

Diabetes Management in Transition: Market Insights and Technological Advancements in CGM and Insulin Delivery

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Continuous Glucose Monitoring (CGM) systems are revolutionizing the real-time tracking of blood glucose levels, a cornerstone in effective diabetes management and optimal glycemic control. Transitioning from the “intermittent readings” offered by traditional Blood Glucose Monitoring (BGM) methods, CGM delivers an “uninterrupted flow” of glucose data, enabling a “more detailed” strategy for meeting treatment goals. Initially, the “uptake of CGM faced hurdles due to doubts about its precision, but continuous advancements in technology have not only resolved these concerns but also confirms CGM as a dependable and impactful instrument in diabetes management”. Concurrently, advancements in insulin pump technology have improved their portability and ease of use, greatly increasing patient adoption. The market reflects a growing demand for such innovative healthcare solutions, driven by an increased awareness of diabetes management and bolstered by supportive healthcare policies. Future prospects for CGM and insulin pump technologies are incredibly promising, offering the potential for highly personalized care and sophisticated treatment strategies. This paper aims to explore how the synergy between ongoing technological developments and evolving market dynamics is set to redefine the diabetes care paradigm, positioning CGM and insulin pumps as essential elements in enhancing the quality of life for individuals with diabetes.

1. Introduction

Diabetes is a rapidly increasing disease worldwide,^[1,2] and according to the World Health Organization (WHO), it is one of the top 10 causes of death worldwide.^[3] The International Diabetes Federation (IDF) estimates the overall prevalence of diabetes at 366 million in 2011, which is expected to rise to 552 million by 2030.^[4,5] The healthcare expenditure is also enormous, with 12% of global health spending going to diabetes and related

complications.^[6] The cost is expected to rise from US\$376 billion to US\$490 billion by 2030 (Table 1).^[7,8]

Diabetes mellitus is a disease by a chronic physiological condition stemming from either insufficient insulin secretion by the pancreas or the body's diminished capacity to effectively utilize the insulin it produces.^[9] Insulin, a pivotal hormone crucial for regulating glucose homeostasis, plays a central role in modulating blood glucose levels. Disruption of this intricate regulatory mechanism leads to hyperglycemia, which exerts deleterious effects on diverse physiological systems, particularly the nervous and vascular systems.^[10–13] Therefore, monitoring of blood glucose levels emerges as a cornerstone in the management of diabetes. Sustaining euglycemia within the physiological range of 4 to 8 mM (72 to 144 mg dL⁻¹)^[14] through vigilant blood glucose surveillance is imperative to mitigate complications and preserve optimal health.

Continuous glucose monitoring (CGM) is a method that allows for regular and long-term monitoring of blood sugar levels, and its application is gradually expanding. The traditional BGM^[15] is an inexpensive and conventional method; however, this approach inevitably relies on intermittent and irregular measurements based on an individual's daily routine. Such measurements ultimately show limitations due to user dependency in identifying detailed blood glucose patterns and collecting comprehensive data, which serves as a significant obstacle in diabetes treatment and management.^[16,17] Therefore, CGM, which allow real-time monitoring of blood glucose levels, overcome these limitations, and provide important information to patients who need insulin control.^[18,19] This technology can help patients improve their eating habits and medications and effectively manage their diabetes.^[20] Insulin treatment is necessary^[21–24] for proper blood glucose control. Insulin can be delivered by oral medications,^[25–27] syringes,^[28,29] pens,^[30,31] pumps,^[21,32,33] and more. Numerous studies indicate that, regardless of gender and age, the appropriate use of insulin in type 1 diabetes (T1DM) patients is clinically crucial and offers significant benefits. Additionally, insulin adjunct therapy has been shown to be effective for type 2 diabetes (T2DM) patients who have decreased physical function due to chronic diabetes, face challenges with diet and self-management.^[34,35]

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Table 1. Global regional statistics on diabetes prevalence.

Region	Number of patients (2021)	Number of predicted patients (2045)	Deaths due to diabetes rate	Undiagnosed diabetes rate	Diabetes expenditure
Global	537 million adult	784 million	6.7 million	44%	966 billion \$
Africa	24 million adult	55 million adult	416000	54%	13 billion \$
Europe	61 million adult	69 million adult	1.1 million	36%	189 billion \$
Middle-East and North Africa	73 million adult	136 million adult	796000	33%	33 billion \$
North America and Caribbean	51 million adult	61 million adult	931000	25%	415 billion \$
South and Central America	32 million adult	49 million adult	410000	33%	65 billion \$
South-East Asia	90 million adult	151 million adult	747000	50%	10 billion \$
Western Pacific	206 million adult	260 million adult	2.3 million	50%	241 billion \$

With the increasing prevalence of diabetes, there is a corresponding rise in the need for effective diabetes management solutions. Since 2006, there has been a proposal for utilizing digital sensors for continuous glucose monitoring, with the additional capability of using smartphones as data receivers and facilitating telemedicine communication.^[36–38] Over the past decade, several digital sensors for minimally invasive blood glucose monitoring have been patented,^[39] approved by the FDA, and have been commercially available.

This review seeks to provide an overview of the transition in diabetes management, focusing on the advancements in CGM and insulin pump technologies, informed by market insights. It emphasizes the dual role of CGM for glycemic management and insulin pump for glycemic control in diabetes management. Furthermore, it underscores the emerging trend of integrated CGM and insulin pump systems as a promising direction for future development in this field.

2. The State of Diabetes and the CGM Market

2.1. Growth of the CGM Market

As illustrated in **Figure 1A**, the prevalence of diabetes is steadily increasing, and the CGM market is expanding correspondingly. This growth is attributed to several factors driven by economic growth. Firstly, with the increase in educated individuals, awareness of the importance of diabetes management has heightened, emphasizing the significance of blood glucose monitoring.^[40–44] This enhanced awareness contributes to the growing importance placed on blood glucose monitoring.^[45,46] Continuous glucose monitoring, facilitated by CGM technology, has emerged as a pivotal tool in maintaining the health of individuals with diabetes. Unlike traditional methods that rely on sporadic blood glucose measurements, CGM allows for real-time monitoring of blood glucose levels, enabling timely clinical decisions.^[47,48] Moreover, CGM enhances the convenience and efficacy of blood glucose monitoring by providing continuous data streams. This continuous monitoring enables individuals with diabetes to promptly identify fluctuations in their blood glucose levels and take necessary actions. Furthermore, advancements in technology and heightened competition in the market have contributed to the refinement of CGM devices, leading to improved accuracy and reliability.^[49,50] CGM devices capable of providing more precise data empower diabetic patients with enhanced management op-

tions, thereby driving market expansion. Additionally, increased research initiatives and investments in the health and medical sectors have spurred innovation and diffusion of CGM technology. Government policies and initiatives from healthcare organizations have also played a crucial role in facilitating the accessibility of CGM devices to diabetic patients.^[51] The alignment of supportive policies with market dynamics further bolsters the growth trajectory of the CGM market. Moreover, there has been a notable shift in blood glucose management practices within hospital settings. Traditionally, blood glucose monitoring primarily relied on finger pricks. However, there has been a recent surge in the adoption of CGM devices in hospitals,^[52–55] as depicted by the revenue increase in **Figure 1B**. These changes have worked toward increasing convenience for both patients and healthcare providers. This has led to a reduction in fatigue associated with long-term blood glucose monitoring and has expanded accessibility to effective blood glucose management. Numerous prior studies have highlighted the positive impacts of CGM adoption. The COVID-19 pandemic has further accelerated this trend,^[54] with hospitals increasingly embracing CGM technology as part of a broader healthcare transformation aimed at optimizing patient care standards. CGM manufacturers emphasize that effective diabetes management is achievable not only through the quantified information they provide for individual self-management but also through the medical advice from healthcare professionals.^[56,57] Consequently, the combined effects of these various factors have significantly contributed to the growth of the CGM market.

2.2. Diabetes Prevalence and CGM by Region

The prevalence of diabetes is increasing globally, and **Figure 2** shows the prevalence by region as of 2019. The prevalence of diabetes in North America and the Caribbean (NAC) was 48 million people, constituting 10.3% of the global prevalence, followed by Europe with 59 million individuals, representing 12.7%. The remainder of the world accounts for 77% of the total incidence.^[5] **Figure 2B** illustrates the regional distribution of diabetes incidence projected for 2045. South Asia, the Middle East and North Africa, Africa, and South and Central Americas are anticipated to increase their share of the total compared to 2019, whereas North America and the Caribbean, Europe, and the Western Pacific region are expected to witness a decrease. In **Figure 2C**, revenue forecasts for North America, Europe, APAC, and the Rest of the

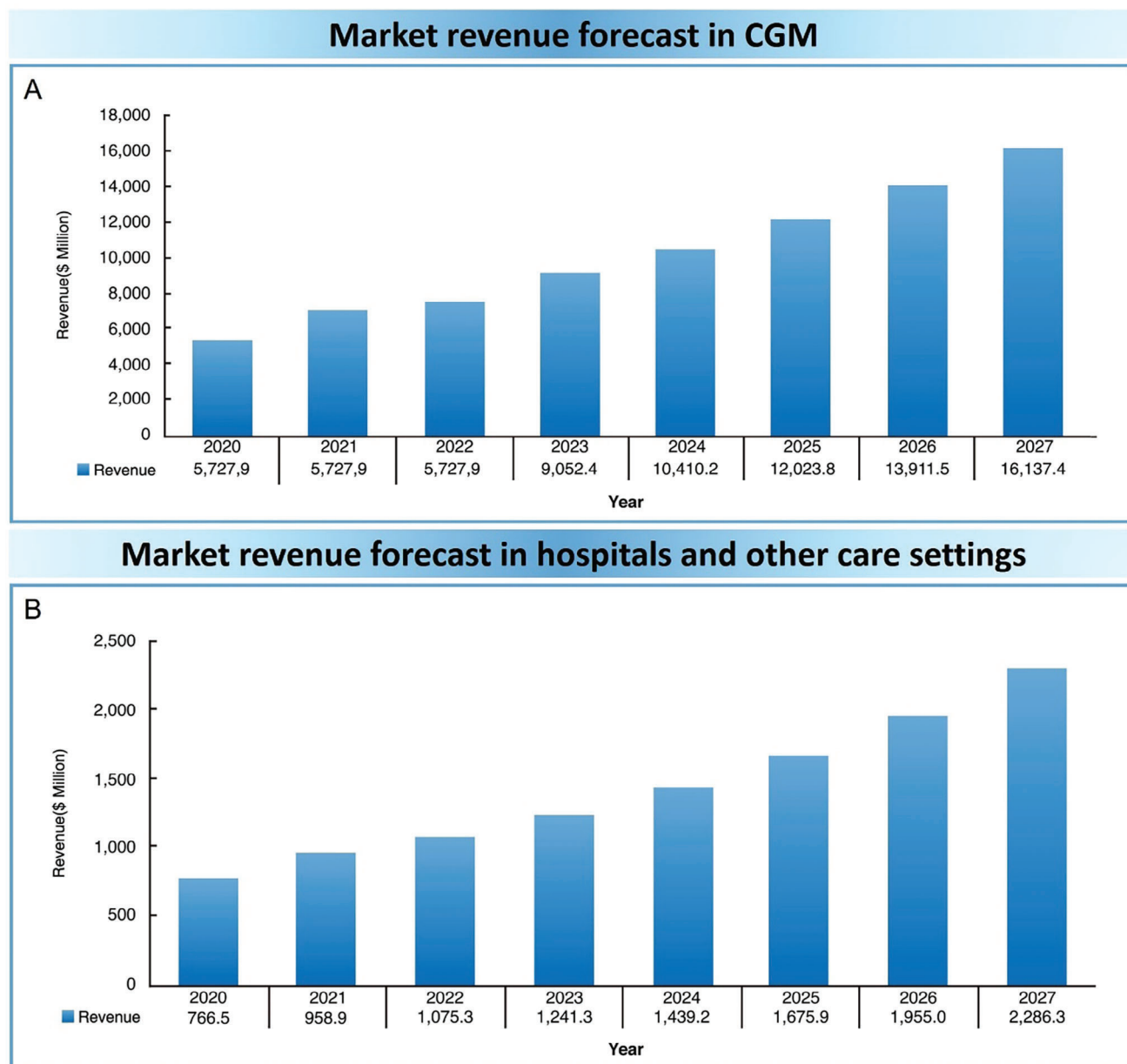


Figure 1. Forecasted CGM Market revenue trends from 2020 to 2027. A) The graph of market revenue forecast in CGM from 2020 to 2027. B) The graph of market revenue forecast in hospitals and other care settings from 2020 to 2027.

World (ROW) are presented. While there is a correlation between the prevalence of diabetes and the adoption of CGM devices, it is important to note that these two metrics do not always align perfectly.^[58] Despite regions experiencing high incidence rates of diabetes, the corresponding revenue generated from CGM device sales may not directly mirror this trend.

North America, being the headquarters of major CGM device companies, serves as the largest market due to high CGM awareness and FDA efforts to promote its use. Europe follows as the next significant market, with increasing CGM adoption, particularly in Western Europe.^[59] However, the approval of non-invasive glucose monitoring technologies by the European

Union^[60–62] may potentially limit CGM adoption. The Asia-Pacific (APAC) region emerges as the fastest-growing CGM market due to its high diabetes prevalence, increasing CGM awareness, and product availability.^[63] This growth has attracted major players to expand their operations in the region. Conversely, the ROW region remains a relatively small market due to the high cost and low awareness of CGM devices.^[64,65] Compared to glucometers that cost around a few dollars per month, test strips that cost a few dollars per month, and lancets that cost \$12 per month, a CGM device can cost up to \$200 per month including all components, and limited health insurance coverage for these products creates a high barrier to entry for CGM.^[66]

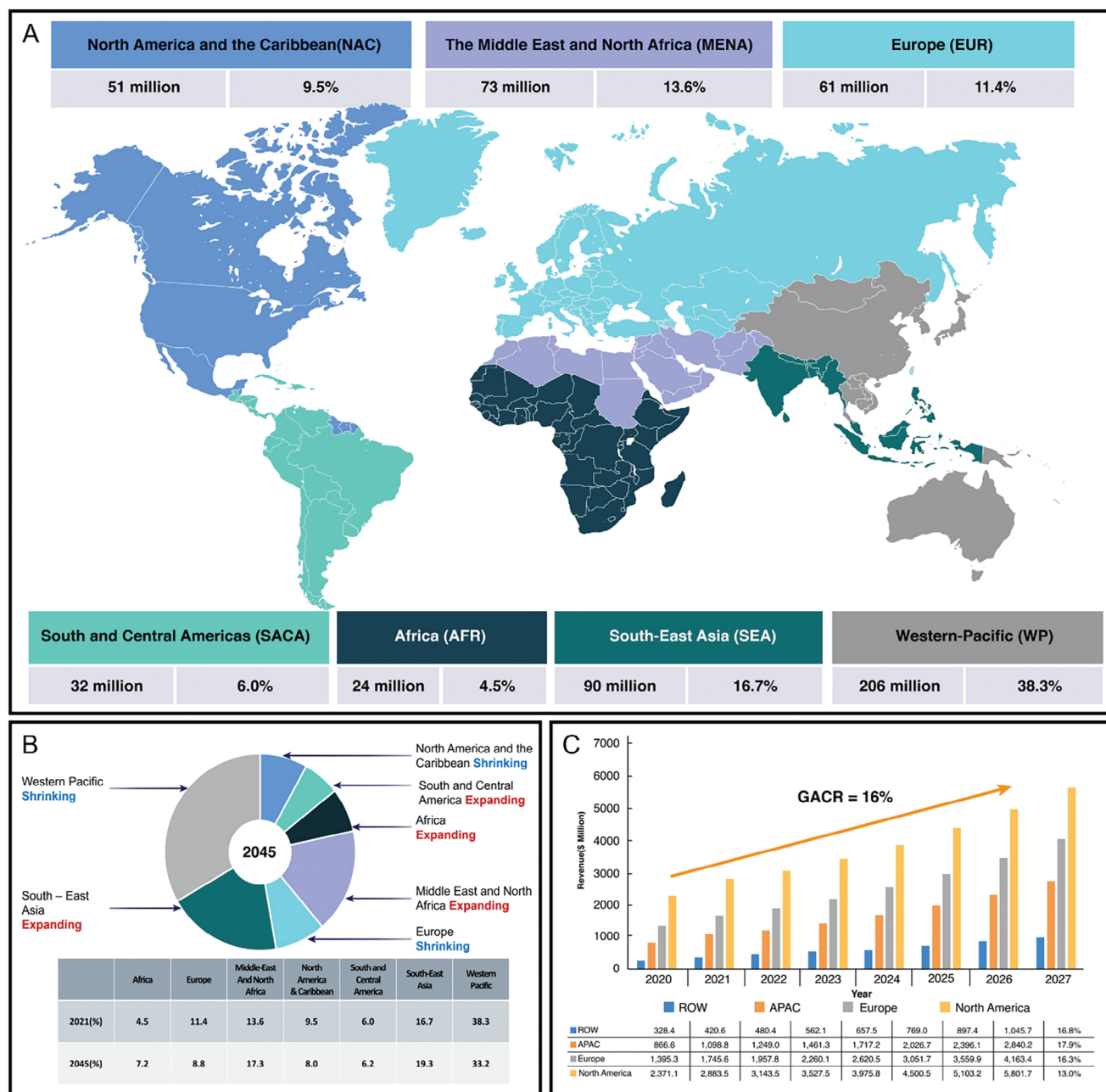


Figure 2. Global diabetes landscape overview with regional variations, future projections, and escalating healthcare costs. A) The illustration of the number of diabetes patients and their proportionate share across various regions worldwide. B) The illustration of the predicted changes in the regional distribution of diabetes patients by 2045. C) The graph of the current status and projected trends in home care costs attributed to diabetes from 2020 to 2027.

However, as diabetes prevalence rates continue to rise, concerted efforts in research and initiatives to lower price barriers are expected to propel the CGM market forward. Reductions in CGM device costs are anticipated to enhance access not only in ROW regions but globally. As more affordable CGM devices become accessible, a larger segment of the population will have the opportunity to benefit from this technology, thereby improving diabetes management and overall health outcomes on a global scale (Figure 2A).^[67–69]

2.3. CGM Clinical Trials

The introduction of real-time Continuous Glucose Monitoring (CGM) systems has garnered significant attention due to their ability to help more patients maintain target A1C levels while reducing the risk of severe hypoglycemia.^[70] To evaluate the efficacy and safety of these systems, clinical trials have been conducted on various subjects.^[71–75] As CGM technology has advanced, the reliability of these systems has improved, and the perception of

Table 2. Development status of CGM products by four major companies.

Company	Abbott	Dexcom	Medtronic	Senseonic
Model	Free style Libre 3	Dexcom G7	Guardian sensor 4	Eversense E3
Detection principle	Electrochemical	Electrochemical	Electrochemical	Optical
Type	Minimally invasive	Minimally invasive	Minimally invasive	Implantable invasive
Dimension (mm)	29*21*4.0	24*27.4*4.6	10*28*5.0	2.54*18.3
Weight(g)	1.1	7.5	8.0	11.1
Sensor lifetime	14 day	10 day	7 day	90 day
Accuracy (MARD%)	7.6	8.2	8.7	8.5
Reading frequency	1 min	5 min	5 min	5 min
Warm up period(hrs)	1	0.5	2	24
Price	200 \$ / month*	299 \$ / month*	300 \$ /month*	250 \$ / month*
Reference	[88]	[86]	[87]	[89]

*The purchase and implantation costs for consumers in the United States without health insurance coverage or support policies.

their effectiveness in reducing hyperglycemia and hypoglycemia has spread, leading to their use as an adjunctive tool.^[76,77] In 2016, the FDA approved the Dexcom G5 Mobile CGM system as the first CGM that allows treatment decisions without the need for fingerstick blood tests. This FDA approval was based on the evaluation of two clinical trials involving 130 adults and children aged 2 years and older with diabetes. The studies compared system readings with blood glucose meter values and laboratory test methods over a seven-day period.^[78] Other companies have also received FDA approval for their CGM systems, increasing the significance of CGM in diabetes management. Examples include the FreeStyle Libre Flash Glucose Monitoring System, which does not require blood sample calibration^[79] and the fully implantable Eversense CGM system.^[80] As these systems received approval, commercial devices based on clinical research data have expanded.

3. Commercial CGM Device

3.1. Evolution of CGM Devices

Medtronic, collectively holding over 95% of the market share. The remaining 5% is distributed among various other companies, such as Senseonic. This market structure is primarily shaped by these major companies' proprietary sensor development technologies and robust marketing strategies. Each of these companies has a long-standing history in producing enzyme-based blood glucose meters,^[81] laying a crucial foundation for the advancement of CGM technology. Moreover, through more than two decades of continuous development and evolution, these companies have amassed a wealth of patient data and have refined technologies for calibrating blood glucose metrics measured by CGM devices. Initially, early CGM devices required frequent calibration with Self-Monitoring of Blood Glucose Meter (SBGM) systems during the measurement process and typically had a shorter lifespan of three days, which accounts for only 20% of the duration offered by modern CGM devices.^[82,83] How-

ever, the CGMs currently sold by the three major companies have leveraged advancements in technology, allowing them to apply factory calibration methods during the manufacturing process. As a result, these devices can operate for up to 15 days without the need for additional calibration (Table 2).^[84–87]

3.2. Characteristics of Each Device

Three major companies in the CGM, namely Abbott, Dexcom, and Medtronic, utilize enzyme-based electrochemical glucose measurement technology.^[90] These enzyme-based sensors are widely recognized for their reliability and have garnered a high level of user trust owing to years of meticulous research ensuring safety and accuracy.^[91] Currently, the accuracy of CGMs is measured using the Mean Absolute Relative Difference (MARD) method, which represents the average absolute relative error between the measured glucose values and the actual glucose values. This is calculated as shown in Equation (1).^[92–94] A lower MARD value indicates higher accuracy of the CGM. The MARD values for Abbott's FreeStyle Libre 3, Dexcom's Dexcom G7, and Medtronic's Guardian Sensor 4 are 7.6%, 8.2%, and 8.7%, respectively, demonstrating excellent reliability and accuracy.^[95–97]

$$\text{MARD} = \frac{1}{n} \sum_{i=1}^n \left| \frac{\text{BG}_{\text{measured}} - \text{BG}_{\text{reference}}}{\text{BG}_{\text{measured}}} \right| \times 100\% \quad (1)$$

$\text{BG}_{\text{measured}}$ = Glucose values measured by CGM, $\text{BG}_{\text{reference}}$ = Reference glucose values (measured by blood test), n = Number of measured data points

Differences emerge in the underlying methodologies employed by Dexcom and Medtronic, which utilize hydrogen peroxide (H_2O_2) from the enzyme's oxidation process for direct blood glucose measurement, while Abbott employs mediator for this purpose.^[98,99] Dexcom and Medtronic's hydrogen peroxide approach is classified as first generation, whereas Abbott's mediator method is classified as second generation. Furthermore, disparities exist in wireless communication systems, with

Dexcom^[100] and Medtronic^[101] employing Bluetooth-based systems for real-time data transmission to electronic devices like smartphones, whereas Abbott utilizes Near Field Communication (NFC) to transmit accumulated data in bulk rather than in real-time (Table 2). Each company is actively engaged in its own research and development endeavors to optimize blood glucose monitoring systems and enhance user satisfaction. Consequently, successive generations of devices have witnessed reductions in size, extended duration of use, and decreased warm-up times.^[102] Nevertheless, there remains room for improvement in terms of pricing, as leading products typically entail maintenance fees exceeding \$200 per month (Table 2). In contrast, Senseonic's Eversense E3 stands out from the competition by employing optical methods. The optical method enables the Eversense E3 to outlast conventional CGMs by more than sixfold prolonged usage periods with a single insertion (Table 2). With an accuracy rate of 8.5%, it is also suitable for non-adjunctive use. However, drawbacks include an extended initial warm-up time (24 hours) compared to other devices and the requirement for insertion and removal by a designated healthcare professional due to its implantable invasive nature.^[103] Additionally, although the device itself is less expensive than other products, the additional costs incurred during the insertion and removal processes ultimately result in similar per-unit period usage costs compared to other products.^[89]

4. The Evolution of Glucose Measurement Techniques and Analytical Methods

4.1. Traditional Glucose Measurement Techniques

The evolution of glucose monitoring technologies within the realm of biomedical engineering has been profoundly influenced by the historical context of diabetes research. Initially, the detection of diabetes relied heavily on the analysis of urine, a practice that can be traced back centuries and is universally recognized across various cultures.^[104] The discovery of glucose in urine during the 18th century was a groundbreaking development, establishing urine analysis as a foundational method for diabetes research.^[105] The advent of urine strips in the latter part of the 20th century significantly transformed the landscape of diabetes management, introducing a more convenient and accessible approach to glucose monitoring.^[106] Despite the popularity of urine strips, their effectiveness is often compromised by the presence of interfering substances such as Vitamin C in urine, which can lead to inaccuracies in glucose estimation (Figure 3A).^[107] To address these limitations, the medical field has progressively adopted more sophisticated techniques, including the use of venous blood samples for a comprehensive analysis of glucose levels and glycated hemoglobin, providing a more accurate and reliable assessment of diabetic conditions (Figure 3B).^[108] Nevertheless, these advanced methods require professional expertise and are generally constrained to intermittent measurements, posing a challenge for continuous glucose monitoring. The ongoing pursuit of innovation in glucose monitoring aims to bridge this gap, striving to develop technologies that offer real-time, accurate glucose readings, thereby enhancing the efficacy of diabetes management and improving the quality of life for individuals living with this chronic condition.

4.2. Modern Approaches to Glucose Measurement

In the evolving landscape of diabetes care, Blood Glucose Meters (BGMs) have undergone analysis, providing valuable insights for optimizing diabetes management and improving patient outcomes.^[98] This technological evolution reflects the ongoing commitment to enhancing the quality of care for individuals with diabetes, highlighting the importance of continuous innovation in medical devices. considerable advancements, offering more accurate and user-friendly solutions for glucose monitoring. Despite these advancements, BGMs still face inherent challenges related to the blood sampling process. The accuracy of glucose measurements can be affected by individual differences in blood properties, necessitating multiple daily blood draws. This requirement not only increases the risk of pain and discomfort for the user but also raises concerns about the potential for secondary infections due to repeated skin punctures.^[75,109] Furthermore, in Figure 3C, the lack of continuous monitoring capabilities, particularly during sleep and active periods, limits the effectiveness of traditional BGMs in providing a comprehensive picture of an individual's glycemic control.^[110] To overcome these limitations, CGM systems have been introduced, marking a significant innovation in the field. Since their FDA approval in 1999, CGMs have evolved to offer extended wear times, now up to 90 days, and feature a minimally invasive sensor that continuously tracks glucose levels in the interstitial fluid.^[111] This continuous monitoring capability, a stark contrast to the intermittent readings provided by traditional BGMs, allows for a more detailed understanding of glucose patterns and variations (Figure 3C). Despite their similarities in relying on enzymatic reactions for glucose measurement, CGMs offer a distinct advantage with their automated, continuous data collection.

4.3. The Transformation of Glucose Analysis Methods

The advancement of CGM technology signifies a pivotal development in diabetes management, enabling comprehensive and systematic tracking of glucose levels over time.^[112] Traditional glucose evaluation methods, such as fasting blood glucose levels and postprandial glucose levels, have been used and validated for an extended period to assess blood glucose.^[113] However, these methods are limited to specific situations and fail to provide a complete picture of glucose fluctuations and trends in an individual's daily life.^[114] To address this issue, the adoption of the Time in Range (TIR) method has increased globally. TIR allows for more personalized treatment and management by aligning with an individual's glucose trends better than traditional methods. In Figure 3D, TIR focuses on the duration an individual's glucose levels remain within a specified healthy range (70-180 mg dL⁻¹), offering a more nuanced view of glycemic control and facilitating more tailored treatment strategies.^[115] Central to this approach, CGM devices have revolutionized diabetes management by continuously monitoring glucose levels, considering the nuances of an individual's diet and lifestyle, thus enabling truly personalized healthcare. Studies have shown that meticulous blood glucose management using CGMs positively impacts the medically important HbA1c evaluation.^[116,117] Consequently, the integrated nature of CGM systems extends their utility beyond mere glucose

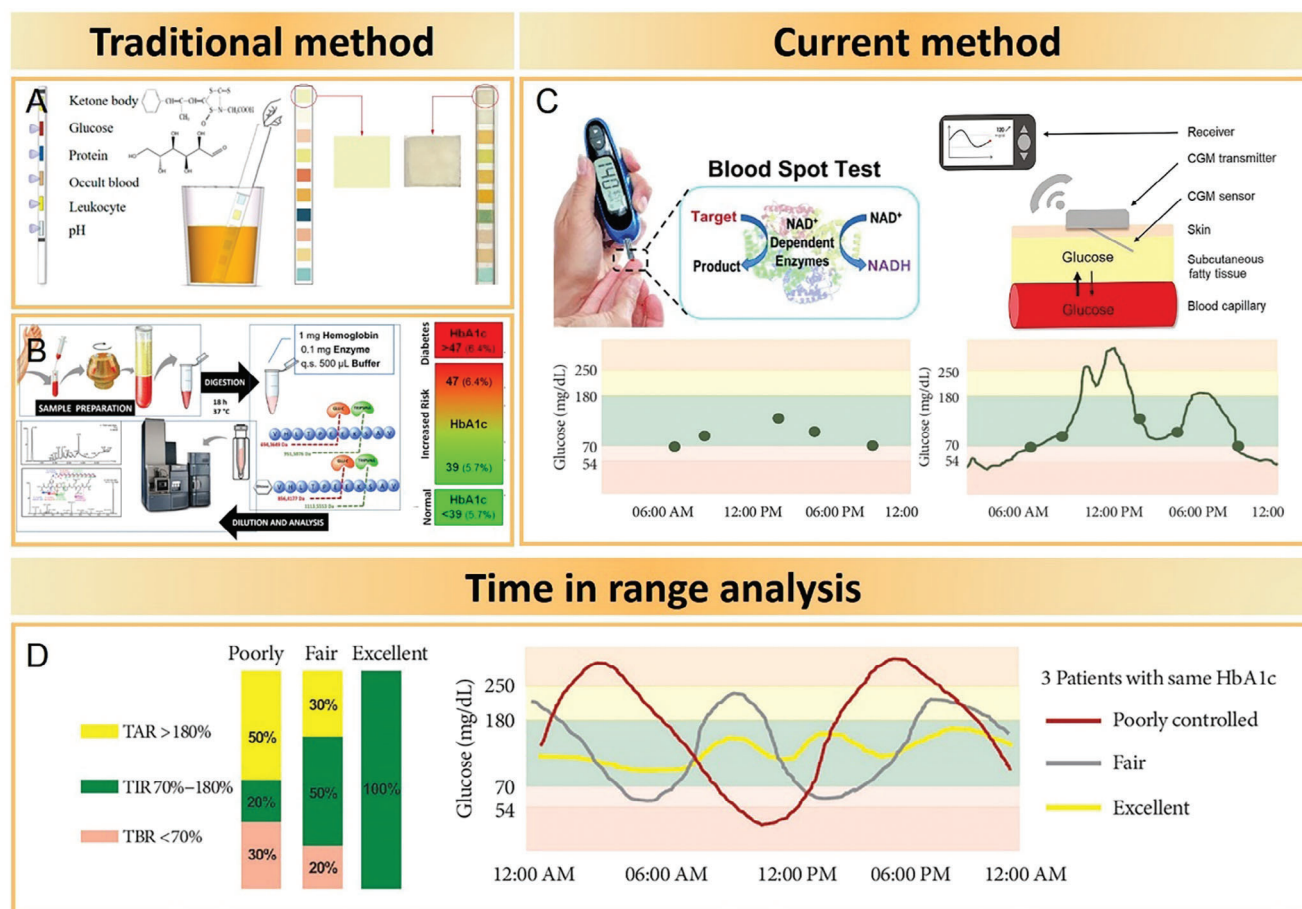


Figure 3. The primary methods for diagnosing diabetes through blood glucose measurement and analysis. A) Blood glucose measurement and analysis through urine strips. Reproduced under terms of the CC-BY license.^[106] Copyright 2022, The Authors, published by MDPI. Reproduced under terms of the CC-BY license.^[237] Copyright 2023, The Authors, published by MDPI. B) Blood glucose measurement and analysis through venipuncture. Reproduced with permission.^[238] Copyright 2020, American Chemical Society. Reproduced with permission.^[239] Copyright 2017, Diabetes Technology Society. C) Blood glucose measurement and analysis through both BGM and CGM systems. Reproduced with permission.^[240] Copyright 2016, WILEY-VCH. Reproduced under terms of the CC-BY license.^[115] Copyright 2020, The Authors, published by De Gruyter. Reproduced with permission.^[114] Copyright 2020, Korean Diabetes Association. D) Blood glucose analysis via TIR method. Reproduced under terms of the CC-BY-NC license.^[114] Copyright 2020, The Authors, Korean Diabetes Association.

tracking, allowing for real-time notifications of glycemic excursions and seamless integration with smart technology for user-friendly monitoring. This innovation enhances patient engagement and compliance, contributing to more informed and effective diabetes management practices.^[118]

5. The Current State of Research on Glucose Sensors in the Academic Field

5.1. Minimally Invasive Device

In contemporary scholarly pursuits, there is a pronounced focus on developing minimally invasive glucose monitoring techniques, which stand at the forefront of innovative medical practices.^[119,120] These methods, characterized by their subdermal insertion to gauge glucose through the interstitial fluid, are revolutionizing patient care by significantly diminishing the discomfort associated with traditional invasive procedures and curtailing the incidence of secondary infections. Among the leading

strategies is the employment of micro-needle arrays, which involve the insertion of tiny needles, only a few hundred micrometers long, into the skin to facilitate glucose measurements within the ISF (Figure 4A).^[121,122] Despite the advantages of reduced pain and infection risk presented by these micro-needles, they encounter intrinsic limitations regarding the sensor's longevity and stability. The inserted micro-needles are prone to gradual displacement due to the natural skin healing process, which can alter the electrode's positioning from the desired ISF area, compromising the potential for sustained monitoring.^[123] Figure 4B illustrates new methodologies employing micro-needles to create small pores in the skin for ISF extraction have been devised. However, these techniques face challenges, including diminished insertion force and heightened infection risks.^[124] Additionally, the use of needle arrays increases the area of skin directly impacted, compared to single-needle applications, presenting a significant concern. Research continues to evolve, with studies focusing on one-time-use patch systems that offer an easier application process and the capability to concurrently measure other

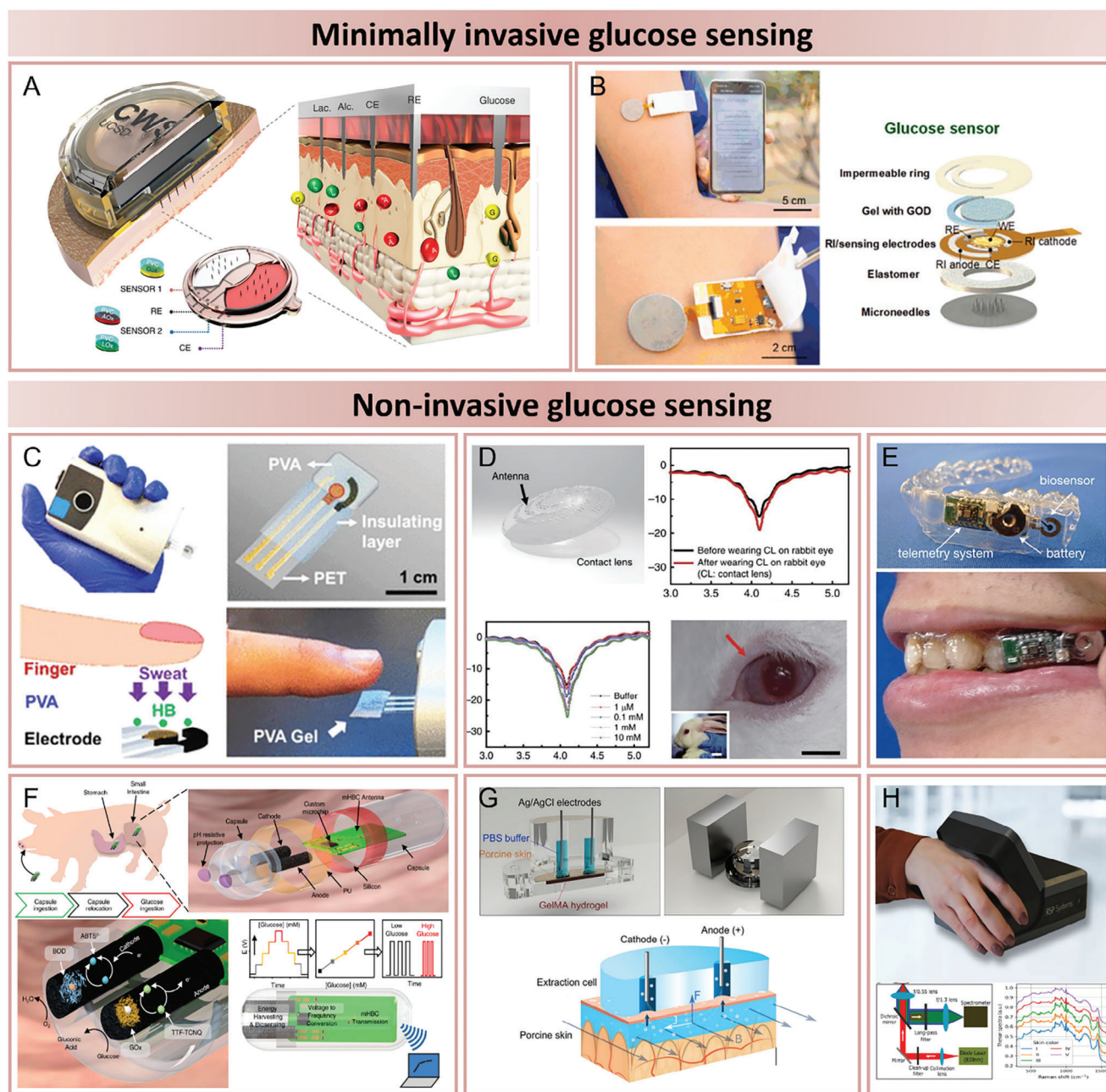


Figure 4. Various methods of blood glucose measurement under investigation in the academic field. A) Microneedle based multiplex device for measuring of glucose, lactate, and alcohol. Reproduced with permission.^[123] Copyright 2022, Springer Nature. B) An integrated system that measures glucose levels through temporary openings created by microneedles. Reproduced with permission.^[124] Copyright 2022, Elsevier. C) A sensor that measures glucose levels by collecting sweat from the skin with a simple touch. Reproduced with permission.^[127] Copyright 2022, American Chemical Society. D) A contact lens device designed to measure glucose levels through the analysis of tears. Reproduced with permission.^[131] Copyright 2017, Springer Nature. E) A device attached to the teeth, designed to measure glucose levels through the analysis of saliva. Reproduced with permission.^[133] Copyright 2020, American Chemical Society. F) A sensor capable of real-time glucose monitoring during the digestive process, operational in extreme conditions. Reproduced with permission.^[134] Copyright 2022, Springer Nature. G) A device utilizing electric fields for non-invasive extraction of interstitial fluid (ISF) and glucose measurement. Reproduced with permission.^[109] Copyright 2021, Springer Nature. H) A non-invasive glucose measurement sensor utilizing Raman spectroscopy. Reproduced under terms of the CC-BY license.^[137] Copyright 2023, The Authors, published by American Chemical Society.

ISF components such as lactate and alcohol, broadening the scope of minimally invasive glucose monitoring (Figure 4A).^[123]

5.2. Non-Invasive Device (Biomarker-Based External Measurement)

The exploration of invasive techniques in medical diagnostics offers a considerable advantage over traditional methods by facilitating the direct analysis of biofluids within the body, thereby significantly reducing the delay associated with the analysis of other bodily fluids. Nonetheless, this approach invariably entails inherent risks, including discomfort and the potential for infection, which are critical concerns. In response to these challenges, significant strides have been made in the fields of modern medicine and engineering toward enhancing sterilization processes to prevent infection and developing minimally invasive strategies aimed at reducing pain, although these advancements have not fully alleviated the underlying fears and accessibility issues for patient.^[125,126] Considering these obstacles, there has been a discernible shift toward the utilization of biofluids that are expelled from the body, leveraging non-invasive methods for diagnostic purposes, with the development of glucose sensors serving as a prominent example. Among the various biofluids, sweat has emerged as particularly advantageous due to its readily accessible nature and the relative ease of collection through methods such as skin-attached devices or the use of absorbent strips (Figure 4C).^[127] Despite the inherent challenges posed by the variable rates of sweat secretion and the consequent necessity for periodic electrode refreshing, this approach is distinguished by its simplicity and greater accessibility compared to other biofluids.^[128,129] Advancements in material science have enabled the integration of microcircuits into soft materials, thus paving the way for the innovative use of contact lenses for glucose monitoring through the analysis of tear fluid.^[130] This technique involves embedding multilayered circuitry within conventional contact lenses, coupled with electrodes that interact with tear fluid to measure glucose levels (Figure 4D).^[130,131] However, this method faces several challenges, including potential obstruction of vision and discomfort arising from increased lens thickness, which complicates further development. An alternative saliva-based method involves the use of dental structures equipped with electrodes and circuits for glucose measurement, offering a consistent biofluid supply and enabling the concurrent monitoring of dietary habits (Figure 4E).^[132,133] Despite its advantages, this approach necessitates regular cleaning to prevent contamination from food intake and is susceptible to damage during chewing, underscoring the ongoing need for innovative solutions in non-invasive glucose monitoring techniques.

5.3. Non-Invasive Device (Biomarker-Based Internal Measurement)

Glucose management is intricately linked to dietary habits and metabolic processes, yet research into glucose monitoring during digestion has advanced at a slow pace. In pursuit of a solution, there has been a concerted effort towards the innovation of devices specifically designed for continuous glucose monitoring during the food intake and digestion phases, reminiscent of

the technology^[134] outlined in Figure 4F. These devices, set apart from their predecessors, necessitate robust safeguards against the corrosive effects of strong acids and enzymes and are engineered to support the intricate requirements of remote data communication.^[135] The application of non-invasive methodologies encounters inherent limitations, particularly due to the erratic secretion volumes of biofluids such as blood and interstitial fluid (ISF), which in turn contributes to substantial delays in the precise representation of glucose concentrations. This challenge has catalyzed focused research into the direct utilization of ISF, leading to the development of cutting-edge techniques that involve the extraction of biofluids through the application of electromagnetic fields to the dermal layer, as depicted in Figure 4G.^[134] This innovative approach enables the selective extraction of specific substances at the electrode interface, contingent upon the orientation of the electromagnetic field, thereby allowing for the comprehensive analysis of a myriad of biomarkers, including glucose and electrolyte levels.^[136] Methods for monitoring blood glucose using various wavelengths of light have recently gained attention alongside active research into non-invasive techniques. These methods measure glucose concentration by employing different spectroscopic techniques, such as infrared and Raman spectroscopy. As illustrated in Figure 4H, the Raman spectroscopy method analyzes signals from Raman scattering that occurs when light passes through the body, thereby determining glucose concentration.^[137] The infrared method, on the other hand, involves measuring the light transmitted or reflected through the body based on the wavelength of the infrared light. This method analyzes the bonds between atoms in glucose to determine its concentration.^[138–140] While these spectroscopic methods utilizing light have expanded the analysis techniques available for minimally invasive and non-invasive methods, several challenges remain. These include improving device accuracy and reliability, accounting for user variability, and developing methods for continuous monitoring. Continued research is necessary to address these challenges and advance the technology.

6. The State of Insulin and Insulin Pump Market

6.1. Growth of the Insulin Market

Insulin, designed to emulate the natural endogenous secretion of insulin, offers unique pharmacokinetics and pharmacodynamics within the body.^[141] In the 1920s, insulin was first successfully extracted from the pancreases of cows and pigs to treat patients with Type 1 Diabetes Mellitus (T1DM). Following this breakthrough, pharmaceutical companies began mass production, leading to the widespread availability of insulin worldwide. However, animal insulin presented challenges: its molecular structure differed slightly from human insulin, causing immune reactions in some patients. Additionally, the extraction and purification techniques of the time were limited, often resulting in impurities that could cause side effects. The supply of animal insulin was also unstable as it depended heavily on the meat processing industry. In the late 1970s, scientists began researching methods to produce insulin using recombinant DNA technology. This research culminated in the production of human insulin, which received approval from the U.S. FDA in 1982 and subsequently gained international approval in countries such as the United

Kingdom, the Netherlands, and West Germany.^[142] In the late 1970s, scientists began researching methods to produce insulin using recombinant DNA technology. This research culminated in the production of human insulin, which received approval from the U.S. FDA in 1982 and subsequently gained international approval in countries such as the United Kingdom, the Netherlands, and West Germany. Human insulin produced through recombinant DNA technology overcame many limitations of animal insulin, offering higher purity and a more stable supply while significantly reducing the risk of immune reactions. Consequently, insulin became a central component in diabetes management, marking a significant advancement in the field.^[143,144]

In 2015, insulin claimed the top spot in the annual ranking of the top 10 most imported pharmaceuticals, with imports totaling 68.3 million US dollars Free On Board (FOB).^[145] Projections indicate substantial growth in the insulin market, with estimates suggesting a market value of 28 billion US dollars by 2032. Various types of insulin contribute to this market growth, encompassing Rapid-Acting insulin,^[146] Biosimilar,^[147] Long-Acting insulin,^[148] Combining insulin,^[149] and others^[150–152] **Figure 5A.**

6.2. Growth of the Insulin Pump Market

Currently, insulin is administered using either the Multi Daily Injection (MDI) method or the Continuous Subcutaneous Insulin Infusion (CSII) method. The CSII method, primarily facilitated by insulin pumps, has been found in research to offer similar or slightly improved blood glucose control compared to the MDI method.^[153,154] Consequently, as illustrated in Figure 5B, the insulin pump market demonstrates rapid growth relative to the overall expansion of the insulin market.^[155] This accelerated growth can be attributed to advancements in insulin pump technology, resulting in pumps characterized by reduced size and enhanced performance.^[155] Consequently, patients are increasingly favoring and accepting insulin pumps as a preferred method of insulin delivery.^[156] Numerous studies have underscored the positive outcomes associated with insulin pump usage, further solidifying their role in diabetes management.^[21,157–159]

6.3. Insulin Pump Clinical Trials

Interest in Continuous Subcutaneous Insulin Infusion (CSII) therapy began in the late 1970s, and advancements in technology have since enabled diabetes patients to choose among various insulin delivery methods.^[160] Initially, insulin pumps faced challenges related to size, stability, and efficiency. However, the release of the Diabetes Control and Complications Trial (DCCT) results in 1993 marked a turning point, significantly boosting the popularity of insulin pump therapy.^[33] Randomized controlled trials (RCTs) have demonstrated that CSII therapy provides superior glycemic control compared to Multiple Daily Injections (MDI). A meta-analysis comparing the average HbA1c levels between MDI and CSII showed that insulin pump therapy offers better blood glucose management. This evidence strongly supports that CSII treatment significantly improves glycemic control, resulting in reduced glycated hemoglobin and mean blood glucose levels.^[32,161,162] As insulin pumps have become smaller

and more wearable, their integration into modern closed-loop systems has become increasingly feasible. Research over the past five years has shown that closed-loop systems can be successfully implemented in routine clinical practice, enhancing diabetes management.^[163–167] Initially, insulin pumps were approved by the FDA as standalone devices or as part of predefined single diabetes management systems. However, in 2018, the FDA approved interoperable insulin pumps, marking a significant advancement in the flexibility and customization of diabetes treatment. Additionally, insulin pump systems integrated with CGM have also received approval, further increasing the automation and efficiency of diabetes management through insulin pumps.^[168]

7. Insulin Pump Device

7.1. Evolution of Insulin Pump Devices

Insulin pumps, once bulky and impractical for portable use, have undergone significant advancements over time.^[32] Through miniaturization and the development of replaceable batteries and reservoirs, insulin pumps have become more accessible to patients seeking convenient diabetes management solutions. Spearheading this evolution is Medtronic's product, commanding approximately 55% of the total market share. Other players represented in Table 3 each hold smaller portions, ranging from 5 to 10% of the market.

Initially, insulin pump technology focused on developing proprietary systems capable of regulating small bolus units and delivering insulin in a personalized manner. The size of the reservoir was optimized for a typical replacement cycle lasting 3–4 days. As advancements in insulin pump technology progressed, the integration with CGMs further accelerated these developments. Each insulin pump company forged partnerships with specific CGM manufacturers, aligning their pump offerings with compatible CGM systems. Notably, Medtronic stands out as the only company currently engaged in the simultaneous development and production of both CGMs and insulin pumps.^[101]

The evolution of insulin pump technology has not only enhanced portability but also improved functionality, allowing for more precise insulin delivery tailored to individual needs. These advancements have been instrumental in facilitating seamless integration with CGM systems, offering patients a comprehensive diabetes management solution that combines real-time glucose monitoring with precise insulin dosing.^[169]

7.2. Characteristics of Each Device

The main features to look for in an insulin pump are the accuracy and speed of insulin delivery and the size and weight of the product. Medtronic's MiniMed 770G,^[170] Sooil's Dana DiabeCare IIS,^[172] and Roche Diabetes care's Accu-Chek Combo^[173] deliver insulin through a tube, while Insulet's Omnipod DASH^[171] delivers insulin through a cannula rather than a tube. In addition, if you compare the battery type & life in Table 3, you can see that Medtronic, Sooil, Roche Diabetes care's products are similar and Insulet's product is different because the insulin pumps

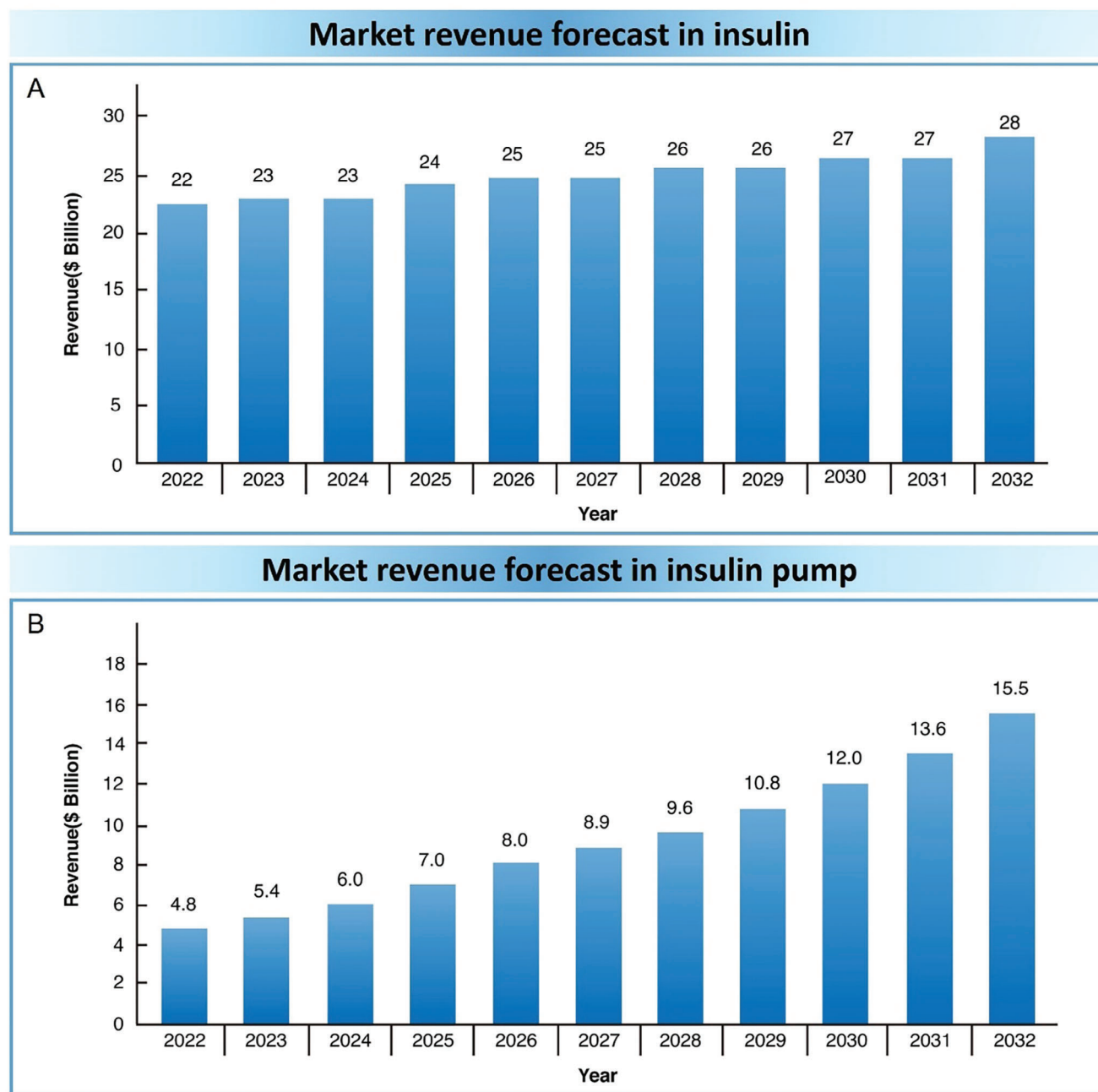


Figure 5. Forecasted insulin market revenue trends from 2022 to 2032. A) The graph of market revenue forecast in insulin from 2022 to 2032. B) The graph of market revenue forecast in insulin pump from 2022 to 2032.

of the aforementioned three companies are aimed at long-term use and guarantee 4 years of use with a single purchase, while Insulet's product is aimed at single use and replacement every 3 days. Each method has its own advantages, but the three mentioned above allow you to use the same device for a long time by replacing consumables, and this is a big advantage for patients because they don't have to learn a new method. However, these insulin pumps also require hose and needle replacement every three days, which is easier to do with the insulet product. Medtronic's MiniMed 770G is compatible with smartphones and

medical apps to communicate glucose results.^[174] It also adjusts basal settings based on CGM readings. Sooil's Dana DiabeCare IIS is highly portable, making it ideal for people who need four glucose readings per day. It's relatively inexpensive but requires the help of a healthcare professional to change your preferences. Roche Diabetes care's Accu-Chek Combo supports real-time diabetes alerts via Bluetooth connectivity and has a large capacity insulin cartridge.^[175] However, the pump is larger than some other models, making it less portable. Insulet's Omnipod DASH, as mentioned earlier, has a cannula that is automatically inserted

Table 3. Development status of insulin pump products by four major companies.

Company	Medtronic	Insulet	Sooil	Roche Diabetes care
Model	MiniMed 770G	Omnipod DASH	Dana DiabeCare IIS	Accu-Chek Combo
Dimension (mm)	53×96×24	52×36×14.5	45×91×20	56×83×21
Weight(g)	113	25	62	110
Reservoir size	300 unit	200 unit	300 unit	315 unit
Basal Increment	0.025 u	0.05 u	0.01 u	0.05
Bolus increment	0.1 u	0.05 u	0.1 u	0.1 u
Basal Delivery	5 min	5 min	4 min	3 min
Battery type & life	AA type, 4 week	Non- rechargeable, 3 day	3.6 V lithium battery 4–6 week	1.5 V AA alkaline,
Price & warranty time	5650\$ 4 year	680\$/year	4160\$ 4 year	4800\$ 4 year
Reference	[170]	[171]	[172]	[173]

rather than a tube, and is controlled by a personal diabetes monitor (Table 3).^[176] As these insulin pumps get larger, they can come with a variety of features to help you control your blood sugar. However, since these devices are now used in conjunction with various smart devices, the size and weight of the pump itself are being minimized by developing a system that can be controlled by a smart device, thus simplifying the size and weight of the device. In the case of batteries, which are the largest contributor to weight, we are developing a device that can be reduced in weight and recharged by switching from standard AA-sized alkaline batteries to lithium-ion batteries (Table 3).

8. The Evolution of Insulin Administration Methods

8.1. Traditional Insulin Delivery Using Insulin Pens

Insulin pens, among the earliest forms of insulin administration, empower patients to manage their insulin dosages manually, aligning with real-time glucose readings or in preparation for glycemic events like meal times (Figure 6A).^[177] This method involves a variety of insulin types, from those that act swiftly within a quarter-hour to those whose effects extend beyond twelve hours, facilitating a customizable approach to diabetes management tailored to individual patient scenarios. Despite the critical role insulin pens play in glucose regulation, their prolonged use, potentially over several months to years, introduces a spectrum of challenges. A significant barrier is the inherent aversion to self-administration due to the necessity of frequent injections. The use of exceedingly fine needles, generally exceeding 30G, is intended to reduce injection pain. However, the repetitive nature of injections can still foster a sense of reluctance and discomfort among users.^[178] The management of spent needles further complicates this, as they must be disposed of with caution, being classified as medical waste.^[179] Moreover, achieving precise insulin dosing proves to be a complex endeavor. The diabetes management system, incorporating insulin pens and glucose meters, operates on an open-loop principle (Figure 6B), necessitating manual verification and adjustments by the patient. This system's inherent lack of real-time, automated feedback

poses a hurdle, making the management process cumbersome and potentially heightening the risk of adverse events such as hypoglycemia.^[180,181] The reliance on insulin pens also demands that patients consider numerous variables, including current glucose levels, physiological conditions, and the nature of glycemic events, which complicates the accurate dosing of insulin. Such complexities can lead to more severe consequences like hypoglycemia. Additionally, the extended use of insulin pens places patients at continuous risk of secondary infections and dermal injuries, highlighting the need for advancements in diabetes management solutions that offer enhanced ease of use, precision, and patient safety.

8.2. Modern Insulin Administration Using Insulin Pumps

In response to the deficiencies observed in insulin pen usage, the development of insulin pump technology emerged as a pivotal advancement in the realm of automated insulin administration. Originating in the 1970s, the initial bulk of these pumps limited their utility to healthcare facilities, where they were primarily employed for inpatient diabetes management. Subsequent technological strides achieved significant reductions in the size of these devices, thereby extending their usability to individual patients while maintaining rigorous safety standards.^[154] While these spectroscopic methods utilizing light have expanded the analysis techniques available for minimally invasive and non-invasive methods, several challenges remain. These include improving device accuracy and reliability, accounting for user variability, and developing methods for continuous monitoring. Continued research is necessary to address these challenges and advance the technology. This system also empowers patients with the ability to fine-tune insulin dosages in response to real-time glucose readings, significantly diminishing the discomfort associated with the repetitive use of needles for insulin administration and thereby enhancing the treatment experience for users.^[154] The early 21st century witnessed a seminal enhancement in diabetes care with the advent of CGM technology, which, when integrated with insulin pump therapy, heralded the inception of a unified diabetes management solution (Figure 6C).^[182]

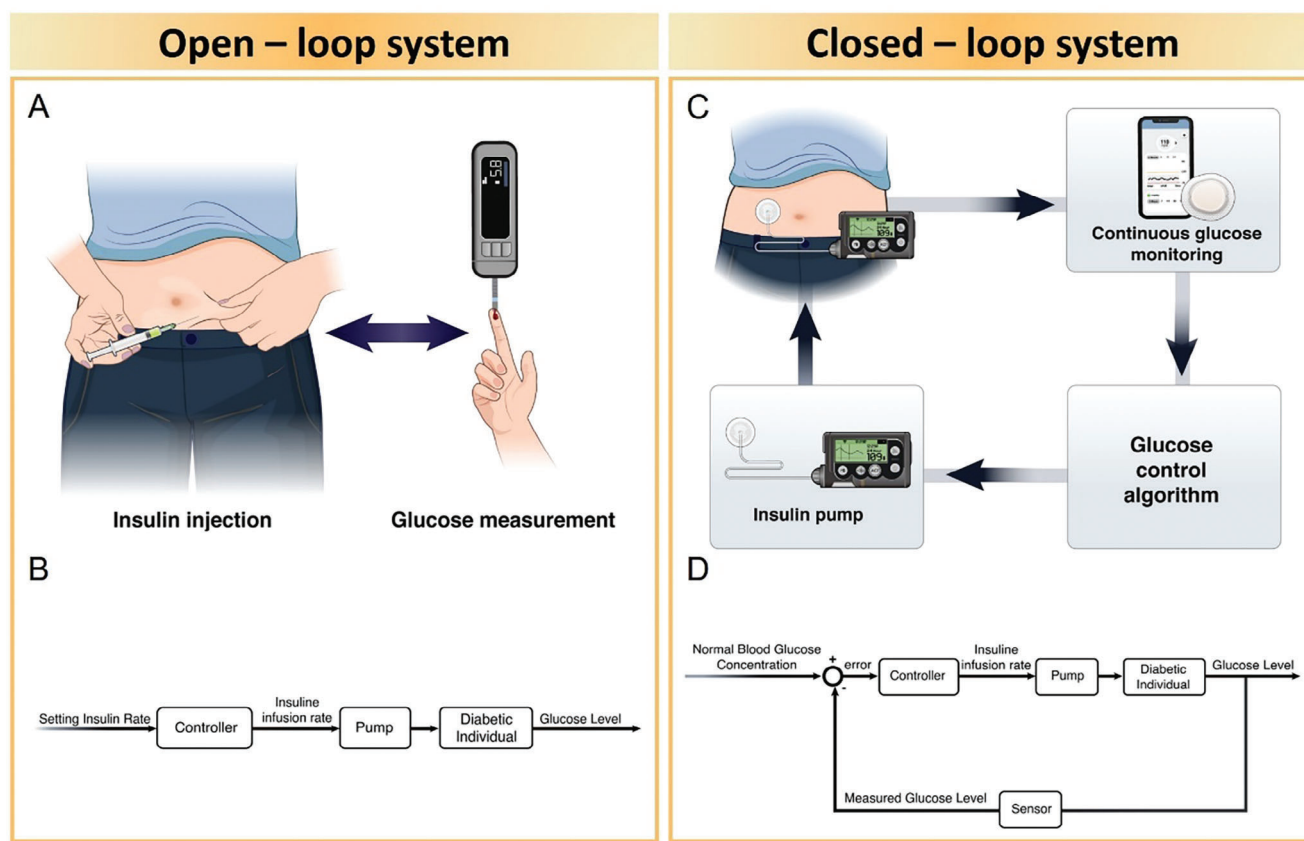


Figure 6. An illustration of a glucose management system, focusing on the measurement and control of blood glucose level. A) Open-loop diabetes management using a BGM and insulin pen.; B) Open-loop system. C) Closed-loop diabetes using a CGM and insulin pump. D) Closed-loop system.

This synergistic integration represented a paradigm shift towards an automated glucose regulation framework, wherein insulin administration is dynamically modulated based on continuous glucose data provided by the CGM system.^[183] The culmination of this technological evolution is the closed-loop system, as illustrated in Figure 6D, which automates the entire process of glucose monitoring and insulin delivery, thereby alleviating the burdens traditionally associated with diabetes management.^[184] The adoption of these integrated systems has seen a marked uptick, attributed to the substantial improvement in patient quality of life they offer. Despite these advancements, the financial implications associated with the procurement and maintenance of insulin pump and CGM systems remain a significant barrier, compounded by the recurrent costs of insulin and related consumables (Tables 2 and 3). Additionally, the efficacy of these systems is contingent upon consistent medical follow-up and patient education, underscoring the need for a committed approach to diabetes management and careful consideration of the potential dependence on these devices.^[183]

8.3. The Transformation of Glucose Management Methods Using AI Technology

The evolution of AI and machine learning in the realm of diabetes care is introducing innovative strategies for glucose

regulation.^[165,185] Previously, insulin pumps based on PID (Proportional-Integral-Derivative) controllers administered insulin and managed blood glucose levels by proportionally responding to the current blood glucose deviation. This approach was advantageous due to its simplicity, making implementation and application straightforward. However, it had limitations in non-linear systems, resulting in reduced accuracy and requiring manual tuning of parameters. Consequently, these issues could lead to hypoglycemic episodes, the most dangerous situation in blood glucose control.^[186–188] Subsequently, the MPC (Model Predictive Control) approach has become the most researched and advanced form of control. MPC uses dynamic models of processes to predict future behavior and considers current control inputs. This method has the advantage of multivariable control and predictive capabilities compared to the PID approach, significantly reducing the risk of hypoglycemia due to insulin infusion. However, the accuracy varies greatly depending on the applied model, and the design and tuning of algorithms are more complex than the PID method. Additionally, processing large amounts of data requires significant power consumption.^[189–191] In contrast, recent big data-based machine learning and AI methodologies offer advantages in creating and modifying predictive models and facilitating data acquisition compared to traditional methods. These personalized models are continuously evolving to predict immediate blood glucose events and long-term glucose trends using individual blood glucose

data, achieving accuracy within a 10% margin of error.^[192,193] The most crucial aspect of developing these predictive models is the accuracy of the predicted outcomes. In this regard, AI-based models' flexibility allows for the development of personalized models using individual blood glucose data. Additionally, using cloud-based services enables the integrated management and analysis of large datasets, separating devices from analytical systems, thus enhancing device portability and power efficiency. AI technology has the potential to promote sophisticated, patient-centric approaches to diabetes and various diseases, advancing personalized care. However, these processes still face challenges such as stringent data security management and transparency issues during the analysis phase.^[194–196]

9. The Current State of Insulin Injection Research in the Academic Field

9.1. The Discovery of Insulin and the Transformation of Diabetes Treatment

The inception of insulin in the early 20th century marked a turning point in the treatment of diabetes, with subsequent advancements in genetic engineering facilitating the mass production of diverse insulin types, thereby solidifying its role in contemporary diabetes care.^[197] Despite this progress, the administration of insulin, particularly through injections, presents challenges, including discomfort and patient aversion, especially in Type 2 diabetes where oral hypoglycemic agents are commonly preferred. However, for Type 1 diabetes and certain complex cases of Type 2 diabetes, insulin injections are not merely an option but a necessity for effective glucose control (Figure 6A). The conventional methods of insulin delivery are primarily invasive, leading to significant discomfort due to needle usage, and are associated with an increased risk of adverse effects such as infections, lipodystrophy, and skin damage over prolonged use. In response to these challenges, ongoing research and development are focused on creating minimally invasive and non-invasive insulin delivery technologies, aiming to enhance patient comfort and reduce the potential for complications.

9.2. Microneedle Injection Method

Emerging as a solution to overcome the challenges posed by traditional invasive insulin administration, the development of minimally invasive microneedle technology marks a significant leap in diabetes management. This innovative approach employs arrays of slender microneedles, each extending hundreds of micrometers, designed to deliver insulin directly upon penetration.^[60,198,199] In one variant, the needles are coated with insulin, facilitating immediate release upon insertion. Another approach incorporates biodegradable microneedles, which gradually release insulin as the material dissolves, providing a sustained supply over an extended period (Figure 7A).^[200] This microneedle system effectively bypasses the outermost skin layer to deposit insulin directly into the dermis, ensuring swift distribution via capillary networks.^[201] Compared to traditional methods, this technique significantly reduces the discomfort associated with injections, accelerates healing at the application site,

and offers a safer alternative with single-use patches that lower infection risks and diminish the generation of hazardous medical waste.^[202–204] Despite these advantages, the technology faces limitations, including the relatively short duration of insulin delivery necessitating regular patch replacement and challenges in precise dosage control.^[199] Additionally, the prolonged use of adhesive skin patches may necessitate further care due to potential allergic reactions or skin irritation not caused by the microneedles themselves but by the adhesive material.^[205]

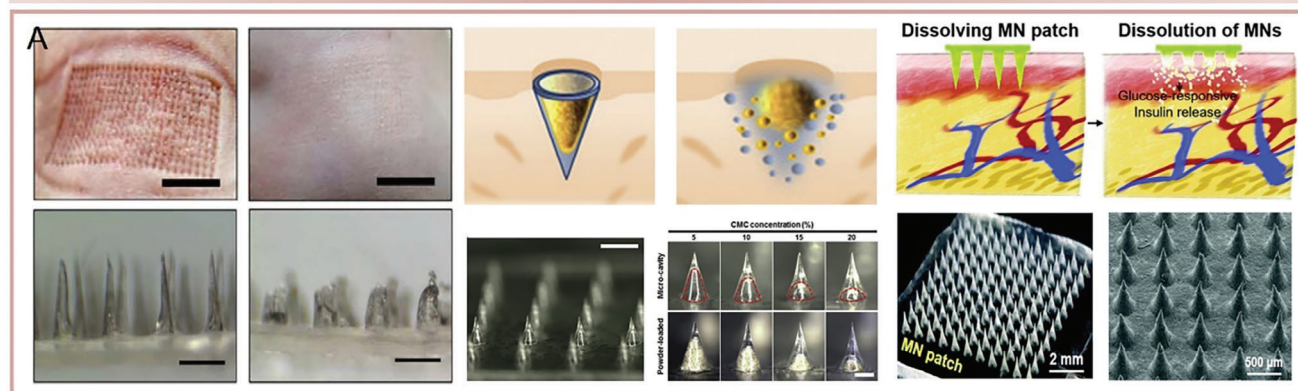
9.3. Nano Carrier Injection Method

Nanocarrier technology introduces a groundbreaking non-invasive method for insulin delivery, navigating the intricate defense mechanisms of human skin.^[201] Engineered to bypass the skin's formidable stratum corneum, which has evolved to shield the body from external physical and chemical threats, this method leverages the potential of nanoscale carriers.^[206] Traditional insulin administration methods, which involve direct subcutaneous injections, often lead to patient discomfort and heightened infection risks due to the invasive nature of needle use. The innovative approach of employing nanocarriers aims to address these issues by facilitating insulin penetration through the skin's lipidic layers without necessitating injections (Figure 7B).^[207] Given the hydrophobic nature of the skin's outermost lipid layer, the application of nanocarriers enables the efficient transdermal delivery of insulin, accommodating both hydrophilic and neutral molecules.^[208,209] This non-invasive strategy not only spares patients from the pain associated with injections but also significantly reduces the likelihood of wound-induced complications. However, the efficacy of this approach is subject to the skin's variability in terms of tissue composition and the specific site of application, which can influence the rate and extent of insulin absorption.^[210] One of the critical challenges in this domain is achieving consistent and controlled absorption levels, as many molecules may not penetrate the skin's protective barrier effectively. Furthermore, the process of synthesizing nanomaterials entails the generation of byproducts, necessitating thorough examination regarding the safety of these materials from their dermal absorption to eventual excretion.^[201] This underscores the need for extensive research and validation to ensure the long-term safety and effectiveness of nanocarrier-based insulin delivery systems.

9.4. Mechanical Assisted Injection Method

The exploration of non-invasive insulin delivery methods leveraging physical energy has made significant advancements. One such method employs electric fields, generated by electrodes attached directly to the skin, creating a pathway for charged particles, including insulin, to migrate (Figure 7C).^[211] This technique allows insulin to permeate the skin and move toward the opposing electrode, ultimately being absorbed through the subcutaneous fat layer into the body.^[209,212] Alternatively, methods utilizing ultrasound and high voltage diverge from electric field-based approaches by enhancing the mobility of skin cells themselves to facilitate insulin penetration.^[213] Typically, skin cells exhibit low permeability to insulin. However, the application of

Minimally invasive insulin delivery



Non-invasive insulin delivery

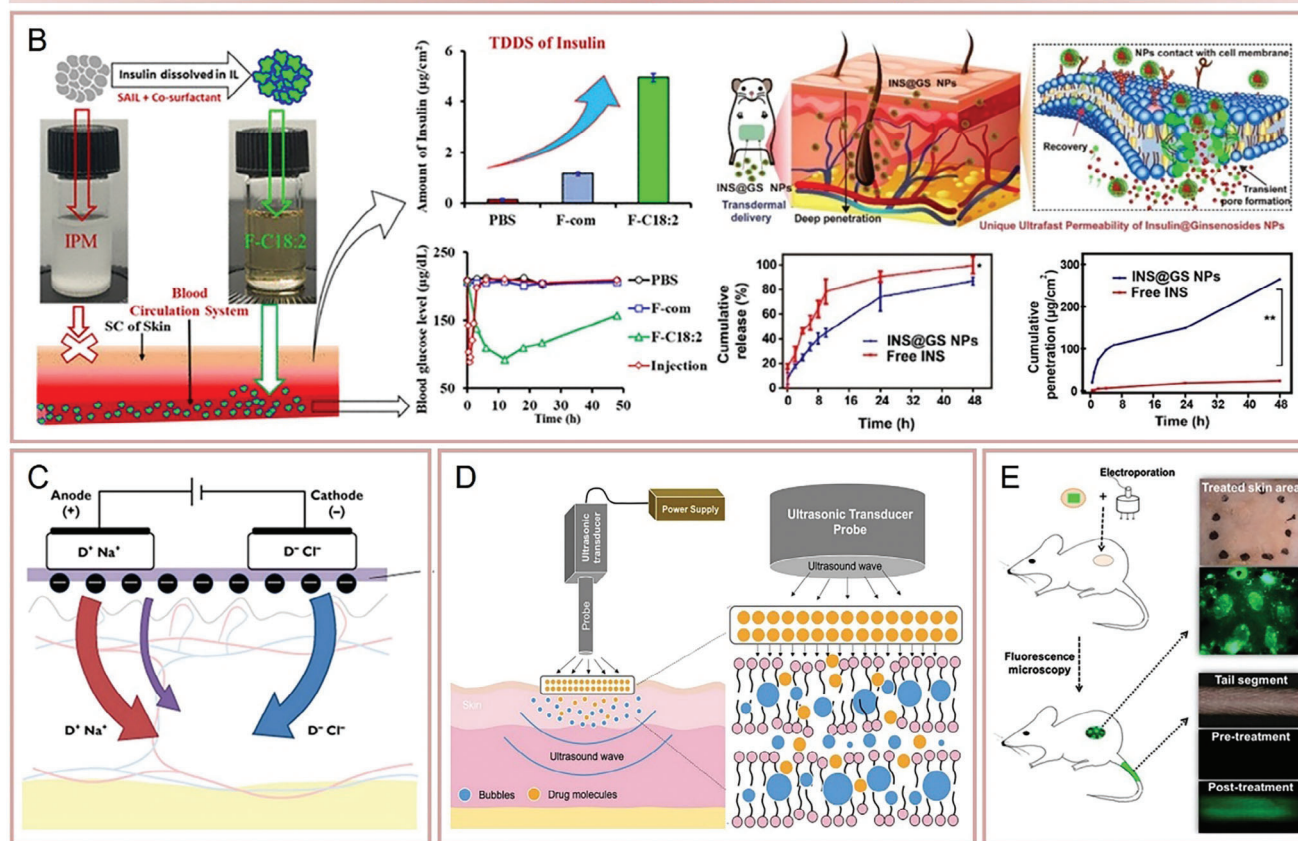
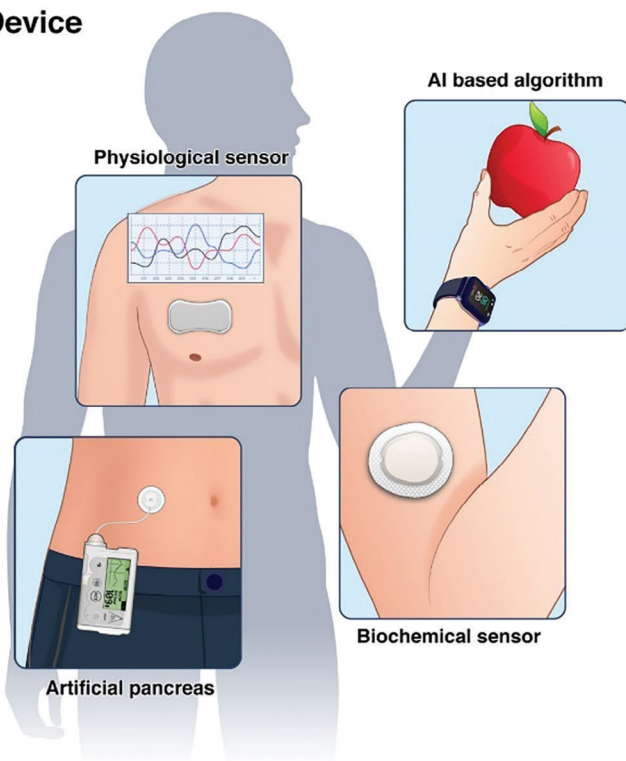
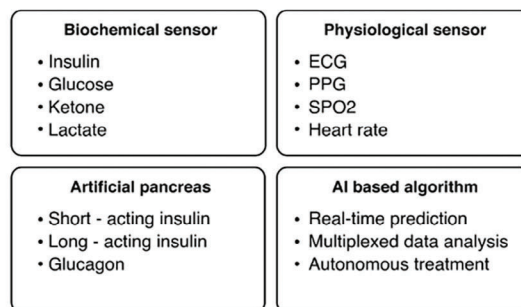


Figure 7. Various methods of insulin delivery under investigation in the academic field. A) Micro needle based minimally invasive insulin delivery. Reproduced under terms of the CC-BY license.^[202] Copyright 2018, The Authors, published by MDPI. Reproduced with permission.^[241] Copyright 2019, Elsevier. Reproduced with permission.^[242] Copyright 2021, The Royal Society of Chemistry. B) Nano carrier based non-invasive insulin delivery. Reproduced with permission.^[207] Copyright 2021, American Chemical Society. Reproduced with permission.^[243] Copyright 2021 Elsevier. C) A non-invasive insulin delivery method using microcurrents. Reproduced with permission.^[211] Copyright 2013, The British Pharmacological Society. D) A non-invasive insulin delivery method utilizing ultrasound. Reproduced with permission.^[214] Copyright 2021, Springer Nature. E) A non-invasive insulin delivery method employing high voltage. Reproduced with permission.^[215] Copyright 2013, Elsevier.

I. Device



II. System



III. Management

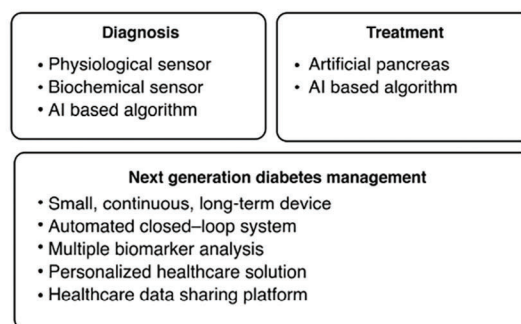


Figure 8. Schematic illustration of the future direction and essential elements of glucose management systems, focusing on advanced devices, integrated control system, and personalized management.

high-energy ultrasound or high voltage induces thermal diffusion and increases the fluidity of the lipid layers within the skin cells (Figure 7D,E). This, in turn, creates gaps in the cell membrane through which insulin can be administered.^[214,215] These mechanically assisted techniques offer the advantage of delivering higher doses of insulin compared to traditional passive delivery methods. Nonetheless, they come with challenges, including the complexity of device operation, difficulties in customizing treatment for individual patients, and potential damage to electrodes or skin tissue during the process.^[216–218] A fundamental issue with these methods is the necessity to apply the insulin solution to the skin for each administration, which can be cumbersome and less user-friendly for patients. This highlights the need for continued innovation and development in the field of insulin delivery to address these concerns and improve the overall experience for individuals managing diabetes.

10. Conclusion

With the evolution of Continuous Glucose Monitoring (CGM) and insulin pumps, a significant transformation in diabetes management is on the horizon. These advancements herald the integration of a comprehensive system composed of biochemical sensors, artificial pancreases, AI-based algorithms, and physiological sensors, promising a more holistic approach to managing diabetes. Enzyme-based glucose sensors dominate both research and the market for blood glucose monitoring. However, the inherently low thermal and chemical stability of enzyme-

based sensors presents significant challenges. To address these issues, ongoing research aims to enhance the stability of these sensors. Concurrently, alternative sensors and methodologies are being developed to measure glucose non-enzymatically in various biofluids. For these new sensors to be viable in practical applications, they must achieve improved stability and reliability while also being cost-effective.^[219–222] Unlike the current CGM systems that solely measure glucose levels, future biochemical sensors will expand their capabilities to include the measurement of insulin levels and other critical biomarkers such as ketones and lactate, directly associated with diabetic conditions.^[192,223] This enhancement will enable a more nuanced understanding of the diabetic landscape within an individual's body. In conjunction, physiological sensors will play a pivotal role by measuring everyday activity-related data, including ECG, PPG, SPO2, and heart rate.^[223] This data, when combined with the insights gained from biochemical sensors, will offer a comprehensive picture of a patient's health, encompassing both biochemical and physiological aspects. Continuous subcutaneous insulin infusion (CSII) via insulin pumps can lead to a rapid decline in insulin levels if the infusion is interrupted, as insulin is not stored subcutaneously. Additionally, there is a risk of infection at the infusion site.^[33] To address these issues and enhance the reliability of insulin pumps, efforts are being made to develop systems that can detect glucose levels and automatically deliver insulin, thereby evolving into an artificial pancreas.^[224] The advent of artificial pancreases will further revolutionize this field by not only administering short-acting and long-acting insulin but also glucagon,

thus fine-tuning insulin levels more precisely than ever before. Furthermore, new approaches to diabetes treatment are currently in the research phase.^[225–228] Methods such as loading insulin-secreting beta cells^[229,230] or creating and implanting Langerhans islets that include beta cells^[227,231,232] are being proposed. It is anticipated that when these treatments are integrated with existing systems, more effective treatment and management of diabetes will be possible.

AI-based algorithms will stand at the core of this integrated system, analyzing the multiplexed data from both biochemical and physiological sensors.^[233] These algorithms will not only provide real-time predictions but also enable autonomous treatment decisions tailored to the individual's current health status. This means that the system can diagnose and determine the most appropriate treatment method based on the analyzed data, with the AI algorithms orchestrating the automated insulin delivery through an artificial pancreas.^[166,234] This futuristic diabetes management system will be designed to be compact, durable, and capable of long-term operation, minimizing inconvenience for the user while seamlessly integrating into their daily life (Figure 8). An automated, closed-loop system will handle diagnosis and treatment, providing personalized health management solutions based on a wide array of biomarker analyses. Furthermore, the related health data will be securely transmitted to medical professionals via a shared platform, enhancing diabetes management and patient care.^[235,236] The shift in the diabetes management paradigm necessitates advancements in electrochemistry and AI technologies. Such progress will simplify glucose management, prevent severe complications, and pave the way for better treatment options and support. This integrated approach will not only enhance the quality of life for individuals with diabetes but also contribute to the broader field of personalized medicine, offering insights and treatment options tailored to the unique needs and conditions of each patient.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

CGM Market, continuous glucose monitoring, diabetes mellitus management, insulin delivery, insulin market, non – invasive glucose device

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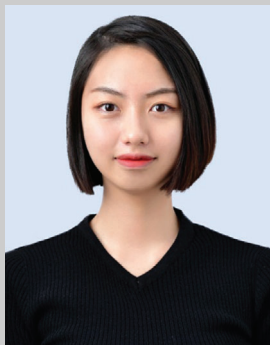
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