Original Article

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False positive hCG testing and upper urinary tract infection

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Abstract

Objectives: Human chorionic gonadotropin (hCG) assays are commonly used as a pregnancy test. False-positive human chorionic gonadotropin (hCG) values in urine were reported in 15 patients (nine males and six females) presenting with urinary tract infection.
Methods: Extopic hCG production and presence of heterophilic antibodies were excluded as potential causes of interference.
Results: Orbitrap mass spectrometry revealed the presence of uromodulin, an abundant urinary glycoprotein, as the likely cause of the interference. Falsely elevated hCG values correlated well with urinary alpha 1 microglobulin (a tubular protein) concentrations and with the urinary leukocyte count. The false positive hCG signal disappeared after antibiotic administration.
Conclusions: These data suggest that false-positive hCG test results in urine may occur in patients presenting with upper urinary tract infections due to uromodulin interference.

Keywords: human chorionic gonadotropin; alpha 1 microglobulin; uromodulin

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Introduction

In clinical studies, determination of human choriogonadotropic hormone (hCG) and urinalysis are common in routine practice. hCG is considered the most acidic and glycosylated glycoprotein, with a molecular weight of 36 kDa. It is produced at high concentrations by trophoblasts of the placenta, with a circulating half-life of approximately 37 h. The structure of this hormone is characterized by two dissimilar subunits (α- and β-subunits), which are held together by non-covalent hydrophobic and ionic interactions, and eight carbohydrate side chains. Five separate variants of hCG have been described (hCG, sulfated hCG, hyperglycosylated hCG, hCGβ, and hyperglycosylated hCGβ) with a common amino acid backbone and variable carbohydrate side chain and meric structures. These molecules are independently produced by different cells and have different biological functions. hCG stimulates progesterone production and is involved in many important placental, uterine, and fetal functions during pregnancy [1, 2].

hCG immunoassays have been developed to detect the presence of hCG and its variant molecular forms in blood or urine. In general, a sandwich principal with two antibodies is used, with at least one antibody binding and immobilizing hCG, and a second antibody raised to a distant epitope and labeled with an enzyme, dye, or chemiluminescence agent for qualitative or quantitative measurement of hCG [3].

Besides normal and ectopic pregnancies, the most common causes of positive hCG are quiescent gestational trophoblastic disease following ectopic pregnancy and spontaneous abortion, false-positive serum hCG, pituitary sulfated hCG, non-trophoblastic neoplasm or placental site trophoblastic tumor, gestational trophoblastic neoplasm, testicular cancer, sportsmen with hCG doping, Munchausen's syndrome, and women using hCG as a dietary aid [4]. In our laboratory, attention was drawn to a number of false-positive hCG values in urine using the Roche Modular Analytic System, which were encountered in non-pregnant women. Using modern immunoassays based on highly specific sets of monoclonal antibodies, false-positive hCG results have become rare. Following the exclusion of common analytical interferences (human anti-mouse IgG or heterophilic antibodies) [5–7] and ectopic hCG production by

non-reported tumors, a striking coincidence with upper urinary tract infection and false positive urinary hCG values was observed. This unexpected finding of hitherto unreported interference prompted us to perform additional biochemical and clinical investigations. The chemical nature of the interference was investigated in detail. Concomitantly, a clinical study was initiated to investigate the clinical correlation between false-positive hCG findings.

Materials and methods

Subjects

Participants in the study were selected based on the clinical diagnosis of upper and lower urinary tract infections (UTIs). The study included urine specimens from 15 patients diagnosed with upper UTI, comprising nine males and six females with a median age of 65 years [interquartile range (IQR): 58–69 years]. A control group of 20 age-matched adults including 10 males and 10 females with a median age of 64 years (IQR: 56–68 years), was selected from individual diagnosed with lower UTI. Pregnancy was excluded in all the cases investigated by urinary HCG testing. Both groups were rigorously assessed using clinical and laboratory criteria to ensure accurate classification. The diagnosis of upper vs. lower urinary tract infection was determined based on clinal and laboratory criteria. Upper UTI (pyelonephritis) was identified by the presence of systemic symptoms such as fever (≥38 °C), flank pain, and elevated inflammatory markers (e.g., C-reactive protein and white blood cell count), alongside bacteriuria and pyuria in urinalysis. Lower UTI was classified in the absence of systemic symptoms and based on localized urinary symptoms such as dysuria, frequency, and urgency, supported by bacteriuria and pyuria without systemic markers of inflammation.

Sample collection

Urine samples were collected and analyzed to investigate false-positive hCG results. The pre-analytical phase of the study was meticulously managed to ensure the integrity of the samples and the reliability of the results. Urine was collected in sterile containers suitable for urinalysis and were transported with a pneumatic tube system. Samples were processed within 2 h of collection to minimize degradation or alterations in analyte levels, adhering to standard clinical laboratory practices.

hCG test

hCG testing in urine (catalogue number: 03271749190) was performed using the Roche Modular Analytics System (Roche Diagnostics, Vilvoorde, Belgium). This assay is intended for use in serum or plasma. Positive results were confirmed with immunoassays from multiple vendors to assess cross-reactivity. The immunobeads (which are a part of catalogue number: L2KCG2) intended for use on the Immulite 2000 System (Siemens, Brussels, Belgium) were used for immunoextracting the interfering protein [8]. The presence of heterophilic antibodies as potential interfering factors was tested by pretreating the urine sample with heterophilic blocking tubes (Scantibodies Laboratory, Villebon, France) [9].

Gel permeation chromatography

Gel permeation chromatography was performed by injecting 30 µL of the patient's serum into a Waters 650E advanced protein purification system (Millipore, Overijse, Belgium) and subjected to high-pressure gel permeation chromatography (HPGPC). A 150 mL volume of human serum was injected using the Wisp 712 automatic sampler (Waters Corporation, Milford, MA, USA). For chromatographic separation, an 8×300 mm^2 Protein PAK glass 300 SW column (Waters Corporation, Milford, MA, USA) was used. Phosphate-buffered saline (PBS) [0.1 mol/L, containing 137 mmol/L NaCl, 2.7 mmol/L KCl, 8.1 mmol/L Na_2HPO_4, 1.47 mmol/L KH_2PO_4 (pH 7.3)] was used as the mobile phase. The flow rate was 1.0 mL/min [10]. The concentrations of various hCG-containing fractions were confirmed by electrochemiluminescence. Simultaneously, cystatin c, albumin, and immunoglobulin G, with known molecular masses, were measured in different fractions.

Immunopurification

Immunopurification of the proteins reacting with hCG antibodies was performed on the urine matrix. The patient's urine was adsorbed onto beads coated with monoclonal anti-hCG antibodies originating from an Immulite 2000 hCG kit (Siemens, Brussels, Belgium), using a solid-phase, two-site chemiluminescent immunometric assay. After elution under acid pH conditions (0.2 mol/L sodium acetate buffer containing 0.15 mol/L NaCl, pH 3), the adsorbed protein was rechromatographed using the same procedure. Following the second incubation step and neutralization with sodium hydroxyde 0.1 mol/L, the hCG in the eluate was assayed. Following chromatography, the eluate was subjected to peptide analysis using an Ultimate 3000 nano-high-performance liquid chromatography (HPLC) system

(Dionex, Amsterdam, The Netherlands) coupled with an LTQ Orbitrap XL mass spectrometer (Thermo Electron, Bremen, Germany).

General biochemical determinations

General biochemical determinations were performed on urine and serum. As uromodulin was repeatedly detected in the peptide analysis, the question was raised as to whether this result could be due to contamination (uromodulin being an abundant urinary protein) or a true identification of an analytical interference. Therefore, urine samples were assayed for uromodulin using a commercial enzyme-linked immunosorbent assay (ELISA) (MD Bioproducts, Egg, Switzerland). Urinary albumin was assayed immunonephelometrically on a BNII nephelometer (Siemens Healthineers, Erlangen, Germany). In addition, total urinary protein was measured using the pyrogallol red method with standard reference material 917a, and urinary alpha-1 microglobulin (catalogue: 08944547190 A1M, 150T, c701/c702 PCH) was determined on a Cobas 8000 analyzer (Roche Diagnostics, Vilvoorde, Belgium). Urinary and serum creatinine was assayed using a rate-blanked compensated alkaline picrate method on a Cobas 8000 analyzer (Roche Diagnostics, Vilvoorde, Belgium). Urinary sediment analysis was performed using a Sysmex UF-1000i flow cytometer (Sysmex, Hoeilaart, Belgium). The Sysmex UF-1000i instrument employs flow cytometry and impedance measurements, featuring two specialized counting channels (for sediment and microbial analysis), a 635 nm semiconductor laser, and a polymethine DNA dye. It utilizes both forward and side-scatter detection for particle identification [11]. In serum, the CRP concentration was determined using the cobas c701/702 system (catalogue: 07876424190, CRP4, 500T).

Statistics

All values were expressed as the median (IQR). Statistical analyses were performed using MedCalc software (MedCalc, Mariakerke, Belgium). For continuous variables, we used the analysis of variance and Kruskal-Wallis test as appropriate. Spearman correlation coefficients were used to express the associations between continuous parameters. Multiple linear regression analysis was performed after log-transformation of the variables to obtain a normal distribution. Statistical significance was set at $p<0.05$.

Results

In our study population group, positive urinary hCG values were reported in 15 patients, showing a broad concentration range [6.69 mIU/L (5.01–8.66 mIU/L)] in both sexes, with the highest hCG levels surprisingly observed in men. Table 1 presents the urinalysis and hCG results of the patients with upper urinary tract infection. No significant difference in hCG values was observed after treatment with heterophilic antibody-blocking tubes. Multiple linear regression analysis (Table 2) demonstrated that alpha 1 microglobulin (Figure 1) and leukocyte count were major determinants of hCG signaling. In addition, urinary casts and uromodulin were positively correlated with hCG. In contrast to patients with an upper urinary tract infection, a positive hCG signal was not observed in those with a lower urinary tract infection. However, following immunopurification of the specimens with positive hCG results, gel permeation chromatography and mass spectrometric analysis did not reveal the presence of human hCG. In contrast, the chromatogram showed a single peak of the hCG signal with an apparent molecular mass of 69 kDa (Figure 2), which did not correspond to the molecular weight of hCG (approximately 36 kDa).

Peptide analysis using an Ultimate 3000 nano-HPLC system coupled to an LTQ Orbitrap XL mass spectrometer did not reveal the presence of human HCG, but surprisingly revealed the presence of uromodulin (Tamm Horsvall protein). In two independent runs, peptides 205–212 and 589–597 were found. Table 3 summarizes the peptides identified

Table 1: False-positive hCG values and urinalysis findings.

Variable [n=15 (6 women, 9 men)]	Median (interquartile range)
Age, years	65 (58–69)
hCG, mIU/L	6.69 (5.01–8.66)
Serum creatinine, mg/dL	1.09 (0.83–1.19)
CRP, mg/dL	13.85 (5.1–23)
Uromodulin, mg/L	735 (493–1080)
Urinary creatinine, mg/dL	96.3 (57.0–226.4)
Proteinuria, mg/L	41 (17–102)
Alpha 1–microglobulin, mg/L	81 (38.5–280.2)
Alpha 1–microglobulin to creatinine ratio, mg/g	12.8 (2.20–22.7)
Urine protein to creatinine ratio, mg/g	61 (23–162)
pH	6 (5–6.75)
WBC, n × 103/µL	75 (52–135)
Bacteria, n/µL	130 (44–603)
Casts, n/µL	5 (3–6.8)
Hyaline casts, n/µL	4 (2–5)
Pathological casts, n/µL	1 (0.03–2)
WBC, n × 103/µL	75 (52–135)

Table 2: Multiple linear regression model of determinants of false-positive urinary hCG (r^2=0.5416; p=0.02).

Variable	Coefficient	t	p-Value
Constant	−7.525	−2.6765	0.018
Log(albuminuria, mg/L)	0.4081	1.732	0.1052
Log(uromodulin)	2.2250	2.337	0.0348
Log(alpha1 microglobulin)	2.2226	0.940	0.3627
CRP	0.0253	1.653	0.1205

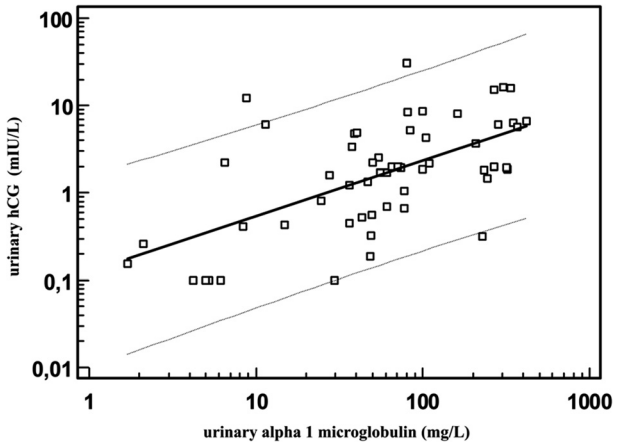

Figure 1: Log-transformed scatter diagram of urinary hCG concentration (mIU/L) vs. urinary alpha 1 microglobulin concentration (log Y=0.00557 + 0.023 X, r^2=0.212, p<0.001). Dashed lines=95 % prediction interval.

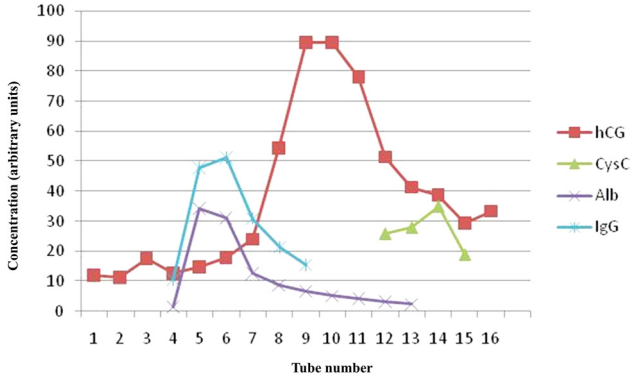

Figure 2: High-pressure gel permeation chromatography of human urine in a patient with an upper urinary tract infection, showing a false-positive signal attributed to hCG, which was later identified as interference caused by uromodulin fragments. The concentration (Y-axis) is given in arbitrary units, the X-axis represents the tube number.

in the Orbitrap mass spectrometric analysis. All these findings point to a false-positive hCG result in patients with an upper urinary tract infection, which is further illustrated by the quick disappearance of the hCG signal after treatment of the upper urinary tract infection with antibiotics.

Discussion

The present study deals with false-positive urinary hCG results, which were reported in patients with upper urinary tract infection/pyelonephritis. Cross-reactivity with structurally related glycoprotein hormones [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)] and heterophilic antibodies could be excluded as the cause of abnormal results. Molecular mass spectrometry analysis revealed a single peak with an apparent molecular weight of approximately 69 kDa, which exceeded the molecular weight of hCG but remained significantly lower than that of immunoglobulin complexes. The lower renal clearance calculated for the patient's hCG confirmed that the mass of the reactive compound was between that of normal hCG (approximately 36 kDa) and the cutoff of the glomerular membrane. As the molecular weight of the compound did not match the molecular weight of hCG, the positive result had to be considered a false positive cross-reactivity with an unknown plasma protein.

Analysis of urine specimens yielding false-positive results for hCG content in casts, performed using an Ultimate 3000 nano-HPLC system coupled to an LTQ Orbitrap XL mass spectrometer, revealed that uromodulin, a major constituent of urinary casts, might be the likely interferent. A marked correlation was observed between the urinary leukocyte count, alpha 1 microglobulin concentration, number of casts, and hCG level. In addition, urinary uromodulin concentration correlated well with hCG level. As urinary leukocyte count, alpha 1 microglobulin concentration, number of casts, and uromodulin concentration are markers of upper urinary tract infection, false-positive hCG signals are associated with upper urinary tract infection.

The hCG sandwich tests make use of specific monoclonal antibodies that recognize holohormones. The biotinylated M-1F7.9 antibody conformationally recognizes the c2 epitope. This was combined with the M-INN22 ruthenylated antibody, which recognizes the b2-epitope in the aa sequence range of 55–92 (hCGb core fragment). The high specificity of the

Table 3: Peptides found following Orbitrap analysis.

Peptide sequence	Protein ID	Protein name	Organism	Start position	End position	Confidence score	Ranking score
FVGQGGAR	P07911	Uromodulin	*Homo sapiens*	205	212	46	36
SGSVIDQSR	P07911	Uromodulin	*Homo sapiens*	589	597	57	36

biotinylated antibody (c2) means that free-chains, nicked forms, and other degraded forms of hCG, which do not occur in the serum of normal pregnant subjects, are not recognized. The conformational recognition of the hCG epitope may explain the fact that unexpected protein uromodulin fragments, which are released into urine during urinary tract infection, may cross-react with the antibodies used [12, 13].

Uromodulin is the most abundant protein encoded by the *UMOD* gene (GeneID: 7369) on chromosome 16p12.3, and is secreted in urine as a high-molecular-weight polymer (molecular weight=105 kDa). The zona pellucida (ZP) domain, a conserved module shared by many extracellular eukaryotic proteins, is responsible for the ability to polymerize extracellularly into filaments [13–16]. In healthy individuals, uromodulin has a relatively short half-life time of 16 h [17], whereas 20–100 mg of uromodulin has been detected in 24-h urine collections [17–25]. Although the biological functions of this protein remain unclear, several studies have reported a relationship between uromodulin and water/electrolyte balance [26], kidney innate immunity [26–30], urinary tract infections [31, 32], nephrolithiasis [33, 34], medullary cystic kidney disease type 2 (MCKD2) [35, 36], familial juvenile hyperuricemic nephropathy (FJHN) [36], glomerulocystic kidney disease [31], type 2 diabetic nephropathy [37], arterial hypertension [38], protection from acute kidney injury through downregulation of interstitial inflammation [39, 40] and development of chronic kidney disease [18, 26]. The urinary excretion of uromodulin is positively correlated with the estimated glomerular filtration rate (eGFR) [41]. However, it remains unclear how uromodulin expression and release are regulated under stress conditions. The distribution of uromodulin in the human body is unique, as this glycosylphosphatidylinositol-anchored protein is exclusively expressed in the apical plasma membrane of epithelial tubular cells lining the thick ascending limb of Henle's loop and the early distal convoluted tubule of the nephron [42, 43]. After its production in the kidneys, proteolytic cleavage by an unidentified protease results in the shedding of uromodulin fragments from the apical membrane of the thick ascending limb of Henle's loop cells [44]. As uromodulin and hCG, both proteins that are upregulated during pregnancy [45], are characterized by a structural homology of 30 %, uromodulin fragments might be recognized as hCG. Increased uromodulin levels have been reported in patients with bacteriuria [46]. Due to its polyanionic phase-like structure, uromodulin may bind uropathogenic bacterial strains and prevent their adherence to glycoproteins and glycolipids on luminal plasma membranes [47–49]. Therefore, it is not surprising that false-positive urinary hCG results are typically seen in patients with an upper urinary tract infection, a pathological condition in which uromodulin plays a crucial role [50].

The observed correlation between urinary hCG and alpha 1-microglobulin can be attributed to the inflammatory processes associated with upper urinary tract infections, which result in elevated levels of alpha 1-microglobulin as a marker of tubular damage. However, alpha 1-microglobulin itself does not cause interference in hCG assays. Instead, mass spectrometric analysis identified uromodulin as the actual source of interference. Uromodulin, a glycoprotein upregulated during UTIs, shares structural homology with hCG, particularly in its glycosylated regions, enabling cross-reactivity with hCG assay antibodies. This structural similarity, combined with its increased levels during UTIs, explains its role in generating false-positive results. Thus, while both proteins correlate with hCG levels in the context of UTIs, uromodulin is the true cause of assay interference.

The present findings may also have major consequences for the interpretation of the doping control tests. As hCG is considered an illicit drug, hCG concentration was assayed as a part of doping control analysis in male athletes. The same methodology was used in our patients. Urinary hCG values as low as 2.3 IU/L are considered decision limits [51, 52]. As cast formation and increased urinary uromodulin values often occur following streneous physical exercise, occasional false-positive results cannot be excluded.

Research ethics: State the appropriate information, including that the study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).
Informed consent: Informed consent was obtained from all individuals included in this study, or their legal guardians or wards.
Author contributions: The authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Use of Large Language Models, AI and Machine Learning Tools: None declared.
Conflict of interests: The authors state no conflict of interest.
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Data availability: Not applicable.

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