Biosensors and Bioelectronics 142 (2019) 111542

Contents lists available at ScienceDirect

Biosensors and Bioelectronics

journal homepage: www.elsevier.com/locate/bios

Sensitive polydopamine bi-functionalized SERS immunoassay for microalbuminuria detection

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ARTICLE INFO

Keywords:
Polydopamine (PDA) chip
SERS
Microalbuminuria

ABSTRACT

Albumin is a significant prognostic marker in diabetic nephropathy and cardiovascular disease. In this work, we developed a rapid, sensitive and inexpensive method for albumin detection based on the polydopamine (PDA) bi-functionalized glass chip and surface-enhanced Raman scattering (SERS) tag. Anti-albumin antibodies were encapsulated on the glass chip and SERS tag through dopamine self-polymerization in alkaline conditions and the immunoaffinity was highly maintained to form the sandwich structure with the addition of target microalbuminuria. Under the optimum experimental conditions, this SERS immunoassay showed the wide linear range of 10–300 mg/L with the limit of detection of 0.2 mg/L. High specificity and selectivity of this SERS method were demonstrated by performing with some common proteins include human hemoglobin protein (Hgb) and human immunoglobulin G (IgG) in urine. This method was also applied to detect albumin in urine samples from 17 patients and 5 healthy control and the results were highly consistent with those obtained from clinical standard immunoturbidimetric method. The volume requirement of urine samples is only 2 μL. Compared with traditional dipstick and immunoturbidimetric methods used in clinic, SERS-based method has higher accuracy, lower sensitivity and less sample consumption.

1. Introduction

Albumin is one of the most important plasma proteins which are normally circulating in the blood. Urinary albumin is a wildly used clinical indicator in patients with diabetes, renal and cardiovascular (CV) diseases (Newman et al., 2005). Under normal circumstances, albumin cannot cross the glomerular basement membrane because of its high molecular weight. Therefore, there is albumin with trace quantity (< 30 mg/L) in the urine of healthy people. While in some diseases, such as hypertension, diabetes and cardiovascular diseases, the glomerular basement membrane is irreversible damaged, thus resulting in the changes in its permeability. The enhanced penetration of glomerular basement membrane caused by various pathologies will lead to albumin leakage and the increase of albumin content (30–300 mg/L) in urine, which is named as microalbuminuria. Microalbuminuria is an important signal for renal, diabetes and cardiovascular diseases (Hillege et al., 2002; Klausen et al., 2005; Newman et al., 2005; Sarafidis and Bakris, 2006).

The semiquantitative and quantitative detections of microalbuminuria provide the earliest diagnosis of renal, diabetic nephropathy and cardiovascular diseases (Mogensen, 2003; Parving et al., 2001). Currently, a variety of dipsticks were widely used for clinical assay of albumin in urine because of the low cost and convenience, but it can only provide semiquantitative results (Meinhardt et al., 2003). Therefore, various quantitative detection methods of microalbuminuria have been developed, including electronic circular dichroism (Habartová et al., 2018), radioimmunoassay (Brodows et al., 1986), immunonephelometry (Marre et al., 1987), immunoturbidimetry (Teppo, 1982), chromatography (Comper et al., 2004), electrochemical immunosensor (Tsai et al., 2016), enzyme-linked immunosorbent assay (ELISA) (Schwerer et al., 1987), chemiluminescence immunoassay (CLIA) (Aoyagi et al., 2001), and etc. Although these methods have their own advantages, electronic circular dichroism and chromatographic such as high performance liquid chromatography require expensive instruments. Radioimmunoassay usually has some false positive results, because the diffusion limitations may occur thus restricting

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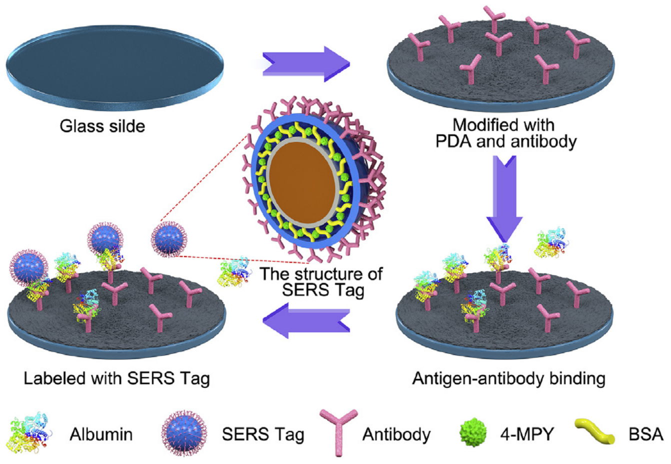
https://doi.org/10.1016/j.bios.2019.111542
Received 21 May 2019; Received in revised form 19 July 2019; Accepted 26 July 2019

protein collisions with the surface (Benesch et al., 2000). CLIA and ELISA are sensitive methods to detect albumin, while the experimental reactants like luminescent reagents needed for CLIA are expensive, and the reagents used in ELISA such as TMB and sulphuric acid are harmful to the environment.

In the past few years, some methods based on biosensor for microalbuminuria detection have emerged. Ting Lai et al. used silver nanoparticles modified localized surface plasmon resonance (LSPR) biosensor to detect the microalbuminuria in the urine samples of mild preeclampsia patients in the range of 10^{-3} mg/L-1 mg/L with the detection limit of 10^{-3} mg/L (Lai et al., 2010). Antibody modified AuNP and PVA modified screen-printed carbon electrode surface was also used to detect the albumin in urine. The linear range was 2.5–200 mg/L with the detection limit of 2.5×10^{-2} mg/L (Omidfar et al., 2011). Although low detection limits could be achieved by these methods, these methods couldn't be applied in clinical urine albumin assay, because the detection ranges didn't cover the entire range of microalbuminuria (30–300 mg/L). To solve this issue, an electrochemical immunoassay for albumin detection with a wider linear range of 10–300 mg/L was developed, but the disadvantages were the long detection time (more than 12 h for electrode preparation process) and high detection limit (9.77 mg/L) (Tsai et al., 2016). Therefore, it is urgent to develop a rapid, sensitive and environment friendly method for albumin assay.

SERS is a sensitive detection method that can enhance the Raman signal by 10^{10}-10^{11} times. SERS has the following advantages: (1) ultrasensitive detection can be obtained at single molecule level (Kneipp et al., 2008). (2) SERS active molecules and tags are more stable and easier to be stored and labelled compared with fluorescent compound (Wang et al., 2012, 2017). Recently, various SERS technologies have been developed for protein detection. Silver nanoparticle-protein-silver cavity array has been employed to detect human IgG with a detection limit down to 0.1 ng/mL (Gu et al., 2014). A biosensor device consisting SERS tags and photonic crystal beads as carriers was designed for the detection of mouse IgG and C-Reactive Protein (CRP) with the detection limit of 672 fg/mL and 478 fg/mL respectively (Liu et al., 2017). In our previous work, an ultrasensitive PDA bi-functionalized SERS immunoassay was developed for the exosomes based diagnosis and classification of pancreatic cancer, and the detection limit is one exosome in 2 μL serum sample (Li et al., 2018). The existing methods for urinary microalbumin detection were not enough for rapid, direct and accurate quantitative analysis, but the SERS-based method provides a reliable, accurate and sensitive detection methods and have not been used for albumin detection yet. In addition, the SERS-based experience accumulated by our research group had been applied for exosome detection. While there are great differences between exosomes detection and protein detection in immunoassay due to their different size and structure, we intended to adapt PDA chip system to a new method for protein detection by optimizing multiple experimental parameters. This method could be applied to the detection of microalbuminuria directly and simplified the experimental steps thus shortening the measurement time.

Based on our previous research on SERS, in this design we employed self-polymerization of dopamine under weak alkaline condition to form PDA which has great biocompatibility and can be easily deposited on almost all types of organic and inorganic substrates for surface modification (Hong et al., 2012; Liu et al., 2014). The schematic representation of the steps of the SERS-based method for detection of albumin is shown in Scheme 1. Albumin antibody was encapsulated on the glass in the process of dopamine self-polymerization while maintaining the antibody's biological activity. The antibody exposed on the surface of the glass could be easily and specifically reacted with target protein, and thus the microalbuminuria was captured and enriched onto the chips. Then the PDA chips were incubated with antibody modified 4-Mercaptopyridine (4-MPY) SERS tag forming a "chip-albumin-SERS tag" sandwich structure. The SERS spectrum was measured and the intensity of peak at 1096 cm^{-1} was selected as the characteristic and quantitative signal for analysis. In this work, we developed a highly sensitive, quantitative, reproducible and quick detection method for albumin in patient urine, and the limit of detection was greatly reduced. This SERS method has been applied to analyze urine albumin from healthy people and patients.



Scheme 1. Illustration of the SERS-based methods for the detection of albumin.

2. Materials and methods

2.1. Materials

Dopamine hydrochloride, bovine serum albumin, trisodium citrate, Tween® 20, 4-Mercaptopyridine, hydrogen tetrachloroaurate ($HAuCl_4{\cdot}3H_2O$), silver nitrate, ascorbic acid and other chemical reagents were from Sigma-Aldrich, United States. 1 × Phosphate-Buffered Saline (PBS), pH 7.4, 10 mM Tris–HCl, pH 8.8 and dimethyl sulphoxide (DMSO) were from Solarbio Co. Ltd, China. Anti-albumin antibody was purchased from Cusabio Co.Ltd, China. Hydrogen peroxide solution and concentrated sulphuric acid (98%) were from Sinopharm Group Co.Ltd, China.

2.2. Synthesis of SERS tag

13 nm Au nanoparticles (AuNPs) were synthesized using Frens' protocol (Grabar et al., 1995). 100 ml deionized water and 1.8 mL of 1% sodium citrate was heated to boiling and then 0.5 mL of 2% hydrogen tetrachloroaurate was added with constant stirring. The reaction solution was stirred for 30 min at 150 °C and then was cooled to room temperature for further use.

The SERS-labelled nanomaterials were synthesized by the following two steps, including the preparation and the modification of Au@Ag NPs. 20 μL of 0.1 M ascorbic acid, 110 μL of 5 mM silver nitrate, 60 μL of 4-Mercaptopyridine and 200 μL of 1% BSA were added to 600 μL of 10 nM AuNPs solution step-wisely. The solution was stirred for 45 min at room temperature. Then the mixture was centrifuged at 6000 rpm for 15 min. After removing the supernatant, the precipitate was re-suspended in 500 μL of Tris-HCl (pH = 8.8). 100 μL of 5 mg/mL dopamine hydrochloride and 100 μL of 100 μg/mL anti-albumin antibody were added to the re-dispersed solution and reacted for 1 h. The solution was then centrifuged at 6000 rpm for 15 min, the precipitate was re-suspended in 500 μL of Tris-HCl for future use.

2.3. Preparation of the PDA chip

The glass slides were cleaned by immersing in piranha solution (98% H_2SO_4: 30% H_2O_2 = 7:3 v/v) for 10 h, the glass slide was rinsed with deionized water and dried under nitrogen gas. Then the slides were immersed in 8 mL of dopamine hydrochloride solution at a concentration of 5 mg/mL for 1 h at room temperature. 8 mL of 10 mM Tris-HCl (pH = 8.8) and 240 μL of 15 μg/mL albumin polyclonal antibody were added and reacted for 1 h. The slides were washed with deionized water. At last the slides were blocked with 8 mL of 2% BSA at 37 °C for 1 h, then the slides were washed with deionized water and dried for use.

2.4. Albumin detection using the SERS method

The standard albumin solution (8 mg/mL) was diluted to the appropriate concentration. 2 μL diluents of different concentrations were added to the chip, and the chip was incubated for 30 min at 37 °C followed by washing with PBST and deionized water. 3 μL SERS tag was added on the spot of the sample and then washed with PBST and deionized water. Horiba Jobin Yvon XploRA confocal micro-Raman system was used to acquire Raman signals using 785 nm excitation laser wavelength. The Raman intensity and Raman spectrum were obtained by Labspec software (Version 6). Each sample was tested by 196 points and its average signal would be used in calculation. The intensity of peak at 1096 cm^{-1} was selected as the characteristic and quantitative signal since it was the strongest peak in the spectrum and there was no interference from other peaks. The data was collected with a laser power of 4 mW and 1s for each point scanning. The whole scanning process took about 5 min. The spectrum of PBS solution without albumin was recorded as a background in each measurement. All the spectrums were subtracted by background spectrum. The data was collected from three independent sets of experiments.

2.5. Patients' information

The urine samples used in the experiment were collected in Shanghai Yangpu central Hospital. 17 urine samples from patients and 5 urine samples from healthy people were detected by SERS methods. The written informed consent had been obtained since the start of the project. The samples were collected and immediately stored at −20 °C for further use. The samples were also detected by clinical standard test through immunoturbidimetry in the hospital. All experiments on clinical urine samples were approved by the Medical Research Ethics Committee, Yangpu Central Hospital, Shanghai, China. Comparisons between the patients group and the healthy group were made by two independent samples' non-parametric Mann-Whitney test. The statistical results or graphs were from Origin 8 and Graph Prism 6.0.

3. Results and discussion

3.1. Characterization of PDA chip and SERS tags

As displayed in Fig. 1a, the scanning electron microscopy (SEM) of PDA chips showed that the PDA chip had a rough surface structure, which confirmed that PDA could be absorbed to the surface of the glass. This rough structure can provide more binding sites for antibody capture.

SERS tag played an important role in albumin detection. The SERS tag synthesized in this work contains four parts, including 1) SERS substrate with high Raman enhancing ability; 2) SERS reporter that produced desired SERS signal; 3) surface coating layer that improved the stability and biocompatibility; 4) surface ligands that was used as conjugation anchors. In order to combine the advantages of the homogeneous superiority of the gold and high SERS intensity of silver, the spherical gold nanoparticles were used as the core with a diameter of about 13 nm (Fig. 1b), and the silver layer around 5 nm (Fig. 1c) was then coated over the gold core thus the SERS intensity can be greatly enhanced. Bovine serum albumin (BSA) was the most commonly used surface-modified molecular to form the protective shell avoiding the interference to the metal core from environment due to its adsorption onto the metal surface through electrostatic adsorption or thiol-metal interaction. The PDA and anti-albumin were absorbed onto the BSA protective layer by self-polymerization of dopamine under weak alkaline conditions forming the Au@Ag/4-MPY@BSA@PDA@antibody SERS tag. Fig. 1d was the TEM image of SERS tag. After modifying the molecules onto the protective shell, the outer layer of SERS tag was coated with a thin layer thus proved that the dopamine and anti-albumin were successfully connected to the BSA shell.

Fig. 1e depicts the UV absorption spectra of SERS tags. When the silver layer was wrapped with AuNPs, the ultraviolet absorption peak of AuNPs disappeared. Au@Ag solution display an absorption at 400 nm corresponding to the absorbance band of silver nanoparticles, which was due to the coating of silver on the outside of the gold core and forming uniformly mixed colloidal particles of Au and Ag nanoparticles (Pande et al., 2007). After 4-MPY was added, the ultraviolet absorption peak broadened, because 4-MPY has an absorption peak at 350 nm. The color of the solution also changed from orange to black, which indicated that the 4-MPY SERS reporter bonded to the Au@Ag NPs successfully. As shown in Fig. 1f, the SERS tag showed various characteristic SERS peaks of 4-MPY reporter including the strongest peak at 1096 cm^{-1} arising from pyridine ring breathing vibration, the peak at 1011 cm^{-1} contributed by the breathing vibration of the benzene ring, the peaks at 1063 cm^{-1} and 1225 cm^{-1} from the pyridine ring C-H in-plane bending mode, and the peak at 1582 cm^{-1} from the C–N symmetric stretching vibration. The intensity of peak at 1096 cm^{-1} was used as the following quantitative analysis due to its strongest signal. The enhancement factor (EF) is an important index to characterize the performance of surface-enhanced Raman scattering. In order to investigate the Raman enhancement capability and EF value of the SERS tag, the Raman spectrums of 1 mol/L free 4-MPY and 3×10^{-6} mol/L 4-MPY absorbed on SERS tag (assuming all 4-MPY molecules are absorbed on the SERS tag surface) were both measured. Generally, the SERS EF is acquired from the average number of absorbed molecules (N) in the scattering volume of the SERS and non-SERS areas. It was supposed that $N = cV$, where c *(mol/L)* is the concentration and V (m^3) is the scattering volume, so the EF was calculated as the following equation(Wei et al., 2018):

$$EF = \frac{(I_{SERS})(c_{bare})}{(I_{bare})(c_{SERS})}$$

The signal intensities of SERS tag and 4-MPY at 1096 cm^{-1} were $I_{SERS} = 6595$ and $I_{bare} = 24.56$. The calculated SERS EF was 8.95×10^7, which met the requirement of the single molecule detection. Therefore, the SERS tag demonstrated superior SERS activity for further practical applications.

3.2. Optimization and verification of SERS assay

Based on our designed PDA chip and 4-MPY SERS tag, a sandwich structure was designed to detect albumin. 2 μL of albumin solution was dropped on the chip and incubated for 1 h at 37 °C. And then, 3 μL of SERS tag was dropped on the sample area and incubated for 1 h at 37 °C, with the following washing with deionized water, PBST and deionized water in sequence. After drying at 37 °C, the Raman spectra was collected.

Since the principle of this method was based on immunoaffinity to form sandwich structure, the optimization of the amount of albumin antibody captured played an important role in detection performance. The effects of different volumes (0, 140, 280 and 420 μL) of 15 μg/mL albumin antibody were investigated. The results are shown in Fig. S1a. The SERS intensity gradually increased with the increase of albumin antibody volume, when the volume reached 280 μL, the SERS intensity decreased with the increasing of albumin antibody due to lower binding efficiency. Therefore, 280 μL of 15 μg/mL albumin antibody was selected.

In order to block the nonspecific binding area of the PDA chip thus

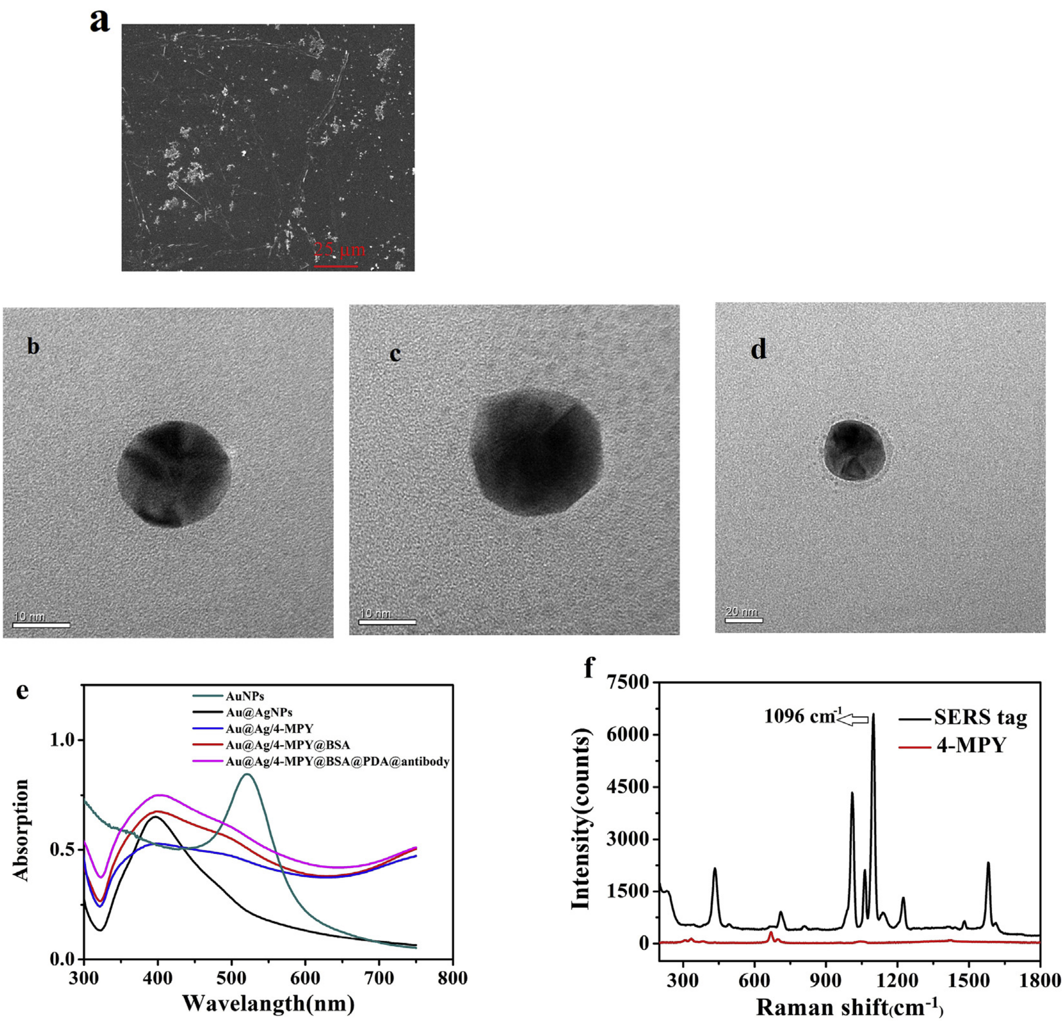


Fig. 1. a). Scanning electron image of PDA chip showing rough structure. b,c,d). TEM images of different particles (Au nanoparticle, Au@Ag nanoparticle, SERS tag). e). UV absorption spectra of Au (green line), Au@AgNPs (black line), Au@Ag/4-MPY (blue line), Au@Ag/4-MPY@BSA (orange line) and Au@Ag/4-MPY@BSA@PDA@antibody SERS tag (purple red line). f). SERS spectra of 4-MPY SERS tag and 4-MPY in solution. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

decreasing non-specific absorption, PDA chips were immersed in BSA solution and the concentrations of BSA (mass percentage is 1%,2%,3%,4%) dissolved in PBS were optimized. Fig. S1b showed that the SERS intensity of the 2% BSA was the highest. The blocking effect was poor and blank background signal was higher when the concentration of BSA was too low, with the increase of BSA concentration, SERS signal will be greatly enhanced. However, when the concentration of BSA reached 3%, all binding sites were occupied by BSA, resulting in signal reduction. Therefore, 2% BSA was selected as the blocking solution.

In order to verify that albumin and SERS tag could be successfully bound to PDA chip, the Raman signal of each step of the binding products were monitored, which is shown in Fig. S2. No SERS signal was observed in both PDA chip and PDA chip with albumin. When the chips were added SERS tag and washed with PBST and deionized water, obvious SERS signal was obtained, indicating that albumin and SERS tag were successfully bounded to the PDA chip.

3.3. SERS detection of the albumin

We further used this PDA modified chip and SERS tag to capture and detect albumin, while the control sample was PBS without albumin. The results showed that the SERS signal intensity increased with increasing albumin concentration (Fig. 2). There was a good linear relationship between the SERS intensity and albumin concentration in the range from 10 to 300 mg/L, which completely contained the range of microalbumin (30–300 mg/L) without the requirement of complex dilution steps for sample with high albumin concentration. The concentration of albumin could be calculated by the formula: $y = 6.2051x + 336.7$ ($R^2 = 0.9973$), where y means the SERS intensity, x means the concentration of albumin (mg/L). The limit of detection was 0.2 mg/L (S/N = 3), which was comparable with the clinical existing methods as shown in Table 1. Although some methods are more sensitive to SERS method, they were not suitable for high concentration albumin detection. Based on these facts, the SERS-based method was more efficient to detect microalbumin.

3.4. The detection specificity of the assay

To evaluate the specificity of this SERS-based albumin method, Hgb and IgG were used as the possible interference proteins due to their existence in the urine of patients with kidney disease. The results are shown in Fig. 3. Anti-albumin was also used in the process of dopamine self-polymerization to form PDA capture surface. After 2 μL of 300 mg/L Hgb and IgG were added and incubated with PDA chip, the unbound analytes were removed by washing with PBST and PBS. And then, 3 μL of SERS tag was dropped on the sample area and incubated. The SERS signal was low due to weak binding of SERS tag and Hgb or IgG

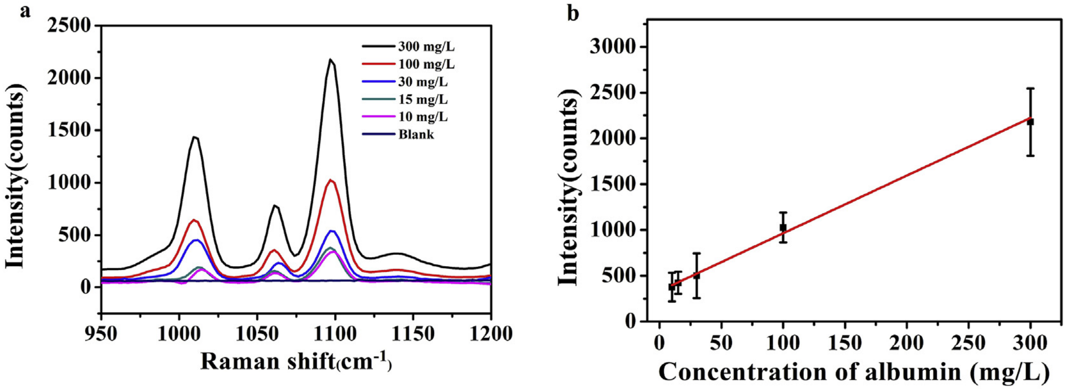


Fig. 2. a) SERS spectra (from 950 cm^{-1} -1200 cm^{-1}) of albumin with different concentrations. b) Linear relationship between SERS intensity and albumin concentration.

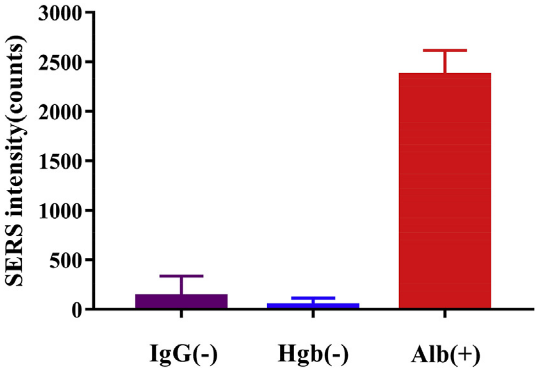


Fig. 3. Different SERS intensity in three sandwich assays, 300 mg/L albumin was replaced with 300 mg/L IgG and 300 mg/L Hgb.

captured PDA chip. These results showed that SERS tag modified with anti-albumin could only bind to positive albumin antigens, but couldn't bind to other negative-control proteins, which indicated that the SERS-based method had good specificity for the detection of albumin in urine.

3.5. Detection of the albumin in clinical urine samples

To evaluate the accuracy and reliability of this SERS-based method, we detected the albumin in real urine samples and compared it with the results of clinical testing. The urine from healthy people was used as control. The SERS tags were dropped on the sample area. After sandwich immunocomplexes were formed and washing by deionized water and PBST, the SERS spectra of immunocomplexes were obtained. Data were collected from three independent sets of experiments. All concentrations of albumin in clinical samples were calculated using the aforementioned formula, which are shown in Table S1 with the concentration detected by clinical immunoturbidimetry. The SERS intensity increased with the increase of the urine albumin concentrations in real samples of healthy controls and patients. The relationship ($R^2 = 0.9918$) between the albumin concentrations of patient samples measured by clinical tests and SERS method is shown in Fig. 4a, which indicated that our method was in good agreement with clinical detection method. As we can see from the SERS method results (Fig. 4b), there is significant difference between the patients' samples and healthy person groups ($P = 0.0057$). These results indicated that SERS-based method distinguished the urine of patients from healthy control, which makes it a promising screening method for clinical test.

4. Conclusion

For the first time, we have combined the SERS-based methods with PDA chips for sensitive detection of albumin in human urine. The PDA chip assay was not affected by the interferences that might exist in the urine. The LOD was relatively low and the detection range was wide enough for clinical samples detection. It was successfully verified to detect the concentration of albumin in clinical urine samples from patients and healthy controls, showing a good agreement with the results of the clinical standard test using immunoturbidimetry that commonly used in the hospital. What's more, this method was versatile, since the antibody can be changed based on different antigen. It is expected to become a new way for detecting other types of protein and will be widely used in clinical applications. Meanwhile, we also found our method has some disadvantages, for example, our method can't detect multiple proteins in urine simultaneously. Our future work will focus on multiple biomarkers detection, and expand this platform in the application of liquid biopsy.

Data and materials availability

Data and materials are available upon request by contacting the corresponding author.

Table 1
Comparison of different albumin detection methods, NM means not mentioned.

Assays method	Detection limit	Linear range	References
immunonephelometry	NM	0.34–43 mg/L	Marre et al. (1987)
immunoturbidimetry	5 mg/L	5–400 mg/L	Teppo (1982)
HPLC	2 mg/L	NM	Comper et al. (2004)
Electrochemical immunosensor (Chronoamperometry)	9.77 mg/L	10–300 mg/L	Tsai et al. (2016)
LSPR biosensor	0.001 mg/L	0.001–1 mg/L	Lai et al. (2010)
Electrochemical immunosensor (Differential pulse voltammetry and square wave voltammetry)	0.025 mg/L	2.5–200 mg/L	Omidfar et al. (2011)
SERS	0.2 mg/L	10–300 mg/L	Our work

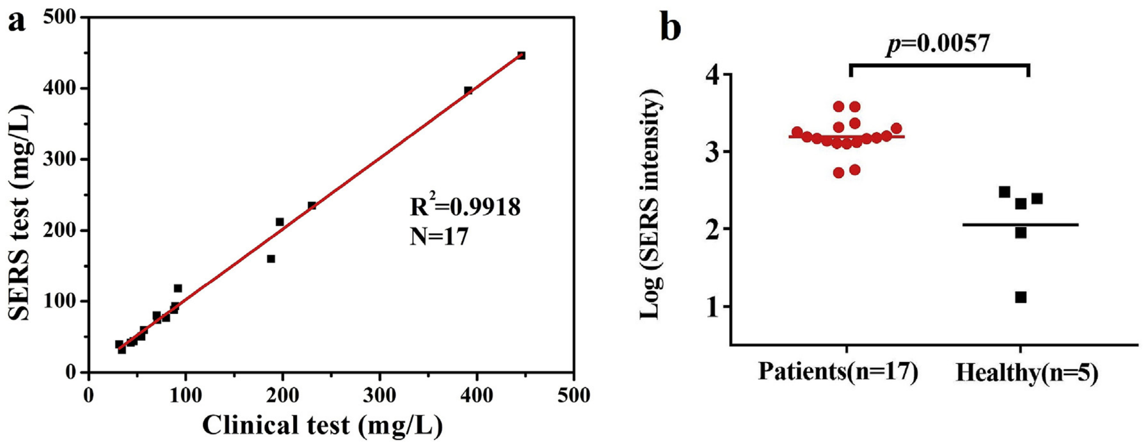


Fig. 4. SERS analysis results of urine samples of patients (n = 17) and healthy control (n = 5). a) comparison of detection of albumin in urine samples by SERS test and clinical test. b) Shapiro–Wilk analysis plots of the SERS results from 5 healthy individuals and 17 patients. The ordinate represents log values of Raman intensity. All measurements were done in triplicate and the data were shown as mean.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could appear to influence the work reported in this paper.

CRediT authorship contribution statement

Zhipeng Huang: Formal analysis, Data curation, Writing - original draft. **Ren Zhang:** Conceptualization, Investigation, Methodology. **Hui Chen:** Conceptualization, Project administration, Supervision, Writing - review & editing. **Wenhao Weng:** Resources, Funding acquisition. **Qiuyuan Lin:** Validation, Software, Visualization. **Zhi Li:** Funding acquisition. **Jilie Kong:** Funding acquisition, Writing - review & editing.

Acknowledgements

This work was supported by the National High Technology Research and Development Program (863 Program) of China (2015AA021107), National Natural Science Foundation of China (21427806, 21375027, 21335002, 81874179 and 81672826), Shanghai Pujiang Program (17PJD001,18PJD047), and Municipal Human Resources Development Program for Outstanding Young Talents in Medical and Health Sciences in Shanghai (2017YQ044).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bios.2019.111542.

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