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A Review On Conventional Analysis to Fiber Grating Sensing for Detection of Chronic Kidney Disease

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Abstract

Chronic kidney disease (CKD) is one of the universal problems which is a long-term condition where the kidney stops functioning the way it should. According to the estimated surveys, at least one among ten adults has been facing this health issue. In order to combat these diseases, there is an essential need for stable diagnostic tests that are simple, accurate, and easily accessible. This paper is a review of the non-invasive diagnosis of CKD and its biomarkers using optical fiber-grating sensors (OFGs) which is one of the most attractive biosensors, playing a vital role in the field of biosensing and chemical sensing based on its label-free configuration. These sensors can be used for label-free diagnostic purposes due to their detection properties even in high electric fields and magnetic environments. However, their exploration into the medical field is fairly emerging in recent trends and yet to be commercialized. This review relates to the recent development in OFGs-based diagnosis and also identifies some of the key challenges for practical applications.

INTRODUCTION

Chronic kidney disease (CKD) is said to be a health burden which is a long-term condition where the kidneys stop functioning the way they should and it is one of the common reasons behind urinary tract infection (UTI), kidney stone, and kidney cancer [1]. Renal insufficiency is classified into two wide categories namely CKD along with acute kidney injury (AKI), where, the gradual loss of kidney function is characterized by CKD and the sudden loss of kidney function is characterized by AKI [2]. According to surveys, this universal public health problem is estimated to affect at least 1 among 10 adults in India, on the other side it is reported that, around 11.6% of the adult population in the United States suffers from similar symptoms of CKD [3, 4].

According to literature, it was estimated that deaths related to CKD falls around 5.21 million in 2008 and there is an expected elevation to 7.63 million in the upcoming years [5]. High blood pressure and diabetes are the common reasons for CKD where 35% of all cases account for diabetes, while 30% accounts for high blood pressure, while the remaining percent accounts for other factors such as systemic lupus erythematous, polycystic kidney disease, and kidney stones [6]. Based on the present techniques available, the inability of early-stage detection is a drawback to laboratory-based techniques, and hence, results in many unrecognized clinical cases. Early-stage detection may favor the patient to take adequate measures and enable prevention at early stages. Over the years, many biomarkers such as cystatin C, creatinine, and beta-trace proteinuric acid have been discovered for the detection of CKD [7]. Due to the increase in diseases such as diabetes, UTI, CKD in developing countries, infectious diseases still enforce the greatest health burden. CKD diagnostics are still inadequate at the clinical level. Hence to combat these diseases, there is an essential need for stable diagnostic tests which are simple, reliable markers, easily available, and accessible [8].

According to the surveys, there is an improved growth of evidence that suggests the usage of OFGs to detect CKD at earlier stages, compared to other techniques [9], which can be helpful in early prevention. Presently, all the available assays which have been used for the detection of CKD require hospital- and/or laboratory-based diagnosis assistance for confirmation [10].

There is a rapid growth in the relevance of biosensors, in various research fields, as well as in biomedical applications [11, 12]. The present health sector and its interdisciplinary sectors such as veterinary, pharmaceutics, food control, and related sectors require the improvement of specific and diverse sensors. There are various biosensing devices that are based on different methods of detection and characteristic properties. OFG is one of them, which has been established and finds a prominent position in the field of bio-sensing and biomedical applications, due to its attractive and implicit properties such as compatibility, small size, and inert nature towards electromagnetic and chemical fields [13-15].

Different sensing-based approaches on optical fibers have been reported in the literature using fiber Bragg gratings [16, 17], long-period gratings [18, 19], refractometers [20], photonic crystal fibers [21], and other optical configurations [22, 23]. Fiber sensors are intrinsically safe i.e. human defense system's immunity response is not affected by their use. They can be used for continuous monitoring or can be left in their position for repeated data acquisition while taking in vivo measurements.

This paper presents a brief review of detection of CKD and its biomarkers such as cystatin C, beta-trace, proteinuric acid, creatinine, aquaporin, and glycosuria using OFGs, the current status and ongoing research around the globe which enables for label-free diagnostics which can be compact and suitable for both laboratory and clinical analysis.

Optical Fiber grating sensors

OFGs have gone through an improved growth of development in the current years in track with the observation of narrowband reflection in the photosensitive core region of silica optical fiber which is Germanium or boron-doped. Intrinsic fiber elements in photosensitive fibers are known as Fiber grating sensors where the RI (refractive index) of the fiber core is modulated periodically by the illumination of UV light. When the light propagates through the modulated structure, one wavelength selectively gets reflected due to Bragg diffraction. High reflectivity occurs at a certain wavelength which is determined by the periodicity of the grating.

Working principle of OFGs

OFG acts as a spectral filter that modulates the refractive index of the core periodically in a single-mode fiber. Co-propagating between the fundamental core mode and other propagating modes which includes cladding modes or leaky modes or radiation modes occurs when the gratings satisfy the phase-matching condition. OFGs are further classified based on the modulation period or the grating pitch as short period gratings also known as fiber Bragg gratings (FBGs) and long-period gratings (LPG).

FBG is a periodic modulation of the refractive index along with the core of a photosensitive fiber. The refractive index changes are made by exposing the fiber to the interference pattern of Ultraviolet light [23]. When the broadband source is incident along with the core of the OFG with periodically modulated structure, the light gets scattered by each phase front, and a small amount of light will be reflected at each plane. These reflected signals combine coherently to one significant reflection at a particular wavelength (λ_B), satisfying the Bragg condition,

$$\lambda_B = 2n_{eff}\Lambda \quad (1)$$

Where n_{eff} is the effective refractive index of the fiber and Λ is the grating period or the pitch of the grating [24-26]. It is an established fact that FBGs are sensitive to external perturbations such as strain and temperature. Any fluctuations in strain or temperature near the grating site lead to a change in effective refractive index or/and grating pitch [27]. Consequentially due to this feature, FBGs are lately employed for various sensing applications. The strain sensitivity of an FBG inscribed in a Germania-doped silica fiber is approximately 1.20 pm/με [28, 29].

In long-period gratings (LPG) fundamental core mode couples with various cladding modes. Phase matching condition occurs when the loss resonance wavelength at which the coupling takes place i.e.

$$\lambda_i = [n_{eff}^{co} - n_{ieff}^{cl}]\Lambda \quad (2)$$

Where n_{eff}^{co} and n_{ieff}^{cl} are the effective refractive indices of the fundamental core mode and *i*th cladding mode respectively and Λ is the period of the LPG. Since the effective index of a cladding mode is dependent upon the refractive index of the surrounding medium, any change in the latter alters the loss resonance wavelength [27, 29].

Optical Fiber Gratings as Biosensors

In the field of biosensing and chemical sensing, there is rapid progress with induced grating in the core region of optical fiber. Applications of fiber optics over planar optical devices have led to the miniaturization of biosensing devices and remote sensing devices. Under certain constraints, the modulated grating induces coupling of the fundamental modes. Since fiber grating couples light, the wavelength (resonance) depends on the index of reflection of the surrounding medium. Hence, fiber grating sensors can be used for label-free and real-time sensing. The capability of Bragg grating to detect refractive index variation has great scope in the detection of clinical analysis. Conversely, the suitable configuration needs to incorporate to allow the core and the evanescent field to interact with the surrounding medium as standard FBGs are non-sensitive to changes in the external medium as the light is only confined in the core region. Various solutions have been reported with respect to the same problem which is obtained by etching the clad part of the FBG either partially or complete removal [30], by writing FBGs directly in microfibers [31, 32], or polishing [33]. In the above cases listed the concept of evanescent wave extends outside the fiber which in turn depends on the external refractive index. Fig. 1 shows the working principle of operation of an etched FBG [34].

Later on, this can be achieved by applying suitable Nano coating and plasmonic coatings to the etched fiber, this coating selectively binds specific target molecules which results in parameter change such as index of refraction. The OFGs are subjected to various substrate coatings which include graphene oxide, gold nanoparticles, polystyrenes (PS), single-walled carbon nanotubes (SWNTs), etc. which acts as the selective biolayer, changing the optical properties and enhancing the sensitivity of OFGs. The shift in central wavelength indicates the presence of a specific target molecule.

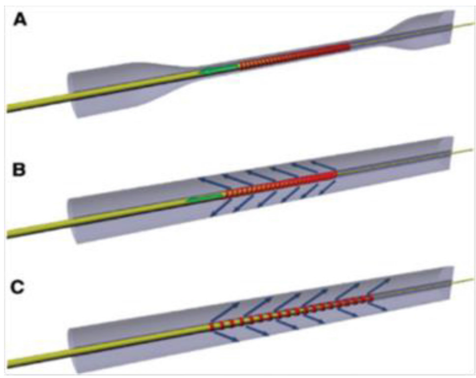

Fig. 1: Schematic representation of RI sensing using three different OFGs with their coupling mechanism (A) etched FBG, (B) tilted FBG, and (C) LPG.

There are various biosensing devices that are based on different methods of detection and characteristic properties [19, 35]. In order to determine and conduct selective measurements of the desired analyte, deposition of a sensitive layer is required on the surface of the fiber [36-38]. The performance of the fiber sensor strongly depends on certain factors such as the physical and chemical properties of the deposited layer, binding capabilities, thickness of the layer. The crucial point in developing and designing is to control the structure and properties of the sensitive element chosen. Functional coating of fiber grating sensors has been employed by various deposition techniques such as Langmuir-Blodgett deposition, dip-and-spin coating, and chemical and physical vapor deposition [20, 39, 40]. This technique is broadening its potential due to its versatility and ease for the fabrication of Nano assembled thin films involving various organic and inorganic materials.

METHOD

The search strategy includes extensively electronic databases such as published journals, literature, and articles which connect the link between CKD biomarkers and OFGs. Adequate and reliable material which is focused on CKD biomarkers detection using OFGs was set as the search criteria set for consideration, abstracts and articles with less or no ample information were excluded. Initial studies were based on abstracts and full studies were extracted for eligibility. The search terms for the chosen articles include terms like "Chronic kidney disease", "label-free diagnosis", "fiber grating sensors", "CKD biomarkers". Table 1 shows the summary of the data collected from 9 relevant articles including all the necessary information in the search field. The search period ended in June 2021.

Minimal works have been seen in the detection of CKD and UTI using OFG sensors, there are no reports of clinical usage of OFGs in the detection of CKD. Moreover, there are no validations of OFGs as in vivo biosensors, with all published work stopping at the proof of concept stage in the laboratory setting. This technology can enable a platform for biomedical label-free diagnostics which can be suitable for both laboratory (centralized) and clinical settings (decentralized).

Table 1: Studies That Evaluate the Association of OFGs in Detection of CKD Biomarkers

OFG based Measurement techniques	CKD biomarker	Mechanism of action	References
Tilted FBG (TFBG)	Protein concentration	Tilted FBG (TFBG) configured biosensor was used in the detection of protein concentration in urine which is a biomarker related to CKD, intrinsic relationship between protein overflow and refractive index variation was demonstrated using an in fiber-based label-free detection device. TFBG configuration was optimized using a metal coating of silver which supported both SPR and evanescent field which enabled a novel data analysis method, minimal cross-sensitivity was shown by the proposed in-fiber biosensor	[41]
Surface Plasmon resonance (SPR)	Aquaporin-2 (AQP2)	Surface Plasmon resonance (SPR) reflective fiber-based biosensor for label-free specific detection of the urinary AQP2 with high resolution which is identified as one of the most important biomarkers for nephrotic syndrome analysis which further leads to CKD. The biosensor used here is a tilted fiber Bragg grating of a 50 nm gold coating in order to excite SPR to note the changes in refractive indices at the fiber surface and the surroundings	[42]
Bragg grating sensor	Glucosuria	Glucosuria which is another biomarker was detected in the natural urine samples of patients with diabetes which showed better results when compared with the commercialized urinalysis devices with high-throughput, which was achieved using Bragg grating sensors coated with silver nanoparticles embedded within a phenylboronic acid-functionalized hydrogel	[43]
Long period grating (LPG)	Ammonia	Ammonia is one of the important biomarkers which has been emphasized recently because of its correlation with dysfunction in the kidney. A long-period grating (LPG) optical fiber sensor coated with a multilayer film of poly (diallyldimethyammonium chloride) (PDDA) and tetrakis (4-sulfophenyl) porphine (TSPP) to detect ammonia gas was demonstrated.	[44-48]
SPR based biosensors	Positive Gram And Negative Gram Bacteria	positive gram and negative gram bacteria's concentration was detected based on the SPR based biosensors using human urine samples was investigated using label-free long-range SPR based biosensor, which defined a supporting protocol to diagnose CKD	[49]

EMERGING TECHNOLOGY AND LIMITATIONS OF OFGS

As discussed, OFGs have great potential for healthcare applications. Some of the emerging trends include lab on chip by reducing the fiber dimension, OFGs can be used as refractive index sensors and hence these sensors can be used to detect chemical changes when imposed with microchips which can form a platform for future diagnostics in the laboratory and have the potential of being incorporated in MTA (micro total analysis) system. There is high scope for miniaturization and integration of optical components such as sensors, light sources, detectors, and corresponding signal processing units which are necessary to implement these concepts for practical analysis. For successful translation of OFG based medical devices into clinical use is to satisfy the end-users without any external effort and with high safety regulations.

Some of the existing problems include handling OFG biosensors, based on the literature interpretation of data is a major bottleneck process, as expertise of various disciplines is required in order to decode the actual information obtained from the wavelength shift, as the data obtained will be wavelength encoded and as this mechanism is not standardized guaranteeing repeatable and reproducible results is tedious, interpretation will not be a major issue and can be sorted by developing software of intelligence via IOT (internet of things) or any other software intelligence. As this technology is in the developing stage, such interrogation systems with high sensitivity cost high which is another problem. There is a need for an appropriate packaging/transducer for optimization of response obtained from changes in multi parameters e.g. temperature, Strain, cross-sensitivity due to refractive index. Additional hurdles include for in vivo applications, initial calibration is required before deployment internally, to overcome varying uncalibrated response and behavior in a complex matrix

To summarize, the motivation behind translating technologies into clinical practices, the key component is to understand the clinical needs and multi-factorial decisions made while experimenting and developing the devices. The development process should enrich the technology design and its application area, which is an important stage wherein early diagnosis is trailed and tested before engaging with the end-users.

CONCLUSION

The paper reviews the applications of OFGs in the detection of CKD disease and its associated biomarkers. It aims to favor the researchers and clinicians to understand the OFG technology and its challenges faced during the development process. The disease of affluence, such as infectious disease is increasing in developing countries, one such disease is CKD (chronic kidney disease), which is the non-functioning of kidney, which is caused due to increase in various biomarkers such as proteinuria acid, cystatin c, Beta-trace, etc. proper diagnosis of this is still a drawback and limited to only clinical analysis, CKD diagnostics are still inadequate at the clinical level. In summary, this paper briefs the current status and its future scope of optical fiber grating-based biosensors (OFGs) for label-free diagnosis of CKD and its biomarkers associated with it. OFGs have been involved in various applications in the medical field. However, OFGs used in the medical field are emerging adequately in recent years and are yet to be commercialized.

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ETHICAL STATEMENT

The presented manuscript is the original study of the authors and each of the authors confirms that this manuscript has not been previously published and is not currently under consideration by any other journal. All of the authors have approved the contents of this paper and have agreed to the Focus on Medical Sciences Journal's submission policies.

CONFLICT OF INTEREST

The author does not have any conflict of interest (financial and other).

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