzer.	Cutoff point: ≥50 ng/mL
Benowitz et al., 2018	Cross-sectional study	469 adolescents	Adolescents with cotinine levels above the limit of quantification: 407 (87%).	LC-MS	Limit of quantification: 0.05 ng /mL.
Nam et al., 2017	Cross-sectional study	1,139 adolescents	N.I.	GC-MS	Limit of detection: 0.26 ng/mL.
Wang, et al., (2017)	Cross-sectional study	368 children and their parents	Children living with 2 or more smokers: 30.7%; Children living with 1 smoker: 69.3%.	GC-MS	Geometric mean for children: 3.94 ng / mL.
Martinez-Sanchez, et al., 2017	Cross-sectional study	49 non-smokers	Individuals living with smoker(s): 25	LC-MS	Perception of intensity of exposure (Median) High: 7.59 ng/mL; Medium: 3.57 ng/mL; Low: 1.25 ng/mL; Very low: 0.44 ng/mL.
Rifai, et al., 2017	Cross-sectional study	843 active smokers	1 to 10 cigarettes/day: 299 10 to 20 cigarettes/day: 443 >20 cigarettes/day: 101	Immulite 2000 Assay	Tercile 1: 7 - 2421 ng/mL; Tercile 2: 2422- 6436 ng/mL; Tercile 3: > 6437 ng/mL.
Hoseini, et al., 2016	Cross-sectional study	222 urban residents	Active smokers: 76 Passive smokers: 57 Non-smokers: 89	ELISA	Cutoff point(active): 100 ng/mL Active smoker: 795.6 ± 396.7 ng/mL; Passive smoker: 7.6 ± 2.8 ng/mL; Non-smoker: 3.56 ± 1.9 ng/mL.
Tranfo et al., (2016)	Descriptive study	446 healthy volunteer residents	Smokers: 93 Former smokers: 156 Non-smokers: 197	HPLC-MS	Limit of detection: 12.41 µg/L. Cutoff point (smokers): 100 µg/g creatinine. > 100 ug/g creatinine: 110

(Table 1) contd....

Author, (year)	Study Design	Study Population	Level of Exposure	Analytical Method	Urinary Cotinine Concentration
Hellemons, et al. (2015)	Prospective cohort	603 renal transplant recipients	Never smoked: 217 Former smokers: 255 Light smokers: 64 Heavy smokers: 67	Immulite 2500 Assay	Limit of detection: 10 ng/mL. Cutoff point Non-smokers: < 100 ng/mL; Passive smokers: 100-500 ng/mL; Active smokers: >500 ng/mL;
Lupsa, et al. (2015)	Cross-sectional study	360 children and their mothers	Mothers Daily smokers: 89 Occasional smokers: 30 Former smokers: 62 Non-smokers: 179	HPLC-MS	Limit of quantification: 0.7 ug/L. Different cutoff points for each subpopulation.
Evlampidou, et al., (2015)	Cohort	175 pairs of non-smoking mothers-children	Children with no exposure to secondhand smoke at 8 months (mothers' self-report): 56%	GC-MS	Total Cotinine (free + glucuronide) Limit of detection: 1.0 ng/mL. Cutoff point: 100 ng/mL.
Mørck, et al., (2015)	Cross-sectional study	75 pairs of mothers/children from urban areas; 70 pairs of mothers/children from rural areas	Smoking mothers from urban areas: 6 Smoking mothers from rural areas: 12	LC-MS	Limit of detection: 0.3 ug/L. Children's maximum value: 16.3 ug/L; Mothers' maximum value: 3.403 ug/L; All smoking mothers: > 200 ug/L
Wang, et al., (2015)	Randomized controlled trial	65 children aged 5 to 6 years and caregivers. 33 pairs received intervention (smoking cessation education); 32 control pairs.	Cessation after 6 months Intervention group: 34.4%; Control group: 0%	GC-MS	Limit of quantification: 0.1 ng /mL.
Khariwala, et al. (2015)	Cross-sectional study	84 smokers with head and neck cancer	N.I.	GC-MS	Urinary cotinine levels correlated with carcinogen levels.
Stelmach, et al. (2015)	Cross-sectional study	144 individuals with Asthma (51) or Chronic Obstructive Pulmonary Disease (53)	Smokers: 20 Never smoked: 20	HPLC-UV	Median concentration Smokers: 2036 ng/mL; Never smoked: 70 ng/mL; COPD: 167 ng/mL; Asthma: 47 ng/mL.
Jones, et al. (2014)	Experimental exposure	10 participants	Non-smokers: 08 Active smokers: 02	LC-MS	Total Cotinine. Limit of quantification: 0.05 ng /mL.
Khariwala, et al. (2014)	Cross section	28 black individuals, 04 Latinos and 25 whites from one community	Smoked at least 1 cigarette in 4-24 days in the last 30 days.	LC-MS	Limit of quantification: 0.05 ng /mL. Mean (standard deviation): 804.40 (917.76) ng / mg creatinine; Median: 409.9 ng / mg creatinine.
Martinez-Sanchez, et al., 2017 (2014)	Observational study	49 non-smoking volunteers from different households	People living with smoker(s): 25; People living in non-smoking households: 24.	LC-MS	Limit of quantification: 0.10 ng /mL. Median: 0.92 ng/mL.
Gill; Krishnan; Dozor, 2014	Cross-sectional study	40 individuals aged 8-18 years, with mild to moderate persistent asthma.	Individuals affected by secondhand smoke exposure: 28 (70%).	ELISA	Indication of exposure to secondhand smoke: ≥ 1 ng / mL.

(Table 1) contd....

Author, (year)	Study Design	Study Population	Level of Exposure	Analytical Method	Urinary Cotinine Concentration
Mateos-Vilchez, et al. (2014)	Cross-sectional study	1,813 women from 03 independent samples: beginning, end of pregnancy and immediate postpartum period.	Tobacco exposure (active and passive smoking) End of gestation: 25.0%; Beginning of gestation: 41.8%;	Competitive chemiluminescent immunoassay	Non-smokers: < 20 ng/mL; Passive or occasional smokers: 20-125 ng / mL; Moderate smokers: 125-500 ng / mL; Heavy smokers: > 500 ng / mL.
Machado, et al. (2014)	Cross-sectional study	125 pregnant women	Current smokers: 37; Individuals subject to secondhand smoke exposure: 25 Non-smokers: 63	HPLC-UV	Urinary cotinine limit of quantification: 10 ug / L.
Matsumoto, et al. (2013)	Cross-sectional study	219 people from a manufacturing company.	Smokers: 102; Non-smokers: 117	GC-MS	Limit of quantification: 0.7 ng /mL. Smokers: 3.948 ng/mL; Non-smokers: < 2.8 ng/mL;
Szumaska, et al. (2013) Tyrpién, et al. (2000)	Cross-sectional study	85 medical students	Active smokers: 40 Non-smokers: 45 Exposed: 25 Not exposed: 20	ELISA for nicotine metabolites, followed by C18 TLC with densitometry	ELISA (nicotine metabolites) Smokers: > 200 µg/g creatinine; Non-smokers: <200 µg / g creatinine; Passive smoker: 20-200 µg / g creatinine; Not exposed: <20 µg / g creatinine. TLC Limit of detection: 13.5 ng/spot. Smokers: 523.1 ± 68.1 ug/g creatinine; Non-smokers Exposed: 40.89 ± 24.8 µg cotinine /g creatinine. Not exposed: not detected.
Vardavas, et al. (2013)	Cohort	367 non-smoking pregnant women	Exposure to secondhand cigarette smoke > 2 sources of exposure: 158; ≤ 2 sources of exposure: 209	LC-MS	Total Cotinine. Limit of quantification: 0.5 ng /mL. Household exposure: 4.40 ng / mL increase; Secondhand smoke exposure in cars: 8.73 ng / mL increase.
Yarnall, et al. (2013)	Longitudinal study	239 volunteers recruited from US Navy submarines.	Pairs of non-smoker samples at seaport (before embarking) and after disembarking: 206	LC-MS	Limit of detection: 0.05 ng/mL. Cutoff point(smoker): 15 ng/mL
Kim, et al. (2013)	Cross-sectional study	925 post-menopause women	Never smoked	GC-MS	Limit of detection: 0.28 ng/mL.
Pacheco, et al., (2013)	Cross-sectional study	96 workers	Smokers: 26; Non-smokers: 70.	GC-MS	Limit of quantification: 5 ng /mL.

*Abbreviations: LC: Liquid chromatography; MS: Mass Spectrometry; GC: Gas Chromatography; ELISA: Enzyme-linked immunosorbent assay; HPLC: High-performance liquid chromatography; UV: Ultraviolet; N.I.: No Information; ln: natural logarithm.

There is evidence that genetic polymorphisms related to nicotine metabolism constitute an important factor in the susceptibility to nicotine dependence; genetic discoveries may allow the identification of individuals at greater risk of tobacco dependence and be used as a more effective strategy in the treatment and prevention of smoking [9, 51]. Understanding interindividual variability in nicotine metabolism is crucial, as there is substantial evidence to suggest that interindividual

differences in cotinine production can be associated with CYP2A6 gene polymorphisms [52]. Japanese individuals, for example, have low CYP2A6 activity, an enzyme necessary for nicotine to be metabolized into cotinine [53].

Another important factor to estimate exposure to cigarette smoke is the establishment of cutoff points for more objective differentiation levels of exposure based on urinary cotinine

concentration [54]; thus, factors influencing cotinine levels in urine should be considered in order to ensure better differentiation in the studied population.

CONCLUSION

Urinary cotinine is a reliable biomarker, widely used for distinguishing between active and secondhand smoke exposure. Although several highly sensitive analytical methodologies such as chromatography or immunoassay can be used for the urinary cotinine quantification, it should be preferably used in association with self-reports interviews or questionnaires, to correctly estimate the most appropriate cutoff points for smoking status classification.

CONSENT FOR PUBLICATION

Not Applicable.

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CONFLICT OF INTEREST

The manuscript authors declare no conflict of interest. This paper was written by using secondary data information, and none of this content has been previously published.

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