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Preliminary study on serum paraoxonase-1 status and chemokine (C-C motif) ligand 2 in hospitalized elderly patients with catheter-associated asymptomatic bacteriuria

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Abstract

Urinary tract infections (UTI) are common among elderly patients in residential care facilities, as well as in the hospital setting. Identifying new biochemical markers of UTI is an active line of research since UTI management is resource intensive. Paraoxonase-1 (PON1) forms part of the patient's immune system, the response-to-injury and inflammation. Our study sought to evaluate alterations in inflammation-related paraoxonase-1 (PON1) and chemokine (C-C motif) ligand 2 (CCL2) in patients with an indwelling catheter, to assess their potential usefulness as biomarkers of infection. Patients (n=142) who had had the urinary catheter removed, and 100 healthy volunteers were recruited. In all participants we measured serum PON1 activity, PON1 concentration, CCL2, procalcitonin and C-reactive protein (CRP). Results indicated that patients had higher CCL2, CRP and procalcitonin concentrations than the control group, and lower paraoxonase activity. There were no significant differences in PON1 concentrations. When comparing the diagnostic accuracy of CRP, procalcitonin, CCL2 and the PON1-related variables in discriminating between patients with and those without UTI, we found a considerable degree of overlap between groups i.e. a low diagnostic accuracy. However, there were significant inverse logarithmic correlations between serum paraoxonase activity and the number of days the urinary catheter had been *in situ*. Our results suggest that measurement of these biochemical variables may be useful in investigating complications of long-term use of these devices and help to improve the economic and clinical investment required in the management of the often-associated infection.

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Abbreviations

ACI	Acute concomitant infection
DTNB	5,5’-dithio-bis-2-nitrobenzoic acid
CAAB	Catheter-associated asymptomatic bacteriuria
CAUTI	Catheter-associated urinary tract infection
CCL2	Chemokine (C-C motif) ligand 2
CRP	C-reactive protein
PON1	Paraoxonase-1
ROC	Receiver operating characteristic
TBBL	5-thiobutyl butyrolactone
UTI	Urinary tract infection

Introduction

Urinary tract infections (UTI) are common among elderly patients in residential care-for-the-elderly facilities, as well as in the hospital setting. UTI is very frequent in hospitalized older patients [1], and the majority of cases of nosocomial UTI are associated with an indwelling urinary catheter. Considerable time and resources are spent reducing the rate of catheter-associated UTI (CAUTI) and this has important implications for the patient and the clinical environment [2]. Several institutions have released guidelines concerning CAUTI and the related condition of catheter-associated asymptomatic bacteriuria (CAAB). CAUTI and CAAB are distinct conditions and should be distinguished from each other, and treated accordingly. Inappropriate treatment is potentially harmful because of the emergence of resistant pathogens, supra-infections, and unnecessary costs [3]. Unfortunately, diagnosis is often complicated by symptoms such as fever, chills and hypotension, which are non-specific [4]. The Infectious Disease Society of America recommended against routine screening for, and antimicrobial treatment of, asymptomatic bacteriuria in elderly, whether community dwellers or institutionalized. Also, antibiotics are not recommended for patients with indwelling catheters and diabetic women, while performing a routine urinary sediment analysis is only recommended in symptomatic patients [5]. Unnecessary treatment can cause potentially undesirable adverse effects of antibiotic use. These include development of resistant organisms and increased risk of drug interaction from polypharmacy. However, treatment is recommended for patients with asymptomatic bacteriuria with abnormal urinary tract morphology, and those with persistent bacteriuria 48 hours after undergoing clean intermittent catheterization, genitourinary manipulation, or instrumentation that carries a high probability of mucosal bleeding [6]. It is also recommended for patients with acute concomitant infection (ACI), or with acute pyelonephritis, acute lower tract symptoms or catheter trauma/obstruction [7].

Therefore, since most patients with an indwelling urinary catheter have asymptomatic bacteriuria, and clinical symptoms associated with CAUTI are unspecific, identifying new biochemical markers constitutes an important area of investigation. Several studies have proposed C-reactive protein (CRP) or procalcitonin as useful markers of infection. However, their usefulness varies with the clinical setting, and remains an unresolved issue [8]. A recent study from our group suggested that that serum paraoxonase-1 (PON1) activity and the chemokine (C-C motif) ligand 2 (CCL2), are useful indices for the diagnosis of an ACI in patients with an indwelling central venous catheter [9]. The possible value of these biochemical parameters in the diagnosis of UTI has yet to be quantified.

PON1 is an enzyme bound to high-density lipoproteins. It degrades oxidized lipids and inhibits the synthesis of CCL2, a pro-inflammatory chemokine that attracts monocytes to the inflammation sites where they are induced to differentiate to macrophages [10] and proceed towards the atherosclerosis process. Several lines of evidence suggest that PON1 participates in the protection conferred by high-density lipoproteins against different infectious agents, including bacteria and viruses [11,12]. Overall, these results indicate that PON1 can be considered part of the innate immunity system [13].

Our study sought to characterize the alterations of PON1 and CCL2 levels in the circulation of hospitalized patients having an indwelling urinary catheter, and in relation to their clinical and biochemical characteristics. The potential usefulness of these parameters as biomarkers for the diagnosis of infection was assessed.

Materials and methods

Ethical approval

The study was approved by the Ethics Committee (Institutional Review Board) of the *Hospital Universitari de Sant Joan*. All the participants provided written informed consent to participation in the study on the understanding that anonymity of data was guaranteed.

Participants

Between March 2011 and June 2013, we prospectively recruited a total of 142 patients ≥60 years of age (males=99; females=43) who had had a urinary catheter removed because of infection, or because it was no longer needed, according to the criteria of the attending physician. Exclusion criteria were: severe alcohol abuse, psychiatric diseases, or liver impairment. At the time of catheter removal, a blood sample was obtained for biochemical and genetic analyses. A urine sample was collected for microbiological analyses. The participants' medical records were reviewed and pertinent demographic data, comorbidities, together with bacteriologic and therapeutic data were recorded. Data on the patients' local and general infection-related clinical manifestations were collected, as well as the presence of other acute or chronic infections. The type of treatment received in the 24h prior to the present study, and the appearance of neoplasia within a 6 month follow-up period were recorded. The McCabe classification [14] and the Charlson comorbidity index [15] were recorded in all patients. Of the participants, 82 (48%) were hospitalized for surgery-related reasons, 52 (30%) for an infectious disease, and the remaining 37

distributed in smaller percentages among various other clinical conditions. Asymptomatic CAAB was noted in 32 patients (19%). Patients with an ACI were suffering from infections (including abdominal abscess, pneumonia) that were not related to an infected catheter. There were 42 patients (25%) who had an ACI without CAAB, 21 (12%) had CAAB without ACI, and 11 (6%) had both infections simultaneously.

The control group consisted of 100 healthy volunteers who were participating in an epidemiological study in our geographical area; the details have been reported previously [16]. These subjects had a similar age distribution as the patients (≥60 years of age; males=68 and females=32), and had no clinical or biochemical evidence of renal insufficiency, liver disease, neoplasia or neurological disorders.

Biochemical analyses

Since PON1 has esterase and lactonase activities [10], we decided to measure the catalytic activity of PON1 using two different substrates: paraoxon (an ester), and 5-thiobutyl butyrolactone (TBBL, a synthetic lactone), as previously described [17]. Serum PON1 concentrations were determined using an in-house enzyme-linked immunosorbent assay [18]. The serum concentration of C-reactive protein (CRP) was measured using a high sensitivity method (Horiba ABX, Montpellier, France). The serum concentration of procalcitonin and the EDTA-plasma concentration of CCL2 were measured by enzyme-linked immunosorbent assay (Biovendor, Brno, Czech Republic, and Prepotech, London, UK, respectively).

PON1 genotyping

Serum PON1 paraoxonase activity is strongly determined by the enzyme genotype [17]. Several polymorphisms in the promoter and the coding regions of the *PON1* gene have been described and, in the present study, we chose to analyze the polymorphisms Arg/Gln at position 192 (*PON1*$_{192}$, with two alleles termed Q and R), and the polymorphism Leu/Met at position 55 (*PON1*$_{55}$, with two alleles termed L and M). *PON1*$_{192}$ is strongly associated with the enzyme's activity and *PON1*$_{55}$ is a surrogate of the *PON1*$_{-108}$ promoter polymorphism [10]. For polymorphism analyses, genomic DNA was obtained from leukocytes (Puregene DNA Isolation reagent set, Gentra Systems Inc., Minneapolis, MN, USA), and the chosen polymorphisms were analyzed by the Iplex Gold MassArray^{TM} method (Sequenom Inc., San Diego, CA, USA).

Microbiology analyses

The urine culture was performed according to the recommendations of the Spanish Society of Infectious Diseases and Clinical Microbiology [19]. Urine samples were inoculated on the surface of one plate with cysteine lactose electrolyte deficient culture medium and another plate with blood agar. After incubation, the count of the colony forming units (CFU) was performed. In general, a culture was considered positive if the count was of at least 10^8 CFU/L of an identified microorganism in the absence of signs and symptoms of a urinary tract infection. Cultures with lower counts were interpreted as positive, depending on the isolated microorganism, presence of pyuria in the sediment, or analytical and clinical data, at the discretion of the microbiologist. Subsequently, the identification and susceptibility testing of the isolated organism(s) were performed using the automated microdilution MicroScan WalkAway system (Siemens AG, Munich, Germany) and/or by the disk diffusion method with complementary biochemical tests.

Statistical analyses

All calculations were performed with the SPSS 22.0 statistical package (SPSS Inc., Chicago, IL, USA). Differences between any two groups were assessed with the Mann-Whitney *U* test, since most of the studied variables had non-parametric distributions. Differences between more than two groups were analyzed with the Kruskal-Wallis test. Qualitative data were analyzed with the χ^2 test. Results are shown as medians and 95% CI. Logarithmic correlations were used to evaluate the degree of association between variables. Biochemical variables' diagnostic accuracy were assessed using receiver operating characteristic (ROC) curve analysis [20].

Results

Clinical and demographic characteristics

Patients with CAAB were significantly older and the percentage of males was lower than those without CAAB. They also had a higher frequency of renal insufficiency, were receiving immunosuppressive treatment more often, and had a longer duration of implanted catheter. They had significantly lower frequencies of history of neoplasia, surgical intervention, and antibiotic treatment. The percentage of patients with no comorbidities, as indicated by the Charlson index, was also higher than in patients with a

catheter infection (Table 1). Urine culture was negative in 113 patients (80%), positive for Gram-negative bacteria in 12 patients (9%), positive for Gram-positive bacteria in 7 (4%), and positive for assorted fungi in 10 (7%).

Changes in infection/inflammation biomarkers and PON1-related variables

Patients with an indwelling urinary catheter had higher CCl2, CRP and procalcitonin concentrations than the control group, and lower paraoxonase and TBBLase activities. There were no significant differences in PON1 concentrations (Table 2). We did not observe any significant differences between patients and controls with respect to genotype frequencies of the $PON1_{192}$ and $PON1_{55}$ gene polymorphisms (Table 3). There were significant inverse logarithmic correlations between serum paraoxonase and TBBLase activities *versus* the number of days the urinary catheter was indwelling (Fig. 1). There were no significant associations between the number of days the urinary catheter was indwelling *versus* the type of microorganism isolated in the urine culture. We did not observe any other significant association between the duration of the indwelling urinary catheter *versus* any other biochemical or genetic variable (data not shown).

We segregated the patients according to the severity of the CAAB, but we did not observe any statistically significant differences in any of the investigated parameters (Table 4). When patients were segregated according to whether or not they had an ACI, we only observed a significant increase in serum CRP, although paraoxonase activity showed a marginal trend towards a decrease (Table 5).

When comparing the diagnostic accuracy of CRP, procalcitonin, CCL2 and the PON1-related variables in the ability to discriminate between patients with and those without an ACI, or those with and those without a CAAB, we found that the AUROC mean values were considerably lower for all the studied variables. This indicates a low efficacy and a considerable degree of overlapping between groups (Table 6).

Discussion

The main objective of the present study was to investigate the alterations of PON1 and CCL2 levels in the circulation in hospitalized patients who had an implanted urinary catheter. We found a significant decrease in serum PON1 activity in these patients, compared with the control group. This decrease was observed in the measured paraoxonase (esterase) and TBBLase (lactonase) activities of this enzyme. PON1 hydrolyzes several substrates including esters, lactones, and lipid peroxides. The main function of PON1 is to degrade lipid peroxides and quorum-sensing lactones and, as such, plays an important role

in the innate defense system against infection and oxidative stress [10]. Our results show that the decrease in PON1 activity in patients with an implanted urinary catheter is not substrate-specific and involves esterase as well as lactonase activities. In addition, serum PON1 concentrations remained unchanged. One possible explanation for this observation is that the decrease in activity was due to enzyme inactivation. Indeed, to degrade lipid peroxides, PON1 requires a free sulfhydryl group at cysteine 284 that covalently reacts with the substrate, leading to enzyme inactivation [21]. Consequently, every PON1 molecule degrading an oxidized lipid becomes inactivated, and the overall enzyme activity is decreased. We did not observe any significant differences in *PON1* polymorphisms between patients with an indwelling urinary catheter *versus* the control group. It is important to highlight these data because, in case-control studies of enzyme activity comparisons, it is imperative that cases and controls have similar genotype frequencies of the $PON1_{192}$ and $PON1_{55}$ gene polymorphisms. If this variable is not taken into account, it is not possible to ascertain whether observed changes are due to the disease *per se* or to coincidental differences in allelic frequencies between cases and controls [22]. Our statistical analyses show that genotypic differences do not explain the observed changes in PON1 activities.

We also observed a significant increase in plasma CCL2 concentrations in our patients. PON1 and CCL2 are closely related and their levels in circulation show alterations in opposite directions in many diseases [23]. Chemokines, CCL2 in particular, are central to the vascular inflammatory response as mediators of monocyte recruitment into the arterial wall [24]. Previous studies found that PON1 inhibits the production of CCL2 induced by oxidative stress in cultured endothelial cells, and that both PON1 and CCL2 are ubiquitously distributed in mouse tissues and, as such, implying combined systemic effects [25,26]. Clinical data suggest that plasma CCL2 concentration measurement may be an important biomarker of diseases involving inflammatory response to an increased oxidative stress [27,28]. However, there is a paucity of information on alterations in plasma CCL2 concentrations in infectious diseases. Recent studies reported that CCL2 levels are elevated in patients admitted to Intensive Care with sepsis, and in patients carrying an indwelling central venous catheter [9,29]. Results from the present investigation conclude that this is also the case in patients carrying an indwelling urinary catheter.

Current guidelines highlight that the diagnosis of symptomatic urinary tract infection requires the presence of clinical symptoms as well as positive urine culture [30,31]. However, results from such methods require considerable time. Simpler, more rapid, urinary dipstick analysis and microscopic examination of urinary sediment are

inadequate for the diagnosis of urinary tract infection due to their lack of sensitivity [32]. Hence, the quest for the identification of appropriate biomarkers for correct diagnosis of UTI is of considerable value. Based on previous knowledge of the biological functions of PON1 and CCL2, we opted to investigate the usefulness of these serum constituents in the present study. Unfortunately, the results were modest. Despite clear alterations in their circulating levels, the diagnostic accuracy of these parameters was not sufficient to distinguish between patients with CAAB from those without, or those with ACI from those without. Results for the standard markers of infection (CRP and procalcitonin) were not much better. The main problems with all of these markers are the variability of the results obtained, and the high degree of overlapping between sub-groups. Other studies have reported inconsistent and variable study findings, and have questioned the diagnostic and prognostic performance of procalcitonin and CRP in infection [33]. However, an interesting observation in our study was the inverse associations between serum paraoxonase and lactonase activities *versus* the duration (number of days) of the catheter's residence *in situ*. This finding could have considerable clinical relevance since localization *in situ* of catheters over the long term can result in local inflammation and, possibly, the formation of bacterial biofilms that become resistant to antibiotic treatments [34]. In Gram-negative bacteria, acyl homoserine lactones have been identified as the major signaling molecules in biofilm formation [35,36]. Evidence shows that PON1 may play an important role against them, due to its lactonase activity [35]. For example, mouse serum, which is an environment rich in PON1, degrades acyl homoserine lactones and decreases *Pseudomonas aeruginosa* biofilm growth; this capacity being lost when serum from PON1-deficient mice was employed instead of from wild-type mice [37]. Conversely, acyl homoserine lactones secreted by Gram-negative bacteria dramatically decrease the protein levels and enzymatic activity of PON2 and PON3; enzymes that are closely related to PON1 [38]. Thus, the formation of bacterial biofilms in the urinary catheters would explain the observed decrease in serum PON1 activity in our patients. We believe that this is an interesting hypothesis that deserves further investigation.

Conclusion

The findings of the present study need to be considered preliminary. The population studied is heterogeneous, and the participants differ with respect to etiology and comorbidities. Additionally, the numbers of participants are relatively low. However, our results show significant alterations in the circulating levels of PON1 and CCl2 in patients with an indwelling urinary catheter. As such, their measurement may be useful in investigating complications associated with long-term use of these devices and the

economic-clinical investment required in the management of the infection that is often associated.

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Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study

Conflict of interest

None for all the authors

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Figure legends

Fig. 1 Relationships between serum paraoxonase and TBBLase activities *versus* the number of days the urinary catheter was indwelling