CHAPTER 1

INTRODUCTION

1.1 Background:

Diabetes Mellitus has advanced as the severe healthcare endemic of the contemporary world. Globally, the aggregate number of individuals with diabetes counts 382 million in 2013 and will overwhelm 592 million in 2030. Similarly, in our country (India) the total number of diabetic population has been 65.1 million in 2013 and will increase up to colossal 109 million in 2030. Overall, the numbers of diabetics are expanding at gargantuan alarming pace. At the end of 2013, nearly 5.1 million people died due to Diabetes and the health care expenditure touched the mammoth 548 United States Dollar [ADA (2014); IDF (2013)].

1.2 Problem statement and Research motivation:

A patient with 20 years of diabetic history, who monitors his/her blood glucose levels 3 to 4 times/day, will prick his/her body more than 21,900 times. This action indicates towards increased infection risks, inconveniences, discomfort (both mental and physical), pain, and high cost per measurement. Further, the invasive procedure lacks potentiality for measuring medically serious fluctuations in blood glucose levels during sleep or driving. Henceforth, any incident of low or high blood glucose levels may remain unnoticed or incurable. In contrast, the Noninvasive technique based blood glucose monitoring does not require blood samples for measurement purposes. In view of that, the noninvasive approach will deliver great advantages to relieve the diabetic patients from such aforementioned complex situations [So *et al.* (2012); Lam (2008)].

Diabetes related landmark studies mainly include **Diabetes Control and Complications Trial (DCCT)** conducted by the United States **National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).** Similarly, **Medical Research Council, Oxford University, England** sponsored **United Kingdom Prospective Diabetes Study (UKPDS)**, which has been designed, run, and completed by late Professor Rury Holman and Professor Robert Turner. In both the research documents of aforementioned studies states, that Diabetes associated major medical complications as depicted in figure 1.1 relies on the degree of blood glucose level-control by the respective Type I and Type II Diabetic subjects. Furthermore, degree of blood glucose level-control depends solely on the proper diet, effective blood glucose monitoring, and medications respectively [IDF (2013); Tuchin (2009); UKPDS (2008); DCCT (1993)].

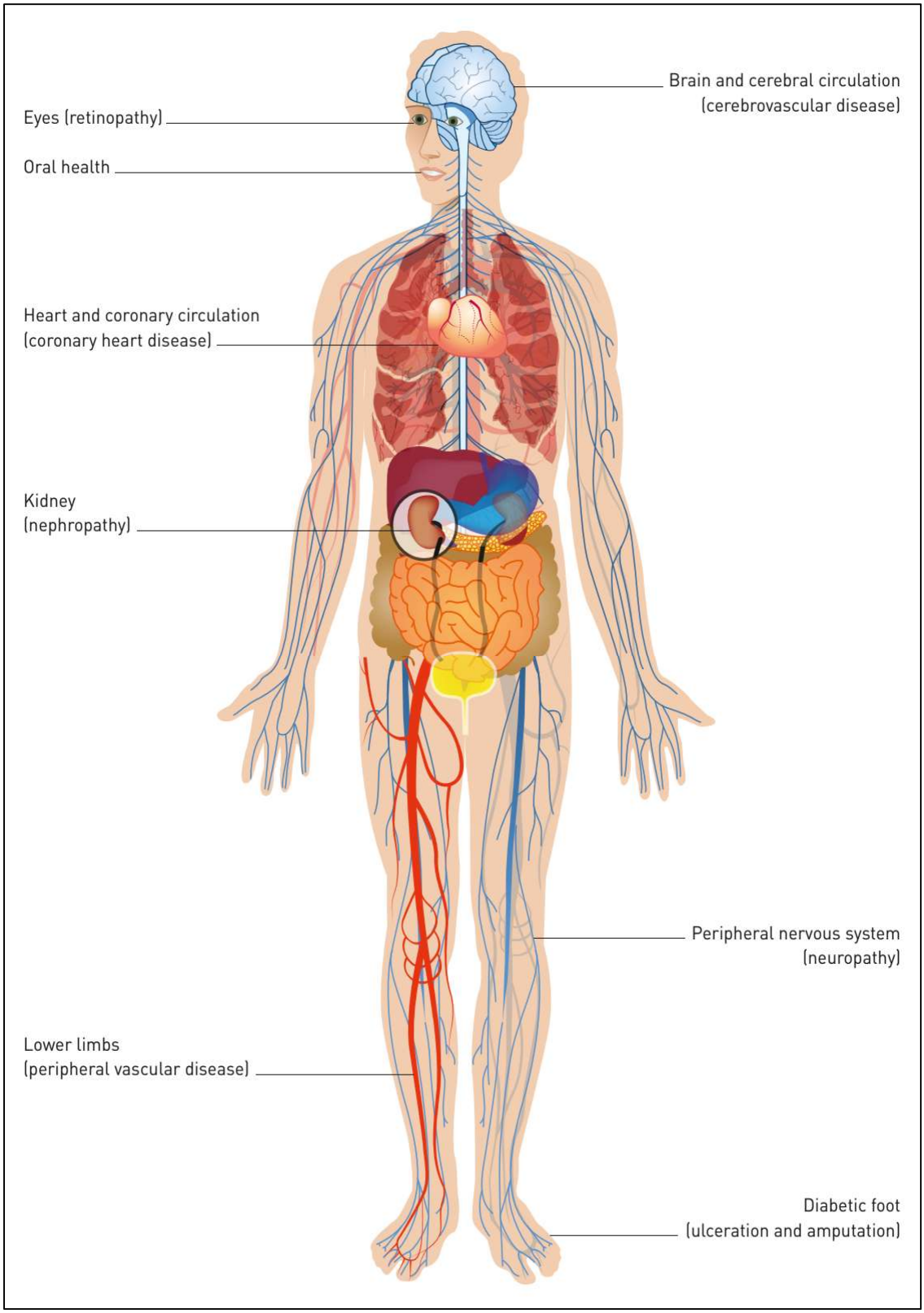

Figure 1.1: Major long-term medical complications in diabetic subjects [IDF (2013)].

Hence, effective monitoring of blood glucose levels in diabetic patients for 24 hours is the primary mandate towards proper diabetes care and management. For instance, when one knows about the glucose levels of the patients, it helps in determining the proper diet and right course of treatment for him/her [ADA (2014)].

As per the currently prevalent invasive systems, for measuring the blood glucose concentrations in the diabetic patients, one of his/her finger/body part puncturing is essential to collect a drop of blood. Afterwards, the glucose meter analyzes the glucose concentration in the biochemical composition of that blood drop and displays it in mg/dl or mmol/l [Tuchin (2009); Lam (2008); Watkins (2003)].

The diabetic patients are generally unwilling to check their glucose levels at regular intervals as prescribed by the clinicians. As the invasive procedure harms the skin and causes some pains too. Owing to such unwillingness of the patients, investigations related to optical noninvasive blood glucose measurement techniques have proliferated in last 20 years or so on [Tuchin (2009); Lam (2008); Watkins (2003)].

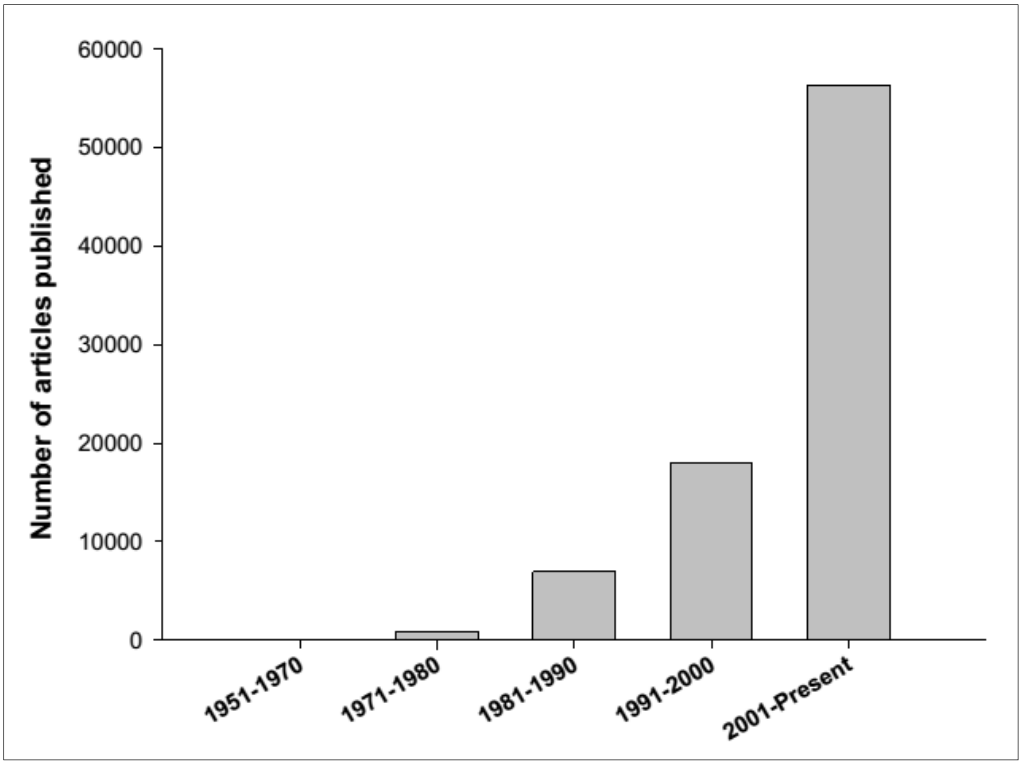

Figure 1.2: The number of research articles on glucose monitoring throughout the stated period [Vashist 2013].

The figure 1.2 depicts the number of articles published in glucose monitoring during last six decades. Increased research activity in last two/three decades reflects the demand for blood glucose monitoring techniques due to steep rise in the diabetic population in this contemporary world [Vashist 2013].

The noninvasive concept arises more than 02 decades ago and numerous researchers had introduced several noninvasive techniques with varying results. However, their results showed a very little effect over the current invasive techniques. Reliability is essential. For the healthy management of diabetes in all types of patients, an accurate in-vivo blood glucose concentration monitoring expertise would be valuable. However, presently available noninvasive techniques are not enough accurate to replace the conventional invasive technology [Yadav *et al.* (2015)].

In perspective of addressing the requirement for this necessity, the present thesis work represents our indigenously developed modulated ultrasound and infrared light-based noninvasive technique for blood glucose measurement in the human subjects.

Further, invasive, and noninvasive blood glucose measurements on all the study subjects were-performed under the controlled conditions of temperature and humidity respectively. Significantly, the useful technique must be free from any harmful bio effects or biohazard chemical agents that cause instantaneous or long-term health related ailments. Generally, the light-based approaches satisfy these aspects. Various such techniques include Raman spectroscopy, Absorption spectroscopy, Polarization techniques, and linear scattering spectroscopy [Yadav *et al.* (2015); Tuchin (2009)].

However, NIR spectroscopy appears to be the most promising technique that will expedite the development of noninvasive blood glucose level measurement techniques [Yadav *et al.* (2015); Tuchin (2009)].

The noninvasive blood glucose determination is feasible by NIR spectroscopy or other optical techniques. Further, many scientists prefer to utilize NIR spectroscopy techniques than other optical techniques for noninvasive blood glucose measurements [Chowdhury *et al.* (2015); So *et al.* (2012)].

Various published results depict positive enhancement in infrared light-based spectroscopy techniques, ultrasonic techniques, and methodologies respectively [So *et al.* (2012); Tuchin (2009); Lam (2008)].

NIR spectroscopy utilizes light wavelength from 750-2500 nm (nanometer), which interacts with the living tissues by means of low energy radiations. NIR wavelengths infiltrates much deeper into the body parts as compared to white light or MIR radiations [Yadav *et al.* (2015); Tuchin (2009)].

Further, NIR wavelength region possess multiple windows in which hemoglobin, lipid and water absorption characteristics are adequately low to permit light transmission through the tissue, facilitating noninvasive measurements. Hence, the explicit absorption characteristics of compounds pertinent for clinical investigation and noninvasive techniques will assist in its harmless and useful in-vivo quantifications. Among the above-mentioned noninvasive approaches, the NIR spectroscopy is important and extensively explored approach for quantification of blood glucose [Chowdhury *et al.* (2015); Yadav *et al.* (2015); So *et al.* (2012)].

More significantly, the NIR technique provides more stability; good signal to noise ratios within normal room conditions and minimum interferences from other biological constituents provides an added advantage [So *et al.* (2012); Raghavachari (2001)].

Zhu *et al.* (2013) and Zhu et al. (2010) demonstrated a new hybridized technique of utilizing ultrasound modulated optical technique for noninvasive blood glucose measurements. Measurement of modulation depth through ultrasound modulated scattered light produces significant in-vitro results. However, their technique lacks data regarding in-vivo experiments.

They had applied ultrasound with light modulation techniques [Zhu *et al.* (2013); Zhu *et al.* (2010)]. However, in our application, the modulated ultrasound utilized produces vibration inside the measurement site and the infrared light quantity those molecule specific vibrations for noninvasive measurement of blood glucose levels in the human subjects [Chowdhury *et al.* (2015)].

Hence, the development of a non-invasive technique for detecting the blood glucose levels will significantly improve the comfort level of the diabetic patients. Further, it will improve their acquiescence for regular blood glucose monitoring and will impede the pace of diabetes related medical complexities and mortality rate.

1.3 Aim and Objective of the present thesis work:

The main aim of this present thesis work is to develop noninvasive technique based prototype unit for blood glucose measurement in human subjects.

Secondly, the main experimental objective includes analyzing and validating our noninvasive technique based prototype unit for blood glucose measurement in human subjects.

The aim and objective based sequential clinical correlation study followed in this present thesis work are as follows:

- To study the role of Amplitude Modulated Ultrasonic waves and Infra-Red (IR) light in the noninvasive detection of blood glucose levels.
- To study the Influence of glucose concentration upon light transport phenomenon.
- To perform clinical correlation based study over healthy normal, pre-diabetic, and diabetic subjects for measuring invasive and noninvasive blood glucose levels.
- To perform clinical correlation based study over healthy normal and diabetic subjects to establish blood glucose relationship with Blood Pressure and Glycated Hemoglobin levels respectively.
- Comparison with the published data in English language based research literatures and various statistical evaluations to judge the significance of our clinical study.

1.4 Research Contributions of the present thesis work:

- Development of amplitude modulated ultrasound and infrared light based technique for noninvasive blood glucose measurement.
- Selection of 40 kHz (kilohertz) ultrasound transmitter to provide vibration inside the measurement site (fingertip).
- Selection and testing 940 nm LED for noninvasive blood glucose-induced signal acquisition purposes.
- In-vitro experiments using aqueous glucose concentration, quasi finger systems to verify our noninvasive technique for performing in-vivo clinical studies.
- Researching and testing blood glucose level variation correlation with the respective change in peak-to-peak amplitude in the Fast Fourier Transform domain.
- Calibration based Look-Up Table preparation to relate clinical correlation between peak amplitude in Fast Fourier Transform domain with the actual blood glucose level in human subjects.
- In-vivo clinical experiments for correlating invasive and noninvasive blood glucose levels in Normal, Pre-diabetic and Diabetic subjects during Fasting, Postprandial, and Random stages respectively.
- In-vivo clinical experiments for correlating the HbA1c (Glycated Hemoglobin) values relationship with the Blood Glucose concentration levels.
- In-vivo clinical experiments for correlating the Blood Pressure with the Blood Glucose concentration levels.

1.5 Outcome of the present thesis work:

- Our indigenously developed noninvasive technique based prototype measures blood glucose levels in Normal, Prediabetic, and Diabetic Subjects respectively.
- Our prototype measures noninvasive blood glucose levels between 70 mg/dl to 250 mg/dl ranges with an acceptable clinical significance as verified by the Error Grid and Statistical Analysis.

1.6 Thesis Organization:

The present thesis contains seven subsequent chapters. The brief outlines of these chapters are as follows:

Chapter-1 Introduction:

This chapter briefly introduces the present scenario regarding regular blood glucose monitoring in diabetic subjects and the essential need for noninvasive blood glucose monitoring technique.

In perspective of addressing the requirements for this necessity, the present chapter briefly portrays the aims and objectives, research contributions and outcome of the present thesis work.

The thesis organization section concisely highlights all the chapters present in this thesis. Further, it contains the full list of published research articles and honors received.

Chapter-2 Literature review:

This chapter provides brief illustration about Diabetes Mellitus, its related medical complications, and blood glucose monitoring techniques.

This section concisely describes various developing noninvasive blood glucose measuring methods and their respective prototypes, mechanism for physiological blood glucose regulation and skin tissue characteristics, optical clearing effect related studies, in-vivo and in-vitro experiments, Glycated hemoglobin and blood pressure relation with blood glucose, and various additional effects.

Chapter-3 Concept, prototype fabrication, and methodology:

This chapter represents the combined concept of Amplitude Modulated Ultrasonic waves and Infrared light-based approach for noninvasive measurement of blood glucose levels.

This chapter describes the block diagram of our fabricated prototype unit including its light wavelength and ultrasound frequency selection criterions, calibration aspects, in-vitro, and preliminary in-vivo results.

Further, this chapter includes concise description of the Clarke error grid and statistical analysis based approaches for measuring the accuracy performance of our prototype unit in measuring predicted blood glucose levels.

Chapter-4 Effect of glucose concentration on light transmission:

This chapter represents the clinical study based on the optical clearing effect of blood glucose concentration over light transmission. The refractive index between the scattering agents and their respective adjacent media decreases with increase in blood glucose concentration levels. This phenomenon causes smaller scattering coefficients and accordingly shorter optical path lengths leading to increased optical clearing effects

Chapter-5 Clinical investigation based results:

This chapter reports the clinical investigation based results of our noninvasive technique applied over

(i) Healthy non-diabetic,

(ii) Pre-diabetic, and

(iii) Diabetic human subjects for blood glucose measurement purposes.

All the clinical investigations mainly focus over noninvasive blood glucose level determining aspects and its clinically significant correlations with the invasive blood glucose measurements.

Various clinical studies reported here include

(i) Standard Oral Glucose Tolerance tests,

(ii) Blood glucose level measurements during fasting stage, postprandial stage and random stage respectively.

Further, it contain results about the clinical correlations of the blood glucose levels relationship with the

(i) Glycated hemoglobin (HbA1c) concentration and

(ii) Blood pressure values in healthy normal and diabetic subjects.

This section also includes comparison of our results with the published results to measure the performance index of our prototype unit in noninvasive blood glucose measurement.

Chapter-6 Discussion:

This chapter contains brief description of our overall study and the medical importance of our results. Henceforth, it compares our overall blood glucose measurements with the published data available in the English language based research literatures.

Further, various statistical methods such as:

(i) Clarke Error Grid analysis

(ii) Parkes Error Grid analysis

(iii) Accuracy Measure analysis

(iv) Pearson Correlation analysis

(v) Rank Correlation analysis

(vi) Bland Altman plot analysis

(vii) Mountain plot analysis

(viii) Independent sample t test based analysis

(ix) CUSUM test for linearity and,

(x) Deming Regression analysis evaluates the statistical significance of our overall results.

Chapter-7 Conclusion and future work related recommendations:

This chapter presents the conclusion of the present thesis work and direction for future research work.

Afterwards, the reference portion enlists overall research papers utilized to pursue this present work.