Continuous glucose monitoring: a systematic review of sensor systems and prospects

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Abstract

Purpose – Continuous glucose monitoring (CGM) is a notable invention introduced in the biomedical industry. It provides valuable information about intermittent capillary blood glucose that is normally unattainable by regular clinical blood sample tests. CGM includes several progressive facilities such as instantaneous and real-time display of blood glucose level, "24/7" coverage, continuous motion of alerts for actual or impending hypo- and hyperglycemia and the ability to characterize glycemic variability. CGM allows users and physicians to visualize and diagnose more accurate and precise rate of change of glucose by capacitating small, comfortable, user-friendly sensor devices. Sometimes, this vital information is shared to the personal message box over Internet. In short, CGM is capable to inform, educate, motivate and alert (IEMA) people with diabetes. Despite the huge expectation with CGM, the available solutions have not attracted much attention among people. The huge potential of CGM in future diabetic study relies on the successful implication of the CGM. This paper aims at disseminating of state-of-the-art knowledge about existing work around the CGM.

Design/methodology/approach – This paper presents a comprehensive systematic review on the recent developments in CGM development techniques that have been reported in credible sources, namely PubMed, IEEE Xplore, Science Direct, Springer Link, Scopus and Google Scholar. Detailed analysis and systematic comparison are provided to highlight the achievement and future direction of CGM deployment.

Findings – Several key challenges are also portrayed for suitable opportunistic orientation. CGM solutions from four leading manufacturers such as Tandem, Dexcom, Abbott and Medtronic are compared based on the following factors including accuracy (% MARD); sensor lifetime, calibration requirement, smart device, compatibility and remote monitoring. Qualitative and quantitative analyses are performed.

Originality/value – This work can be a valuable source of reference and guidance for future research in this field.

Keywords Sensors, Medical

Paper type Literature review

1. Introduction

Diabetes is a serious life-long physical condition in humans caused by insulin resistance in pancreas, resulting in uncontrolled and sufficiently high amount of glucose in blood stream. Abnormal life style, food habit, high blood pressure, genetic factor, immunological disease and environment are the other factors inducing diabetes (Gross *et al.*, 2000; Damiano *et al.*, 2014; Bailey *et al.*, 2015; Pleus *et al.*, 2015; Nakamura and Balo, 2015; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, 2009, 2010). Figure 1 represents the glucose synthesis cycle involved in type 1 (T1D) and type 2 (T2D) diabetes causing imbalance in pancreas, blood vessel and body muscle (Chase *et al.*, 2010; Lawson *et al.*, 2014; Vigersky, 2015; Klonoff *et al.*, 2011). Similar to other diseases, diabetes has an adverse impact on human livelihood, at the personal, social and economic levels. In fact, diabetes has emerged as an epidemic in developing nations, thus affecting its citizens. A recent report shows that 8.23 per cent of the population worldwide is affected by diabetes (Ehrhardt *et al.*, 2011; Roze *et al.*, 2015; Golden *et al.*, 2012; Heinemann *et al.*, 2012; Kovatchev, 2015; Diabetes prevalence, 2017).

Medical practitioners and the research community are constantly engaged in the identification and development of the existing techniques to counter the diabetes menace (Kovatchev *et al.*, 2015; Weiss *et al.*, 2015; Buckingham *et al.*, 2015). In spite of the massive efforts taken in finding a cure for diabetes, unfortunately to date no effective measure has been undertaken. Several methods have proven to be beneficial for patient monitoring and management that includes changes in life style, food habit, regular check-up, and consultation with specialist doctor. (Forlenza *et al.*, 2015; Thabit *et al.*, 2015). In day-to-day life, it is often observed that a patient with diabetes is less comfortable with a due medical visit at the doctor's chamber (Battelino *et al.*, 2015; AP@home Consortium, 2015; Brown *et al.*, 2015; Chase *et al.*, 2014; Russell *et al.*, 2014); when a patient feels uncomfortable (e.g. dizziness, fatigue, nausea, frequent urine, shortness in breath, etc.), he/she seeks instant medical advice and clinical support (Nightscout, 2015; Dexcom Inc, 2015; Diatribe, 2015). These situations can often be seen in our society. But, such negligence is considered quite dangerous and may further cause several health disorders,

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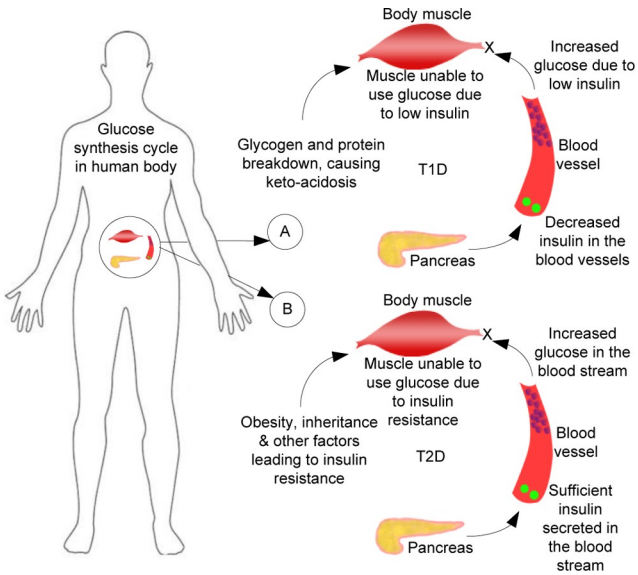
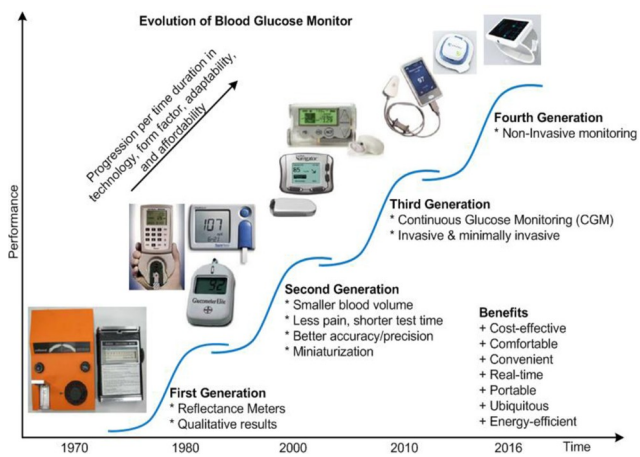
Figure 1 Glucose synthesis cycle in human body responsible for type-1 and type-2 diabetes



sometimes leading to death (Heinemann and Freckmann, 2015; Mazze *et al.*, 1987, 2008, 2009).

Continuous glucose monitoring (CGM) involves simultaneously counteracting operations, i.e. real-time monitoring, analysis, injecting and alerting the patient and caregivers using a sensing system (Bergenstal *et al.*, 2013; Wong *et al.*, 2014; T1D Exchange Clinic Network, 2015). Figure 2 presents the complete evolution of a generation-wise blood glucose monitoring system since the 1970s (Walsh *et al.*, 2015; Garber *et al.*, 2015). Starting from the reflectance meter, it has witnessed several versions of low-volume miniaturization of minimally invasive glucose mentoring systems in this timely scape. This evolution has been constantly supported by progressive inclusion and assimilation of MEMS-based sensor design and fabrication process (AACE Continuous Glucose Monitoring Task Force, 2010), and CGM is the current system in this regard.. The growth chart also shows a promising

Figure 2 Evolution of glucose monitoring system during the past decades



increase at gradual intervention of the CGM system. Although, an accu-sensor-based instant glucose monitoring system is prevalent in the current market, CGM will play a great role in efficient monitoring and management of patient with diabetes in future (Bailey and Grunberger, 2015; Diabetes prevalence, 2017) This is because of the following features: cost-effective, comfortable, convenient, real time, portable, ubiquitous and energy efficient, as shown on Figure 2 (Ho *et al.*, 2014).

A generic CGM system comprises four essential components, including glucose sensor, glucose signal transmitter, CGM monitor and insulin pump (Figure 3). In general, a CGM-based glucose sensor is attached to the epidermis layer of the skin (preferably on fatty part, e.g. belly) by an adhesive patch. The glucose sensor seeks for blood glucose concentration by aggregating epidermal signals and periodically transmitting to a CGM monitor. CGM monitor particularly carries a signal processing unit, a computation unit and an actuation unit. Upon completion of instantaneous calculation, if found crossed over the predefined threshold limit, CGM monitor orders its actuation unit to inject appropriate amount of insulin though the insulin pump. All the stated process is designed to be performed "24 × 7" while being attached on human body.

To date, various discussions are made to present a vivid scenario on what diabetes is, how it gets synthesized in human body, how diabetes creates livelihood challenges, how glucose monitoring system is gradually evolving, what CGM system is and how CGM is becoming a perfect alternative toward a real-time management and monitoring of diabetic patient. But the focus of this paper is to not just sharing generalized information about CGM, also to review various design aspects of existing CGM sensors and allied systems. To achieve this goal, few contributions are leveraged, as follows:

- to identify and compare market ready CGM systems;
- to perform state-of-the-art review on CGM sensor systems based on available research literatures;
- to compare the selected CGM systems based on six factors such as invasiveness, type of sensor, interfacing technology, wireless monitoring, body implantable, and key applicability remarks (cost/accuracy/energy efficiency/adoptability/user experience/parametric values);
- to point out crucial challenges that are resisting CGM system toward adoption among human society; and
- to pave vital opportunistic aspects in this regard to facilitate a way for possible correlation with human civilization.

The paper is organized as follows (Table I). Section 2 presents the detailed methodology behind the review process carried throughout. In Section 3, the key segment of this review paper, 29 selected research articles are thoroughly elaborated per their

Figure 3 Systematic architecture of the CGM system

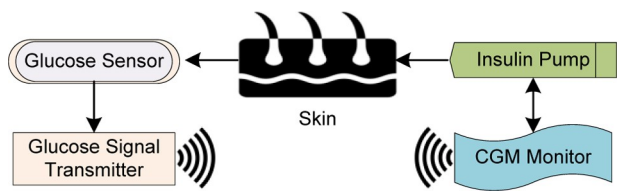


Table I Recent CGM sensor devices from various manufacturers

Sensor Device	Accuracy (% MARD[a])	Sensor lifetime (days)	Calibration requirement	Smart device compatibility	Remote monitoring
Tandem t:slim X2™ Insulin Pump	NA	<7	No	Yes	Yes (t:connect®)
Tandem t:slim G4™ Insulin Pump	NA	<7	No	Yes	Yes (t:connect®)
Tandem t:flex® Insulin Pump	NA	<7	No	Yes	Yes (t:connect®)
Abbott FreeStyle® Libre Flash	11.4	14	No	Yes (Android)	Yes
Abbott FreeStyle® Libre Pro Flash	11.1	14	No	No	No
Abbott FreeStyle® Navigator II	12.3	<5	4/Day 1; 1/Day 3	No	No
Dexcom G4®	Adults: 13; Pediatric: 15	7	2/day	No	Yes (Share™)
Dexcom G5™	Adults: 9; Pediatric: 10	7	2/day	Yes (iOS/Android)	Yes
Medtronic Minimed® Veo (530G)	13.6	6	2/day	Yes (MiniMed)	Yes (MiniMed)
Medtronic 640G SmartGuard®	Adults: 14.2; Children	6	2/day	Yes (MiniMed)	Yes (MiniMed)
Medtronic iPro®2 (SofSensor)	Adults: 9.9; Pediatric: 10.1	6	4/day	No	No
Medtronic iPro®2 (Enlite)	Adults: 11; Pediatric: 12.2	3	3/day	No	No

Note: [a]Mean absolute relative difference (MARD) values should be assumed by direct methodological analysis

merits. Section 4 presents results and analytic remarks. Section 5 elaborates on the challenges and prospects of CGM-based systems. Section 6 states concluding remarks.

2. Methodology for review

2.1 Search methodology

While searching for literatures, seven key databases, including PubMed, PubMed Central, IEEE Xplore, Science Direct, Google Scholar and Springer Link, are taken into consideration where potential studies might present in the time duration of 1980 to 2016. The keywords in this search operation consist of "continuous glucose," "glucose monitoring," "continuous glucose monitoring," "CGM" and "glucose sensor." Other forms of available and reliable online materials such as thesis, seminar talk reports and book chapters are also looked into for potential eligible incorporations. Overall selection and exclusion criteria were based on the PRISMA guidelines (Soffar, 2017). The flow diagram of the overall review process is shown in Figure 4.

2.2 Inclusion and exclusion criteria

First, the title and abstract of all the studies identified by the search operation are reviewed for potential relevance. Next, the full texts of these articles are screened. Articles aimed at designing CGM sensor and/or CGM-based systems are only included in this review. Studies that are novel, focused on CGM sensor development and published (e.g. conference/workshops/journals) during 2006-2017 are selected. Review- or survey-based studies, generic forms and duplicative works are excluded. Earlier research studies that were published before 2006 are also excluded.

2.3 Parametric information extraction

During the process of parametric information extraction, the following perspectives have been considered and included in this article: invasiveness of the laid CGM system; types of sensors used; interfacing technology; wireless monitoring; body implantable; and key applicability remarks (cost, accuracy, energy efficiency, adoptability, user experience and parametric values).

2.4 Validity assessment

The relevant potential information extracted from these literatures has been analyzed for systematic review. Most of the information inclusions are limited to peer-reviewed journal as well as conference articles (Table II).

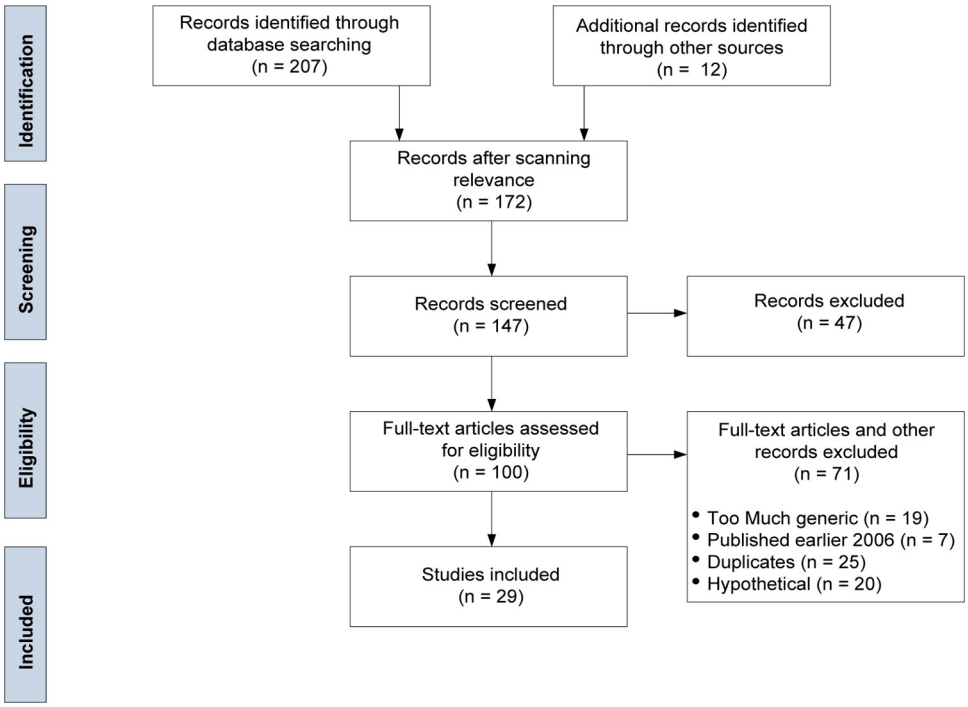
3. Review of the existing CGM systems

This section presents the available CGM systems based on two broad areas: the existing market deployable products and the reviewed literature.

3.1 Manufactured CGM systems

Market-ready solutions are thoroughly selected from four business leaders in this field which includes Tandem, Abbott, Dexcom and Medtronic. These CGM systems are further compared by five key benefits including accuracy [(per cent mean absolute relative difference; (MARD)], sensor – lifetime, calibration requirement, smart device compatibility and remote monitoring. Table I compares several such sensor devices obtained from these four manufacturers (Rodbard,

Figure 4 PRISMA Flow diagram of article selection process



2016). MARD is an essential parameter for such CGM systems where accuracy in insulin dosage concerns health. On an average, 11 per cent MARD seems to be prevalent in all types of CGM systems. An average sensor lifetime is measured to be seven days. Sensor lifetime normally indicates the number of days after which the sensor patches should be replaced. Before using any sensor patch with any CGM system, calibration must be carried out. This could be attributed to its adaptability (the tolerance level of a human body is different from the other, hence needs to be differently approached). Currently, smart devices (i.e. smart phone, tablets, netbooks etc.) are very common among all types of people. Hence, CGM should be capable to communicate its vitals with the patient's smart devices "24x7". Remote monitoring is an added advantage over these parameters that facilitates a patient to get connected with caregivers and medical support who are located remotely. The selected list of CGM systems do infer most or all the parameters itself. Although every manufacturer has devised a unique method to measure, analyze and notify a patient, no such differences have been observed that may invoke biasness in a random model. It implies that patients are free to adopt any of the four CGM systems to know his/her glucose levels; however, cost comparison has to be made, if any.

3.2 Literature review

A total of 219 articles were extensively examined, as shown in Figure 4. Only 29 articles were chosen for review, which fulfilled the inclusion criteria as mentioned earlier. As per the sensor technology, these studies are finally classified into three categories: optical, electrochemical and MEMS. The categories of the CGM systems are discussed briefly in the following subsections, and an overall comparison table (Table V) is included at the end of this section.

3.2.1 Optical sensor

Optical sensor-based CGM systems are mostly common in the surveyed researches. It is observed that infra-red, i.e. IR-based sensor system is simple than the others. Essentially, surface plasmon resonance, i.e. SPR-based CGM, is mostly acceptable technique and is under study by various researchers. Eight out of 29 reviewed studies (i.e. 27.5 per cent) are based on optical sensor-oriented CGM systems alone. Several more optical sensing methods have been devised that include single-loop fiber attenuated total reflection (ATR), double-split ring resonator, optical coherence tomography (OCT), photoacoustic (PA) and fluorescent hydrogel microfibers. In all the cases, the accuracy of the measured glucose levels is low and error-prone. Extra digital circuitries are incorporated to act ad LED/LASER light sources. Above all, wearable capability seems to be quite less in nature. Let us discuss about these briefly: Kossowski and Stasinski (2016) presented a wearable and robust IR (wavelength range of 790-1050 nm)-based glucose measurement system that performs all the computations upon attenuation of IR signal through human skin. This design was quite easier, resulting in low accuracy. To overcome this, Li *et al.* (2012) designed an implantable fiber-optic SPR sensor that can detect the glucose concentration in interstitial fluid (ISF).

Owing to its inherent sensitivity to body temperature drift, a long-period fiber grating (LPFG) system is integrated in this context. The main objective of LPFG is to compensate measurement errors with regard to temperature. The erroneous measurement issue is further reduced by incorporating a glucose-specific boronic acid polymer, i.e. PAA-ran-PAAPBA

Table II Abbreviations and full forms of key terms

Abbreviation	Full form
AAM	Acrylamide
ATR	Attenuated total reflection
AuNP	Gold nanoparticle
CEDA	Clarke error grid analysis
CGM	Continuous glucose monitoring
CMOS	Complementary metal oxide semiconductor
DMAPAA	3-acrylamidophenylbirinic acid (3-APB), N-3-dimethyl-aminopropyl acrylamide
EGL	Estimated glucose level
FPGA	Field programmable gate array
IR	Infra-red
ISF	interstitial fluid
LASER	Light amplification by stimulated emission of radiation
LED	Light-emitting diode
LPFG	Long-period fiber grating
LSK	Load-shift keying
MARD	Mean absolute relative difference
MEMS	Micro-electro-mechanical systems
Oct	Optical coherence tomography
PAA-ran-PAABA	acrylamide-ran-3-acrylamidophenylboronic acid
PA	Photoacoustic
PAS	Photoacoustic spectroscopy
PDMS	Polydimethylsiloxane
PET	Polyethylene terephthalate
PLGA	Poly lactic-co-glycolic acid
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PVA	Polyvinyl alcohol
RF	Radio frequency
RFID	Radio frequency identification module
SiC	Silicon carbide
SPR	Surface plasmon resonance
T1D	Type 1 diabetes
T2D	Type 2 diabetes

Figure 5 Side-polished SPR sensor

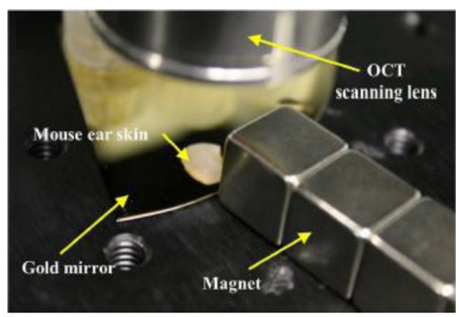
Source: Lu *et al.* (2016)

which is immobilized on the prescribed SPR sensor. A similar approach is adopted by Lu *et al.* (2016), with a slight modification in the SPR (see Figure 5). It is achieved by polishing the sides of SPR along with graphene and borate polymer instead of a borate polymer alone.

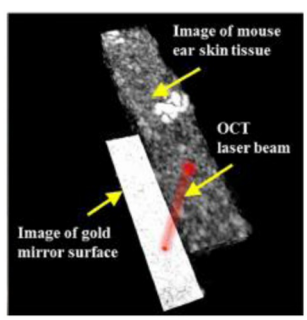
A different miniaturized fiber ATR sensor is proposed to attain high accuracy in glucose monitoring, yielding 4.45 mg/dL (Sun *et al.*, 2015). Silver nanoparticles (AgNPs) were gradually deposited onto the cylindrical surface of a single-loop fiber ATR sensor resulting in an accurate CGM system. Choi *et al.* (2014) presented a pair of microwave split ring resonators placed in close proximity to each other. One ring is vibrated at 1.4 GHz, whereas the other is kept at a high reference frequency to compensate the expansion of rings due to changes in body temperature. Both coils are coated with silver paint on top of the copper coil (1-mm in diameter and the distance between coils is 200 μm). This ring resonator sensor is generalized to be worn around an abdominal area with a patch in a non-invasive manner. An optical coherence tomography (OCT) technique, proposed by S. Wang *et al.*, captures an image and detects 2.8-μm diameter micro-particles under the skin. The OCT intensity signal can count the micro-particles and measure the OCT response (Wang *et al.*, 2013). Figure 6 presents an experimental setup and a 3D OCT image under skin.

Another article uses photoacoustic spectroscopy (PAS) toward CGM, while using a photoacoustic (PA) apparatus under FPGA-based computational facility (Pai *et al.*, 2015). A LASER beam is first deposited onto a human finger, placed upon a piezo sensor. The attenuated PA signal (received through finger) is then amplified and computed at the FPGA side. If the measured glucose level is more than the threshold, the data are sent directly on the patient's smartphone. Takahashi *et al.* find a more compact and simplified way using an implantable fluorescent-hydrogel sensor. This wearable CGM system uses a photodetector, microcontroller and XBee wireless device to monitor and inform the user about the glucose level.

Figure 6 (a) Experimental setup for studying the OCT monitoring of microparticles' movement under skin tissue in vitro. (b) 3D OCT image showing the ear skin tissue and the gold mirror surface with a vertical distance of 0.7–1.0 mm between them



(a)



(b)

Source: Wang *et al.* (2013)

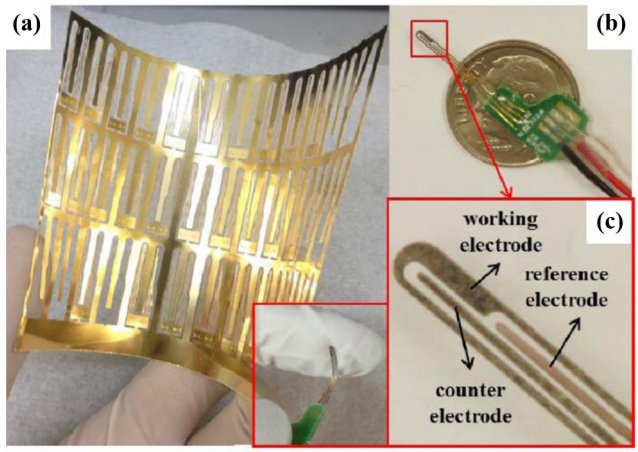
3.2.2 Electrochemical sensor

Electrochemical sensor-based CGM systems are more popular in terms of its practicality. Essentially, commercially available CGM with platinum electrode is mostly acceptable technique which is under study by various researchers. Ten out of 29 reviewed works (i.e. 34.5 per cent) are only based on an electrochemical sensor-oriented CGM system. Several electrochemical sensing methods have been devised including *platinum*-based, silicon carbide (SiC)-based, flexible, piezo-resistive pressure-based, microfiber-based and polymer film-based. These have been discussed briefly. Jung *et al.* designed a CGM sensor system based on Dexcom G4 PLATINUM and Dexcom G4 Receiver Tools Devkit, the key information of which is given in Table I. This system works on the principle of an estimated glucose level (EGL) that ranges between 100 and 150 mg/dL. Upon EGL calculation, a control system with more than more than 150 mg/dL exerts the insulin pump inject system to pump insulin per +0.5 dL/min into human blood (Jung and Lee, 2016). Similar approach is studied in Vaddiraju *et al.*, 2015 where Glucowizzard^{TM} electrochemical sensor (key characteristics: operating potential: 0.7 V, selectivity: ca. 99 per cent, observed linearity: > 30 mM, sensitivity: 35 nA/cm^{2}·mM, limit of detection: 50 μM and temperature dependence: none) is used to calculate EGL. Rosenbloom *et al.* (2009) have developed an on-board probe toward CGM. They use Medtronic CGMS® iPro^{TM} glucose sensor along with a CMA Microdialysis IView catheter to perform in vitro glucose level analysis. The syringe pump used in this experiment uses 100 μM fluorescein in 1X calcium magnesium free phosphate-buffered saline (CMF-PBS) as its source buffer. An MSP430 microcontroller performs all the necessary computational tasks related to this system. Afroz *et al.* (2013) presents an SiC sensor along with an RF module to measure and monitor glucose level. The RF module is made up of Ti/Au substrate attached with metal patches. This sensor antenna is capable to work under medial frequency at 402 MHz and 2.4 GHz. In another work, Pu *et al.* (2015) developed a polyimide-based flexible electrochemical sensor made with gold nanoparticles (AuNPs). A better form of similar flexible structure is seen in Yoon *et al.* (2015), wherein a nanoporous Pt and Ag/AgCl was used as the working/counter and reference electrode, respectively. Figure 7 presents the flexible structures of the Pt- and Ag/AgCl-based fabricated sensor. Lee *et al.* (2009) presented a similar sensor based on PET (polyethylene terephthalate). Figure 8 shows the fabrication process of PET-based glucose sensor in detail.

Hydrogel-based piezo-resistive pressure sensors are also under consideration toward CGM (Tathireddy *et al.*, 2010). The developed sensors are fabricated on top of 410-μm-thick silicon wafers. The hydrogel used contains acrylamide (AAM), 3-acrylamidophenylbirinic acid (3-APB), N-3-dimethyl-aminopropyl acrylamide (DMAPAA) and N, N-methylenebisacrylamide (BIS) in a nominal mole ratio of 80:8:10:2 synthesized via free radical crosslinking copolymerization.

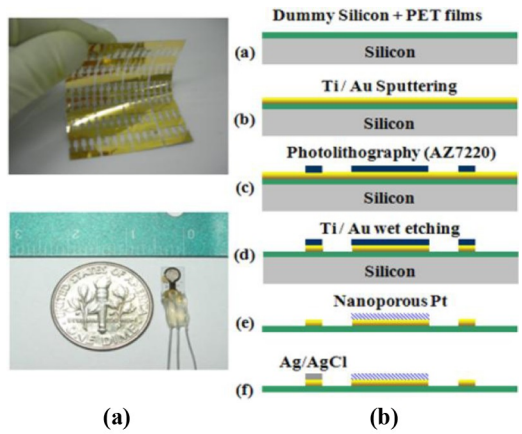
Yoon *et al.* (2016) presents a semi-implantable non-enzymatic glucose sensor based on dual-stacked biocompatible polymeric film. All the surveyed articles in this context use either flexibility, hydrogel, or piezo-resistive electrochemical elements for effective and accurate CGM.

Figure 7 Optical images of the fabricated glucose sensor



Notes: (a) SUS-based micro-needles through batch fabrication process; (b) the fabricated glucose sensor mounted a PCB jig; (c) a close-up view of sensor
Source: Yoon *et al.* (2015)

Figure 8 Photomicrograph of fabricated flexible enzyme free glucose micro-sensor (3 mm × 3 mm) (a) and its fabrication sequences (b)



Source: Lee *et al.* (2009)

3.2.3 MEMS sensor

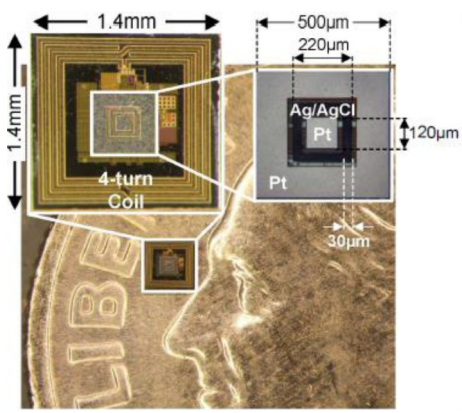
MEMS sensor-based CGM systems are most popular in terms of its usability. As found, CMOS-based CGM is the mostly acceptable technique of all, which is under study by various researchers. Twelve out of 29 reviewed works (i.e. 41.3 per cent) are based on MEMS sensor-oriented CGM system. Several electrochemical sensing methods have been devised that include CMOS and purely MEMS based. This has been discussed briefly. While discussing the CMOS-based MEMS CGM sensing systems, the parameters include 0.18 μm, TSMC 0.18 μm, osmotic, amperometric and SMIC. Nazari *et al.* (2014) presents a CGM system made of two Pt electrodes

(working and counter) and an Ag/AgCl-based reference electrode. Figure 9 elaborates the final fabricated design of the glucose sensor. Ahmadi *et al.* (2006) have designed two versions of TSMC 0.18 μm CMOS-based CGM sensor system. It uses Ir/IrOx, RFID 13.56 MHz as a key enabler of the set up. It also used a three-electrode concept (i.e. working electrode-OE, reference electrode-RE and auxiliary electrode-RE) as earlier used.

First, the glucose sensor senses the level of glucose from the human body. The signal is then sent to the data acquisition unit which then transmits the signal toward outside of body using a 13.56-MHz RF signal link, where an external signal reader comprises class E power amplifier and AM modulator.

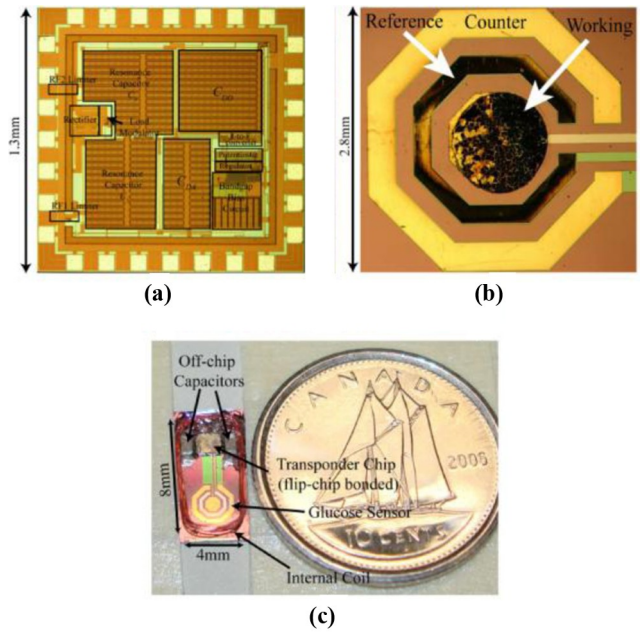
M. M. Ahmadi *et al.* have further enhanced its design as shown in Figure 10. This compact form is integrated with load-shift keying (LSK) to make the signal high in susceptibility (Ahmadi and Jullien, 2009). Trung and H«afliger (2013) present an osmotic pressure CMOS piezo-resistor-based glucose sensor. It uses a 90-nm CMOS fabrication technique to design the CGM system. The USP of this design is its very less power consumption, i.e. 48.5 pW. Further, its sampling rate is 3.3 mHz, whereas the active period is of 96 μs and resolution 8.42 bits. The next form of CGM is amperometric. Anabtawi *et al.* (2016), Guan *et al.* (2011) and Croce *et al.* (2013) have introduced an efficient glucose sensor system that can be implanted in human body. The design of Croce *et al.* (2013) is the simplest of three, as it uses thick polyvinyl alcohol (PVA) hydrogel containing poly (lactic-co-glycolic acid) (PLGA) in designing the glucose sensor. The glucose level signal received is seamlessly sent to the patient after performing signal processing. The system-level design of Anabtawi *et al.* (2016) and Guan *et al.* (2011) is almost similar. Figure 11 illustrates the system design of body implantable glucose sensor tag.

Figure 9 CMOS 0.18-Mm-based CGM system next to a US dime, sensor closeup



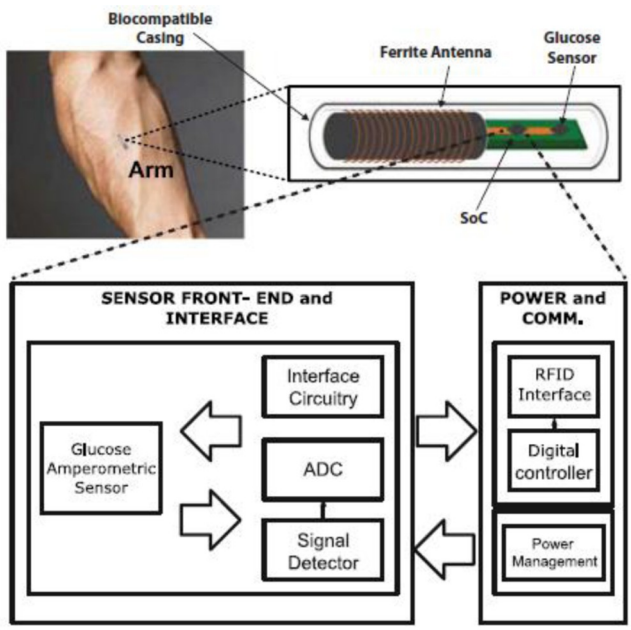
Source: Nazari *et al.* (2014)

Figure 10 (a) Microphotograph of the transponder chip; (b) microphotograph of the glucose sensor; (c) photograph of one of the assembled microsystems (before packaging and enzyme immobilization) next to a dime



Source: Ahmadi and Jullien (2009)

Figure 11 Wireless-powered implantable sensor tag for continuous glucose monitoring



Source: Anabtawi *et al.* (2016)

Xiao *et al.* (2015) also uses a similar approach the signal processing is characterized by a 10-bit Δ ADC. The implant coil is made from a Ferrite material, i.e. NiZn. The command control is dependent on the ISO 15693 RFID standard. Modulation and demodulation schemes are developed around LSK and ASK, respectively. The CMOS technology used in this study is SMIC 1P8M and 0.13 μm. Huang *et al.* (2009) proposed to build an MEMS glucose sensor using PAA-ran-PAAPBA solution, Parylene cantilever, Laser Diode, PSD, Microheater and PDMS microfluidic chamber. X. Huang *et al.* and D. Li *et al.* proposed a similar type of microfluidic system for interstitial fluid (ISF) transdermal extraction toward CGM. Both these techniques implement PAA-ran-PAAPBA polymer to design the glucose sensor (Huang *et al.*, 2012; Li *et al.*, 2013). Figure 12 presents the MEMS glucose sensor based on the work of Huang *et al.* (2012). Samyuktha *et al.* (2015) uses another form of MEMS i.e. capacitive pressure based on glucose monitoring.

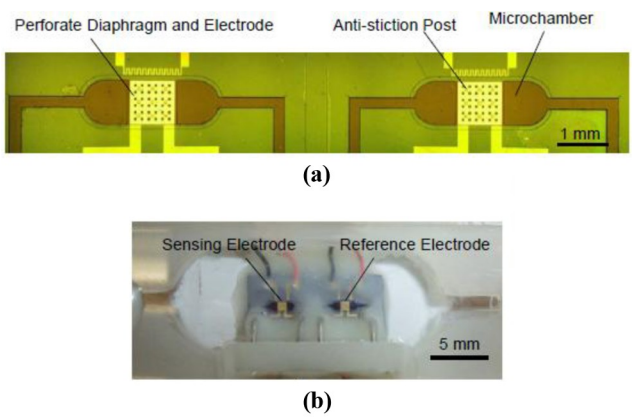
4. Results and analysis

This section presents quantitative and qualitative outcome from this review. First results discusses various parametric extraction and second result mentions qualitative marking against accuracy, lifetime, calibration, complexity, applicability and cost. An overall review on studied reviews is presented in Figure 5.

4.1 Quantitative outcome

Table III points out several grouped parameters in terms of quantity that were found during this work. Right column of the table indicates the total number of evidences and its percentage. In total, eight groups were combined to evaluate different characteristics such as methodology, optical sensor, electrochemical sensor, MEMS sensor, invasiveness, communication technology, country of research and sources of publication. It is found that MEMS-based designs are most prevalent (i.e. 41.3 per cent) than the other two types. Fiber optics proved to be most accessible (i.e. 50 per cent) optical element in same genre. IR-type are sensors less popular in this domain. CMOS and amperometric sensors are equally efficient in electrochemical-based sensing (i.e. 33.3 per cent). Novel interventions such as TSMC and SMIC are in place, but needs more implications. As expected, Platinum is the most used MEMS sensor. Approximately, 66.6 per cent of deployments have chosen Platinum for CGM sensor development. Invasiveness is another key factor for

Figure 12 Images of a differential MEMS affinity glucose sensor



Notes: (a) Before; (b) after packaging
Source: Huang *et al.* (2012)

Table III Grouped parameters of IV saline water level detection in reviewed studies

Parameters	*n* (%)
Methodology Based (n = 29)	
Optical	8 (27.5)
Electro-chemical	9 (31)
MEMS	12 (41.3)
Optical Sensor Type (n = 8)	
Infra-Red	2 (25)
Fiber Optic	4 (50)
LED	1 (12.5)
Laser	1 (12.5)
Electrochemical sensor type (n = 9)	
Osmotic	1 (11.1)
Amperometric	3 (33.3)
SMIC	1 (11.1)
TSMC	1 (11.1)
CMOS	3 (33.3)
MEMS sensor type (n = 12)	
Platinum	8 (66.6)
Silicon	1 (8.3)
Gold	1 (8.3)
Hydrogel phosphate	1 (8.3)
Stainless steel	1 (8.3)
Invasiveness Type (n = 29)	
Invasive	23 (79.3)
Non-invasive	6 (20.7)
Communication Technology (n =29)	
Bluetooth	3 (10.3)
ZigBee	1 (3.4)
RFID	2 (6.8)
Infrared	1 (3.4)
RF	5 (17.2)
Not Specified	17 (58.6)
Country of Origin (n = 29)	
Canada	2 (6.8)
China	6 (20.6)
India	2 (6.8)
Japan	1 (3.4)
Norway	1 (3.4)
Poland	1 (3.4)
South Korea	3 (10.3)
UK	1 (3.4)
USA	12 (41.3)
Source of Publications (n = 29)	
Journal	7 (24.1)
Conference/Workshop	22 (75.8)

acceptance of CGM devices in the current market. It is found that 79.3 per cent solutions indicate invasive approaches. Similarly, RF has shown its promising stature for applicability in communication technology development. Bluetooth is just lagging behind RF's intrusion. The reason behind such implication is that most of the related experiments have mainly relied on the inductive coils to either wireless powering the system or data collection. RFID is thus getting acknowledged into various studies being performed over similar topics. However, 17 articles did not mention their communication methodology. But the trend is more with RF and Bluetooth (Table IV).

To date, researchers from USA, China and South Korea have mostly contributed toward CGM sensor development research, while mixed reactions have been received from Asia and UK. The trend in research production is mainly bend toward conference and locally organized workshops (i.e. 75.8 per cent). SCI/SCIe indexed journals are not preferred as much popular destination as of the conferences. Although the outcome from this quantitative analysis is purely based on the stipulated amount of data received from these 29 articles, it could be inferred as a mere generic output toward understating the current trend only.

4.2 Qualitative outcome

A qualitative analysis was performed to analyze the effectiveness and overall quality of this study. It is worth to note that none of the research includes real-patient's data due to ethical issues and/or scope of functionality, resulting in non-inclusion of the Cochrane's quality and risk bias study. QUADAS tool was summarily excluded due to the similar reason. Table IV depicts the quality-wise investigation on 29 reviewed articles. Six vital parameters (e.g. accuracy, lifetime, calibration, system complexity, real-life applicability and development cost) are selected to mark these 29-reviewed works. The evaluation is given based on high – H, medium – M and low – L susceptibility per parameter per article. NA is used in such places where meaningful inference was not perceived. It is apprehended that article (Jung and Lee, 2016; Xiao *et al.*, 2015; and Huang *et al.*, 2012) outperforms other articles under review. This comprehension was made based on accuracy, cost and average of other parameters. Upon further clarifications (if any) on NA specified values, more research could be accommodated in a series of most affective research outcomes. Table IV presents the overall marked evaluation of qualitative analysis.

Table IV Grouped parameters of IV saline water-level detection in reviewed studies

	Parametric quality index					
Paper ID	**Accuracy**	**Lifetime**	**Calibration**	**Complexity**	**Applicability**	**Cost**
Kossowski and Stasinski (2016)	M	M	H	NA	M	NA
Trung and Häfliger (2013)	M	H	L	M	H	M
Jung and Lee (2016)	H	H	L	H	M	H
Anabtawi *et al.* (2016)	H	L	L	H	L	H
Guan *et al.* (2011)	M	L	L	H	L	M
Croce *et al.* (2013)	L	M	M	M	L	L
Vaddiraju *et al.* (2015)	L	M	NA	NA	L	NA
Rosenbloom *et al.* (2009)	H	M	L	H	H	H
Li *et al.* (2012)	M	L	M	M	L	L
Afroz *et al.* (2013)	L	M	L	L	M	L
Sun *et al.* (2015)	M	M	M	M	L	NA
Pu *et al.* (2015)	NA	M	M	H	L	M
Tathireddy *et al.* (2010)	NA	NA	NA	M	L	M
Choi *et al.* (2014)	M	M	L	L	L	NA
Xiao *et al.* (2015)	H	L	L	H	L	H
Wang *et al.* (2013)	M	M	H	H	L	M
Ahmadi *et al.* (2006)	M	M	NA	H	M	M
Pai *et al.* (2015)	L	H	M	M	H	H
Huang *et al.* (2009)	M	M	H	M	L	M
Huang *et al.* (2012)	H	L	M	M	L	M
Takahashi *et al.* (2013)	L	M	L	M	M	M
Yoon *et al.* (2016)	M	L	L	M	M	H
Lu *et al.* (2016)	L	H	L	L	L	H
Lee *et al.* (2009)	M	L	L	H	L	H
Ahmadi and Jullien (2009)	H	L	L	H	L	H
Samyuktha *et al.* (2015)	NA	NA	L	M	L	M
Li *et al.* (2013)	M	NA	M	M	L	M
Yoon *et al.* (2015)	M	H	L	H	L	M
Nazari *et al.* (2014)	H	M	L	M	M	NA

Notes: H – High; M – Medium; L – low; NA – not apprehended

4.3 Comparative discussion

A comparative discussion is presented herein to understand and analyze actual differentiation among presented solutions, as prescribed in 29 articles. Two main attributes (e.g. power consumption and sensitivity wise parameters) are elaborated as follows.

- *Power consumption*: Most of the articles did not explicitly mention how much power the implemented CGM sensor consume, although apprehended by analyzing the architectural notions. However, seven had mentioned the amount power consumed by particular CGM sensor such as 48.5 pW, 47 mW, <100 μW, 140 μW, five days battery life, <10 μW, 6 μW in Trung and H«afliger (2013), Anabtawi *et al.* (2016), Guan *et al.* (2011), Croce *et al.* (2013), Rosenbloom *et al.* (2009), Ahmadi and Jullien (2009), and Nazari *et al.* (2014), respectively. Hence, it may be assumed that overall CGM sensors are energy efficient with a few exceptions.
- *Sensitivity*: Reviewed articles present sensitivity metrics in different forms that include glucose concentration range, implied signal sensitivity, R^2 curve fitting signal wave excitation wavelength, etc. Jung and Lee (2016), Afroz *et al.* (2013), Golden *et al.* (2012) and Huang *et al.* (2009) provided range of body glucose measurement as 100-150, 120-530, 0-40 and 0-324 mg/dL, respectively. Approximation on CGM-based glucose sensitivity was measured as 35 nA/cm^2 . mM, 0.75 nA/cm^2 . mM, 5.7 μA/cm^2 . mM, 20.16 μA/cm^2.mM, 1 μA/cm^2 . mM in Vaddiraju *et al.* (2015), Xiao *et al.* (2015), Yoon *et al.* (2016), Lee *et al.* (2009) and Yoon *et al.* (2015), respectively. R^2 curve fitting is found to be 0.99509, >0.98, 0.92514 and 0.999 in Li *et al.* (2012), Sun *et al.* (2015), Lu *et al.* (2016), and Li *et al.* (2013), respectively. Similarly, the glucose concentration sensitivity level was found promising as 2-22, 0-20, 0-40 and 0-20 mM in Croce *et al.* (2013), Tathireddy *et al.* (2010), Ahmadi and Jullien (2009) and Nazari *et al.* (2014), respectively. Effective detectable intensity changes were measured as 2.91±0.5% in Wang *et al.* (2013). An experimental tissue intrusion current flow was found to be within the range of 10 fA to 100 pA for glucose level measurement (Guan *et al.*, 2011). Other studies obtained expected results by either simulation or LED/RF wave excitation (Kovatchev *et al.*, 2015; Diatribe, 2015; Pleus *et al.*, 2015; Forlenza *et al.*, 2015; Brown *et al.*, 2015).

5. Prospects of CGM systems

Section 2 and Section 3 present a detailed survey on the CGM sensor systems in terms of commercially available products and research materials. From this discussion, it is undoubtedly clear to comprehend that the CGM system paves strong hold on monitoring and alerting diabetic patients be it Type-1 or 2. Now the vital question is "If CGM systems can perform so well, why are they not being widely used?" Several researchers have had many discussions to seek answer of this question (Soffar, 2017; Vigersky, 2015; Endocrine Society, 2011; T1D Exchange Clinic Network, 2015; Walsh *et al.*, 2015; Bailey *et al.*, 2015). This section shall discuss on some of these here. Initially, the key challenges toward implementing of CGM in clinical practices are discussed; later, several opportunities in terms of CGM's potentials are briefed.

5.1 Challenges

1 *Human interface*: Human interface is the most vital challenge in CGM utilization and implementation. Several product manufacturers are in continuous trial to find efficient ways to neutralize human interface such that CGM may be popularized among citizens. However, fewer articles present such discussions and answering the following questions may take time:
   - How effective is the information usually obtained from CGM after being translated into human actions and behaviors?
   - How do the following metrics improve measurable clinical outcomes such as: (i) quality of glycemic control (QoGC), (ii) quality of glycemic variability (QoGV), (iii) quality of treatment satisfaction (QoTS) and (iv) quality of life (QoL)?
   - What is the amount of time needed for the clinician to acquire ample knowledge on how to operate a CGM system?
   - What is the amount of time needed for the clinician to teach and train the patient with diabetes about the basics of CGM system operation and infer its outcome i.e., data?
   - What is the amount of time needed for the patient to become familiar with the use of the CGM system on how to insert, remove and transmit of the data to a local/remote computer with/without using internet?
   - What is the amount of time needed for the medical trainer and patient to interpret CGM data analysis?
   - How much reliable, consistent, and effective do the medical practices and patients feel, infer and imply int countering diabetes?

2 *Accuracy*: Until recently, glucose metering solutions available in world market had far better accuracy than the CGM systems. But the current situation is gradually changing (Pleus *et al.*, 2015; Nakamura and Balo, 2015; Kovatchev, 2015; Kovatchev *et al.*, 2015; Joubert *et al.*, 2015). Several issues, including detection of hypoglycemia, self-adjustment of insulin dosage, change of insulin-injection needle evaluating response to therapy etc., have been studied and seamlessly upgraded. Accuracy of CGM strictly depends on the calculation and measurement of bodily glucose level. Surveyed articles show promising approach in this regard.

3 *Regulatory approval*: The process for regulatory approval to the use of CGM systems seems neglected (Soffar, 2017). India and USA are the mostly diabetic affected countries in the world. However, no such initiatives have been taken by the Government agencies that may regulate the usage patterns, especially insulin dosage and adjustment. Researchers and manufacturers of CGM have opted their own way to select insulin dosage, but it is too generic and not accurate and optimized for patient-to-patient basis.

4 *Cost*: Cost is the most crucial factor in this regard. The existing medical facilities such as check-ups, treatment, hospitalization, emergency care and even death of patient with diabetes are normalized in terms of other similar diseases. Medical insurance terms and conditions never talk about real-time CGM solutions, although retrospective discussions are seen. In such situations, a patient with diabetes faces several monetary issues that are obviously not in favor of his/her health. Hence, medical insurances and even health regulatory bodies of the Governments should define a policy toward cost reimbursement toward CGM-supported hyperglycemic treatment, monitoring and hospitalization of such patients (Table V).
5 *The physician and clinical inertia*: Physicians are often found to work against the systematic *insulin therapy*. This occur due to some factors such as lack of time, unwillingness toward new methodology, education background and social demands. Pharmaceutical companies do sometimes incorporate some sorts of unobvious voracity among the medical practitioners and abuse them to prescribe particular medicine as clinical therapy to the patients. Whatever the reason is, most of the time physicians are benefited from such "system" leading patients to suffer from an unsystematic approach of treating diabetes. To date, developing countries like India face huge unobtrusiveness in a clinical diagnosis approach. Although there lies a hope that a few percentage of physicians tend to use the CGM systems in diabetes care and treatment, without any formal and approved training courses. This inertia is dangerous in the case of type-2 diabetes. Medical councils, Government agencies, medical practitioners and health-care provides (e.g., hospitals, nursing homes, super specialty health centers etc.) should come together to formulate a way to use the CGM system as a systematic solution to diabetes.
6 *Sensor lifetime*: Sensor lifetime is another vital factor that is constantly repelling patients and medical caregivers from using of the CGM systems. Most of the cases, sensors, expire in seven and ten days. It really creates a situation of cost crunch resulting in severe conditions among diabetic patients of under-developed and developing countries. One should think about how to design sensors such that it can work for a life time.

5.2 Opportunities

1 *Calibration*: In section 5.1, we discussed the key issues hindering the promising aspects of CGM systems. Calibration is a factor that uses capillary method to measure blood glucose. Such a technique becomes clumsy when patients use blood glucose meters along with reagent strips. It incurs high cost, inconvenience and discomfort. Notwithstanding above, it may also increase the complexity, number of glucose meters and sometimes psychological burden. In most of the cases, patients should select an undeterministic amount of insulin to treat hyperglycemic symptoms. Fortunately, this problem has been totally solved by Abbott's FreeStyle Libre (Bailey *et al.*, 2015). It is hoped that such solutions can be seen more in CGM systems in near future.
2 *User experience*: As generally observed in blood glucose meters, CGM systems may provide much better user experience in terms of cost, pain and complexity and is user friendly. These have recently been improved by incorporating Internet into it (Pettus *et al.*, 2015). Now, users can visualize, store and analyze day-to-day glucose levels. Fortunately, cloud-based solutions are in practice that may be helpful when a patient is in danger. When the glucose level drops below the threshold level, it promptly sends an alert message to the caregiver's phone and even calls up medical emergency services.
3 *Rapid obsolescence*: The sensor technology, along with related ICT tools, is rapidly changing with time. It is certain that the patients and medical practitioners shall soon be able to willingly use CGM systems for treating diabetes.
4 *Overcoming the reproducibility to results*: To date, blood glucose metering solutions provide simple visualization capability of glucose levels. But intervention of smart CGM systems have eradicated such simplistic behavior by allowing users to store the glucose level in local or remote cloud servers in real time. Users can download or analyze the variations of glucose levels as and when needed. Such result reproducibility was never opted in earlier variants of glucose monitoring systems.
5 *Commitment to intensive insulin therapy*: CGM systems allow its users to use it with or without an insulin pump i.e., injector. This obviously add an inherent long-term insulin therapy mindset among the patients and medical caregivers.
6 *Awareness*: Undoubtedly, an awareness campaign provides better results in any form of practical life, be it politics, personal, or product advertisement. It is true for CGM systems too. Proper channeling and campaigning may surely pave a better orientation among citizens about CGM systems.
7 *Time Lag*: Time lag is the amount of time that starts with positioning of blood sample on glucose sensor to its measurement. CGM systems, unlike blood glucose meters, are compacted with smart microcontrollers and complex circuitries that yield instant results.

6. Conclusion

CGM systems have attracted great attention in terms of scientific and clinical advances, among its users worldwide. This paper presents such systems, first by comparing the available products in market and then reviewing sensor design-specific studies from 29 research articles. Development of the CGM systems has yielded three key solutions: optical, electrochemical and MEMS. Several challenges toward the usage of the CGM systems persist, but are being sincerely examined. The mind-set of the physicians and their approach to cooperate with the patients is the major challenge in this regard. Similarly, lack of awareness and related education is the key problem among users. The advancement in sensor accuracy and calibration may take CGM systems a step forward in curing and treating diabetes from the world.

Table V Comparison between various sensors for continuous glucose monitoring studied

Author/ Research article	Invasiveness CGM	Type of Sensor	Interfacing technology	Wireless monitoring	Body implantable	Key applicability remarks (Cost/accuracy/energy efficiency/ adoptability/User experience/ parametric values)
Kossowski and Stasinski (2016)	Non-invasive	Infra-Red	IR Transceiver module	No	No	Wrist wearable using IR Spectrophotometry
Trung and H«afliger (2013)	Invasive	Osmotic CMOS Piezo-resistor	13.56 MHz RF, Load Shift Keying, Coil Antenna, ASIC	Yes	Yes	Extremely low power consumption (48.5 pW), Sampling rate 3.3 MHz
Jung and Lee (2016)	Invasive	Dexcom G4 Platinum	USB/RS232, Bluetooth, CMA 402 Syringe Pump	Yes	Yes	Automatic insulin injection system, Estimated Glucose Level (EGL), Real-time
Anabtawi *et al.* (2016)	Invasive	Amperometric CMOS Glucose Sensor	13.56 MHz RF, NFC, RFID interface, Load Shift Keying	Yes	Yes	Integrated SoC, frequency Modulation, PID controller-IIR Filter
Guan *et al.* (2011)	Invasive	Amperometric CMOS Glucose Sensor	RFID HF, Command ISO/IEC 15693 protocol	Yes	Yes	Integrated SoC-based biosensor Tag, correlated double Sample, Low power consumption (50.968 μW)
Croce *et al.* (2013)	Invasive	Amperometric CMOS Glucose Sensor	LabVIEW, Bluetooth	Yes	Yes	Highly miniatured (0.665 mm2) and low power (140 μW)
Vaddiraju *et al.* (2015)	Invasive	Glucowizzard™ Electro-Chemical Sensor	Clark-type enzymatic sensor, Proximity communicator, Needle	Yes	Yes	Implementation of the "smart" targeted drug delivery system, 'user-independent'
Rosenbloom *et al.* (2009)	Invasive	Medtronic CGMS® iPro™	100 μM fluorescein, TI MSP430, CMF-PBS buffer	Yes	Yes	Portable and smart micro-dialysis, probe fouling, osmosis flow rate monitor
Li *et al.* (2012)	Invasive	Fiber-optic Surface Plasmon Resonance (SPR) Sensor	Long Period Fiber Grating (LPFG), Boronic Acid Polymer PAA-ran-PAAPBA	No	Yes	CGM is measured by reading the transmission spectrum, LPFG temperature drift is included
Afroz *et al.* (2013)	Invasive	Silicon Carbide (SiC) based biosensor	RF, Microstrip patch antenna, Ti/Au metallization	Yes	Yes	Frequency shift for blood mimicking is 40 MHz, antenna frequency at 10 GHz
Sun *et al.* (2015)	Invasive	Single-loop fiber ATR sensor	Ag NPs, Infra-red molecules absorption, Wave length tunable CO2 LASER, LabVIEW	No	Yes	High accuracy, radius of ATR fiber optic 2.5 mm, minimized error rate 4.45 mg/dL
Pu *et al.* (2015)	Invasive	Electrochemical- flexible sensor	Graphehen, AuNPs, Printhead, Miniaturized Venturi and pneumatic valves	No	Yes	Linearity range 0 $\sim$ 40mg/dL, amperometric response 5 mg/dL per |0.2V|
Tathireddy *et al.* (2010)	Invasive	Hydrogels integrated piezo-resistive pressure sensor	Phosphate Buffer Saline (PBS), Pressure sensor array	No	Yes	Swelling cycle, 12 min; shrinking cycle, 5 min
Choi *et al.* (2014)	Non-invasive	Double split ring resonator sensor	Ag coated Cu coil at 1.4 GHz, LC resonator, low-loss PTFE pillar	No	No	Microwave, precise, safe, Fast, Interval data sampling

(*continued*)

Table V

Author/ Research article	Invasiveness CGM	Type of Sensor	Interfacing technology	Wireless monitoring	Body implantable	Key applicability remarks (Cost/accuracy/energy efficiency/ adoptability/User experience/ parametric values)
Xiao *et al.* (2015)	Invasive	Electrochemical SMIC 1P8M 0.13- μm CMOS Sensor	13.56 MHz RFID, Near field Ferrite antenna, Load Shift Key (LSK), low-power low-dropout regulator (LDO)	No	Yes	SoC-based integrated design, low power (50 μW) consumption, linear potentiostat differential output
Wang *et al.* (x2013)	Invasive	Optical Coherence Tomography (OCT) based sensor	Au Mirror, laser, fiber optic coupler, fiber adaptor, achromatic lens, transmission grating, scan lens	No	Yes	The information of glucose density is calculated by detecting the change of light reflection from the gold mirror surface using OCT
Ahmadi *et al.* (2006)	Invasive	TSMC 0.18 μm CMOS	Ir/IrOx, RFID 13.56 MHz	Yes	Yes	Reproducible, biocompatible, and linear sensor
Pai *et al.* (2015)	Non-invasive	Photoacoustics (PA) based sensor	Pulsed Laser Diode (PLD) at 950 nm, lead zirconate titanate piezoelectric transducer, a Xilinx Virtex-II Pro FPGA at 274.823 MHz	No	No	Fast, memory efficient system architecture, Clarke Error Grid Analysis (CEDA), 18.03% MARD, MAD of 23.75 mg/dL
Huang *et al.* (2009)	Non-invasive	MEMS sensor	PAA-ran-PAAPBA solution, Parylene cantilever, Laser Diode, PSD, Microheater, PDMS microfluidic chamber	No	No	Biocompatible, stable, excellent reversibility, long-term usability
Huang *et al.* (2012)	Invasive	MEMS differential dielectric sensor	PHEAA-ran-PAAPBA solution, Capacitance Digital Converter (CDC)	No	Yes	Difference in the permittivity changes is measured via the differential capacitance, permittivity change between 10 and 100 KHz, long-term, stable, reliable
Takahashi *et al.* (2013)	Invasive	Fluorescent Hydrogel Microfibers based sensor	LED (405 nm), LD, XBee, Arduino Fio	Yes	Yes	Portable, ear clip-based, real-time, fluorescent intensity wise glucose measurement
Yoon *et al.* (2016)	Invasive	Dual-stacked biocompatible polymeric film sensor	Nanoporous Pt (nPt), SU-8, Bluetooth, Ag/AgCl reference electrode	Yes	Yes (Semi-Implantable)	Excellent sensitivity for interferences 5.7 μA/mM.cm^2
Lu *et al.* (2016)	Invasive	Side-polished fiber Surface Plasmon Resonance (SPR) sensor	PAA-ran-PAAPBA, Borate Polymer, Long-Period Fiber Grating (LPFG), Spectrograph	No	Yes	653.44-656.11-nm wavelength shift in the range of glucose concentration for 10-300 mg/dL, Temperature self-compensation
Lee *et al.* (2009)	Invasive	Flexible nano-sensor	Polyethylene Terephthalate (PET), nPt engraved	No	Yes	

(*continued*)

Table V

Author/ Research article	Invasiveness CGM	Type of Sensor	Interfacing technology	Wireless monitoring	Body implantable	Key applicability remarks (Cost/accuracy/energy efficiency/ adoptability/User experience/ parametric values)
						Flexible, bio-compatible, enzyme free, stable, reproducible, electrode surface RF (roughness factor) of 106.5
Ahmadi and Jullien (2009)	Invasive	TSMC 0.18-μm CMOS micro sensor	RF 13.56 MHz, Load-Shift Keying (LSK)	Yes	Yes	Flip-chip bonding, transponder chip, low cost, real time
						Non-consumptive, competitive affinity binding, COMSOL
Samyuktha *et al.* (2015)	Invasive	MEMS capacitive pressure sensor	Dextran and Concanavalin-A (Con A) microchamber gel	No	Yes	Multiphysics, low cost
			ISF transdermal extraction, volume	No	No	Ag micro PDMS
Li *et al.* (2013)	Invasive	Microfluidic sensor	Pt, Ag/AgCl	No	No	Enzyme-free, high sensitive
Yoon *et al.* (2015)	Non-invasive	Stainless steel (SUS)	Pt, Ag/AgCl, Bovine Serum Albumin (BSA)	Yes	Yes	Inductive coupling link 900 MHz, wireless power
Nazari *et al.* (2014)	Non-invasive	CMOS 0.18-μm sensor				

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