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A Novel Method for Blood Glucose Measurement by Noninvasive Technique Using Laser

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***Abstract*—**A method and apparatus for noninvasive measurement of blood glucose concentration based on transilluminated laser beam via the Index Finger has been reported in this paper. This method depends on atomic gas (He-Ne) laser operating at 632.8nm wavelength. During measurement, the index finger is inserted into the glucose sensing unit, the transilluminated optical signal is converted into an electrical signal, compared with the reference electrical signal, and the obtained difference signal is processed by signal processing unit which presents the results in the form of blood glucose concentration. This method would enable the monitoring blood glucose level of the diabetic patient continuously, safely and noninvasively.

***Keywords*—**Anisotropy factor, Blood glucose, Diabetes Mellitus, Noninvasive method, Photo detectors.

I. INTRODUCTION

DIABETES Mellitus has probably been known to medical science longer than any other hereditary metabolic disease. It is a chronic, deliberating and costly disease, causing severe complications including blindness, cardiac and kidney failure. Twenty years ago, diabetes was considered as an uncommon disease with an adult prevalence of 1.3 percent. The latest World Health Organization estimate (for the number of people worldwide, in 2000) is 177 million. This will increase to atleast 300 million by the year 2025[1]. Many methods for measurement of diabetes mellitus which influence the tissue blood flow have been reported over the years.

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The principles of those methods are based on widely different physical phenomena such as changes in electrical impedance or optical conductance, clearance of radioactive tracers or heat, and changes in surface temperature due to alterations in the degree of vascularization. No one of those methods has to date been generally accepted as superior to the others, however, and there is still a demand for a versatile method for measurement of tissue blood flow that can be used both in clinic and experimental medicine.

The possibility to study circulation of he human skin by a laser Doppler technique was first pointed out by Stern in 1975[2]. By illuminating the skin surface with the light beam from a 15 mW Helium Neon (He-Ne) laser selective irradiation of the cutaneous blood flow was accomplished. The reflected portion of the incident beam was found to be spectrally broadened by the Doppler effect. This phenomenon is primarily caused by the frequency shift of radiation scattered in moving red cells in the superficial blood vessels.

A portable laser Doppler instrument, which made possible clinical measurements of the skin blood flow, was later constructed by Holloway and Watkins[3], and comparisons between the laser Doppler technique and the ^{133} Xenonclearance technique in measurement of the blood flow of forearm skin were made.

As the method was improved, a significant problem caused by mode interference in the laser cavity occurred. This mode interference has its origin in internal modulation of different longitudinal modes in multimode lasers [4].

In heterodyne detection by a square- law photodetector beat frequencies between different laser- modes in an unstable multimode laser are manifested as intermittent noise-like signals sweeping through the frequency range under study. This high amplitude noise which is present for approximately one – half of the observation time, allows measurements to be made only during noise-free periods [5].

Attempts have been made to eliminate the mode interference noise by introducing a single-mode laser as a monochromatic light source. Such a laser may have a short resonance cavity or utilize etalon as a mode discriminator [6]. The low power output of the former and the large size of the latter however, call for a still better solution to make laser

Doppler Flowmetry a useful technique for clinical evaluation of microcirculatory and metabolic disorders like Diabetes Mellitus.

Some of the methods existing already are in the intensity measuring instruments, including the Rosenthal instrument, suffer from the noise level of the measured signal is affected by the components of the tissue other than blood, and variation in tissue temperature, ambient temperature, and the amplitude of the laser source. Also the absorption due to the glucose concentration is very small compared to other components such that statistical errors may be greater component of the determine value that the actual glucose component [7].

Linearly- polarized light through the anterior chamber of an excised human eye and determine the glucose level of the aqueous eye humor based on the phase shift between the reference signal and the measurement signal that was converted by the glucose. Therefore, the frequency of rotation of the motor falls into the frequency range (1 Hz to 600 Hz) of mechanical vibrations produced by the different sources interferes with those mechanical vibrations and produces high measurement noise [8].

With chemical bio-sensors having a limited life span due to bio-fouling, optical sensors are a promising alternative, being less susceptible to bio-fouling from blood protein absorption. Proposed optical techniques include polarimetry, Raman spectroscopy, absorption [9] and reflectance spectroscopy [10]. Near – infrared spectroscopy can be used for analysis of biofluids such as whole blood, plasma, or serum. These optical methods have been widely used for non-invasive glucose monitoring. However, due to challenges of interference, poor signal strength, and calibration issues; they are not yet accurate enough for clinical use. These challenges would be reduced if the optical sensor had direct access to interstitial fluid or blood plasma, which would be made possible by a small and low power He- Ne laser.

There is major wavelength bands that have shown promising correlation between their absorption spectra and glucose concentration: that is 632.8 nm and this band has been shown to be very effective for predicting glucose concentration.

The purpose of this paper is to describe a method for reduction of the adverse effects of mode interference and wide-band beam amplitude noise in laser Doppler blood flow studies, with the utilization of a low-cost He-Ne- laser as a light source.

This method would enable the monitoring blood glucose level of the diabetic patient continuously, safely and noninvasively. Use of noninvasively technique offers several advantages, such as the absence of pain and exposure to sharp object and biohazard materials.

II. LASER OUTPUT FIELD

Generally the total output field which can be described as in the form

$$D_{out}(t) = b \sum_{m=-M}^{M} \tilde{D}_m(t) e^{-j\omega_m^0 t} \quad (1)$$

Where b is a coupling factor, $\tilde{D}^0_m(t)$ is the complex time-dependent amplitude of the mth mode, and ω^0_m is the mode frequency [11]. The longitudinal modes are separated in frequency by $\omega^0_m - \omega^0_{m-1} = c/2l$, where c is the velocity of light and l is the optical path length of the laser cavity. The length of the laser cavity and the linewidth of the temperature-broadened the neon resonance are determined by the number of modes.

Due to the nonlinearities in the laser medium, the real multimode laser the absolute value of the amplitude $|\tilde{D}^0_m(t)|$ of the individual modes may vary widely, although the total laser output intensity is fairly constant [12]. By mode interference of the different laser modes, the unstable amplitude conditions result in a slowly varying frequency component in the light beating spectrum will be caused. The measurements were made possibly during noise - free periods only. Unfortunately, this high amplitude noise interacts strongly with the blood flow related Doppler-signal, thereby making measurements possible in the noise free conditions.
In addition to mode interference equilibrium, the wide-band beam amplitude noise also make worse by the signal to noise ratio in customary condition laser Doppler Flowmetry.

III. REFLECTED FIELD

The laser beam is directed towards the tissue which is under study where absorption and scattering occurs during measurement. Radiation scattered due to the movable structure, such as red cells, is shifted in the frequency as per the Doppler effect, while radiation scattered in nonmoving soft tissue is unshifted in the frequency. A portion of the total scattered radiation is brought to impinge on the surface of a photo detector. Since the effective radiation penetration depth is approximately 1 millimeter in soft tissue [13]-[15], scattering and absorption takes place primarily in the papilla region and the underlying corium [16] two dermal layers containing many complex interrelating capillary network of the skin.

The total field D_T (t, r) reaching the position x at the photosensitive area of the detector at time t is expressed as

$$D_T(t,x) = \sum_{m=-M}^{M} (D_{Rm}(t,x) + D_{Qm}(t,x) \quad (2)$$

D_{Rm} (t, x) is the complex electromagnetic field produced by the mth laser-mode and scattered due to the nonmoving structures

$$D_{Rm}(t,x) = \underset{Rm}{\overset{\sim 0}{D}}(t,x)\, e^{-j\omega_m t} \quad (3)$$

This component of the total field, corresponding to the reference beam in ordinary heterodyne light beating process is, therefore, unshifted in the frequency, but has a randomly fluctuating phase factor and, if the laser is not stabilized, a time dependent absolute value of the complex amplitude $\tilde{D}^0_{Rm}$ (t, x) (7).

D_{Qm} (t, x) is the complex electromagnetic field produced by the mth laser-mode and scattered in movable structure like red cells. If the Doppler frequency shift is small in comparison with ω^0_m the field can be considered a narrow-band random process and expressed in the form

$$D_{Qm}(t,x) = \tilde{z}_m(t,x)\, e^{-j\omega_m^0 t} \quad (4)$$

Where $\tilde{z}_m$ (t, x) is the narrow-band complex amplitude of the field scattered in movable structures.

IV. PHOTODETECTOR CURRENT

The values arbitrarily close to but greater than zero photocurrent I (t, x) produced by the field D_T (t, x) at position x on the photosensitive area of the detector is proportional to the instantaneous intensity when the noise is neglected [17]-[18].

$$i(t,x) = K(D_T(t,x)\, D_T^*(t,x)) \quad (5)$$

Where K is instrumentation constant including the quantum efficiency of the detector and the asterisk denotes the complex conjugate.

Inserting the expressions for the total field equations (2)-(4) in (5) gives

$$i(t,x) = K\left(\sum_{m=-M}^{M} (\tilde{D}_{Rm}^{0}(t,x)) e^{-j\omega_m^0 t} + \tilde{z}_m(t,x) e^{-j\omega_m^0 t} \right) \left(\sum_{l=-M}^{M} (\tilde{D}_{Rl}^{0*}(t,x))\, e^{+j\omega_l^0 t} + \tilde{z}_l^{*}(t,x) e^{+j\omega_l^0 t} \right) \quad (6)$$

As a conclusion derived through the derived expression the narrow-band nature of D_{Sm} (t, x) the spectral power of the photocurrent will be concentrated around the discrete frequencies which are mode-spacing frequency multiples. If the photo detector output signal is low-pass filtered only terms with indexes l = 1 in (6) need be considered and the photocurrent can be expressed in the form

$$i(t,x) = K \sum_{m=-m}^{m} \tilde{D}_{Rm}^{0}(t,x) + \mathrm{K} \sum_{m=-M}^{M} \tilde{z}_m(t,x)) + \mathrm{K} \sum_{m=-M}^{M} (\tilde{D}_{Rm}^{0}(t,x)\, \tilde{z}_m^{0*}(t,x) + \tilde{D}_{Rm}^{0*}(t,x)\, \tilde{z}_m(t,x)) \quad (7)$$

The integration of the overall photosensitive area current of the radiation intensity of the total photocurrent i(t) which are impinged is given

$$i(t) = i_R(t) + i_{QR}(T) + \eta K(\tilde{D}_R^{0}(t) + \tilde{D}_R^{0*}(t)\, \tilde{z}^{*}(t) + \tilde{D}_R^{0*}(T)\, \tilde{z}(t)) \quad (8)$$

The first term in the equation (8) is represented the current produced by the beam unshifted in frequency. The dc current component is the stable-mode amplitudes of the light source.

The second term in the equation (8) corresponds to heterodyne mixing of the unshifted frequency field and shifted frequency field on the photosensitive area of the photo detector. Stochastic fluctuations in phase over the detector area will generate a total light beating current according to the central limit theorem, obeys Gaussian statistics. The effect of incomplete spatial coherence over the detector area is considered by the introduction of the heterodyne efficiency η(|η|≤ 1).

In the multimode laser source, if no amplitude uncertainty are presented as well as the flow under study is assumed to be stationary, the first term in the equation (8) is independent of time and the mean value of the photocurrent i(t) can be written as

$$\langle i(t) \rangle = i_R + \langle i_Q \rangle \quad (9)$$

Since the optical field is a Gaussian random process the autocorrelation function of the low-pass filtered photocurrent can be expressed in the form [19].

$$\langle i(0)\, i(\iota) \rangle = i_R^2 + 2 i_R \langle i_Q \rangle + \langle i_Q \rangle^2 + \eta^2 \langle i_Q \rangle^2 g_Q(\iota)^2 + \eta^2 i_R \langle i_Q \rangle (e^{+j\omega_l^0} g_Q(\iota) + e^{-j\omega_l^0} g_Q^*(\iota)) \quad (10)$$

The normalized autocorrelation function for the optical field scattered due to the moving structure is $g_Q(\tau)$.

The photocurrent spectrum P_i (ω) can be calculated according to the Wiener-Khintchine theorem, the photocurrent autocorrelation function[20].

$$P_i(\omega) = \frac{1}{2\pi} \int_{-\infty}^{+\infty} \langle i(0)\, i(\iota) \rangle e^{-j\omega\iota}\, d\iota \quad (11)$$

The homodyne part of the spectrum will generally give rise to frequency expansion while the heterodyne part is unchanged in shape to the corresponding optical spectrum. A thorough review of light beating spectroscopy has been presented by Cummins and Swinney [20] and more recently by Berne and Pecora [21].

The standards deviation (rms value) of the photocurrent can be calculated according to

$$0_i^2 = \langle i(t)^2 \rangle - \langle i(t) \rangle^2 \quad (12)$$

Inserting (10) with τ = 0 and (9) in (12) gives

$$0_i^2 = \eta^2 \left(\langle i_Q \rangle^2 + 2 i_R \langle i_Q \rangle \right) \quad (13)$$

and

$$i(t) \in M(i_R + (i_R + \langle i_Q \rangle, \sigma_i) \quad (14)$$

If the major portion of the radiation incident on the skin is scattered in nonmoving tissue, i_R >> $\langle i_Q \rangle$ and the homodyne part of the photocurrent spectrum may be neglected. Under this condition $\langle i_Q \rangle$ can be considered proportional to i_R and

$$\langle i_Q \rangle = u^2\, i_R \quad (15)$$

Where u^2 is a constant related to the density of moving scatterers. The photocurrent is then determined by the heterodyne beating of the shifted and unshifted frequency beams alone and

$$i(t) \in M(i_R, \sqrt{2}\, \eta u i_R \quad (16)$$

The instantaneous value of i(t) may, therefore, be expressed in the form

$$i(t) = i_R\, (1 + A(t)) \quad (17)$$

Where A(t) is Gaussian distributed and

$$A(t) \in M(0, \sqrt{2}\, \eta u) \quad (18)$$

The effect of mode interference on the photo detector current can be represented as a noise component Q(t).i(t) with

zero mean value, superimposed on the detector current i(t). If also the wide-band noise of the laser beam ($M_L(t)$) and the photo detector dark current and short noise ($M_D(t)$) [22], both assumed to be Gaussian random variables, are considered, the total photocurrent i_M (t) can be written as

$$i_M(t) = i(t)(1+Q(t))(1+M_L(t)(1+M_D(t)) \quad (19)$$

Where $M_L(t) \in M(0,\sigma_L)$ (σ^2_L is the variance of the wide-band laser beam noise) and $M_D(t) \in M(0, \sqrt{2e\Delta f/i_R})$ (e is the electron charge and Δf is the sampling bandwidth). Inserting (17) in (19) gives

$$i_M(t) = i_R(1+A(t))(1+Q(t))(1+M_L(t))(1+M_D(t)) \quad (20)$$

V. MATERIALS AND METHODS

A noninvasive glucose monitor process optical signals transmitted through or reflected by the stratum Corneum, dermis and epidermis layers, subcutaneous tissue, interstitial fluid and blood vessels (both arterial and venous blood), which represent independent compartments. We approach the problem by means of following steps: (a) collecting noninvasive signals from non diabetic individuals and diabetic patients; (b) simultaneously measuring blood glucose concentrations by an invasive method; and (c) computing the values based on the correlation between measured blood glucose values and noninvasive optical signals.

A. Laser Multisensor Meter

This instrument is based on the principle that photons which are back scattering and transillumination on the tissue surface close to their point of injection mostly travel in the superficial layers, whereas, those remitted farther away radially on the surface mostly originate from the deeper layers [23] , [24].

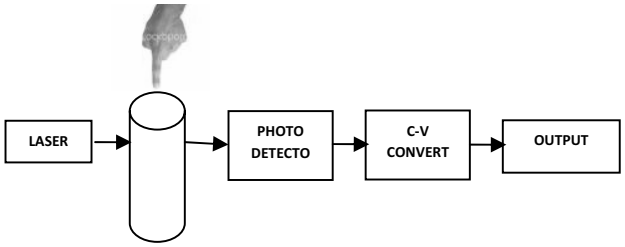

Fig.1 The schematic of the multi-sensor block diagram

The schematic of the multi-sensor meter is shown in the Figure.1.Laser light beam of 0.8- mm diameter from a laser source module (SIL – 5X, Suresh Indu Laser, India), which is a compact atomic gas (He –Ne) laser of 5 mW power, operating at 632.8nm, was directed to the glucose sensing unit, where the Index finger is placed.

The diffusely backscattered light and transilluminated light from the tissue surface are collected by the optical detectors. These sensors are arranged at circular arrangements.

The light signals from the tissue surface are collected by optical detectors (L14G3, Fairchild). The current outputs of these photo detector where converted into their proportional voltages by conventional method.

B. Tissue optical properties

To measure absorption coefficient μ_a, scattering coefficient μ_S, reduced scattering coefficient μ_S' and anisotropy factor 'g' of circulating human blood. At 632.8 nm approximately 633 nm the optical properties of human blood with less percentage of hematocrit and maximum of 98% oxygen saturation were found to be 2.10± 0.02 cm^{-1} for μ_a , 773± 0.5 cm^{-1} for μ_S , and 0.994± 0.001 for the g factor. An increase of the hematocrit upto 50% led to increase of absorption and reduction of scattering linearly. Variation in physiological condition led to changes of all three parameters, while variations in the oxygen saturation led only to significant change in the absorption coefficient. Spectra of all three parameters were measured in the wavelength range of 400 to 2500 nm according to oxygenated and deoxygenated blood; the results showed that blood absorption follows the absorption behaviour of hemoglobin and water [25].

C. Effect of glucose on absorption and scattering properties of Tissues

Glucose can affect the measured transmitted or reflected signal by absorption and scattering of light at 632.8nm wavelength.

Attenuation of light in tissue is described, according to light transport theory, by the effective attenuation coefficient μ_{eff}., which is explain in the following equation (21) i.e.:

$$\mu_{eff} = \sqrt{3\mu_a(\mu_a+\mu_s')} = \sqrt{3\mu_a[\mu_a+\mu_s(1-g)]} \quad (21)$$

An exact solution of the light transport equation in turbid media can be modified by following the path each individual photon and calculating the probability of scattering or absorption in a series of steps, using the Monte Carlo simulation [26,27].

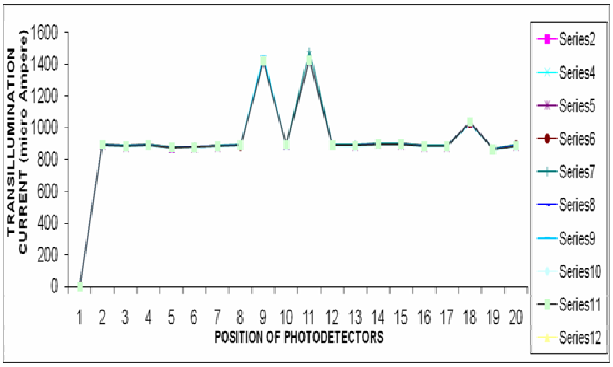

Fig. 2. Effect of various angles on transillumination and scattered signals

The effect of various angles on scattered and transilluminated and scattered signals are shown in figure.2. Changes in glucose concentration can influence the measured μ_a of tissue through changes in absorption corresponding to water displacement (absorption decrease as glucose concentration increases) or changes in its intrinsic absorption (absorption increases as glucose concentration increases). Changes in μ_a because of water displacement are nonspecific, and analysts with higher molecular weights will displace more water than does glucose. Changes in the temperature and hydration status of the body may affect water absorption bands and act as noise sources for an noninvasive glucose measurement. The glucose in the near- IR is low and is much smaller than that of water. It is higher at longer wavelengths. However, its magnitude is too small to allow for direct absorption measurements at wavelengths, 632.8 nm.

Attenuation of light (632.8 nm) in a small body part such as an average sized finger varies in the range 3 -4 absorbance units, and the expected change in absorbance because of a 5 mmol/L change in glucose concentration is approximately 10^{-5} absorbance units. [28-42].

VI. RESULTS AND DISCUSSIONS

This paper presents a method for estimation of blood glucose level of diabetic and non diabetic patients from the microcirculation. The He-Ne laser operating at 632.8 nm wavelength is used. From blood flow we can compute various associated parameters viz blood pressure, blood cholesterol and blood glucose. The capability of continuous learning governs the blood flow and gives output with respect to standard blood composition (Red Blood Corpuscles, White Blood Corpuscles, Platelets, Blood Cholesterol, etc) was determined with the condition that all the other blood parameters are constant. Following the results of the experiment, it can be started that any alteration in the blood glucose level may result in alteration of blood flow. Blood flow is indirectly proportional to the blood glucose level.

The steady-state spatially resolved diffused transillumination profile is a characteristic of a tissue's structure and its metabolic state. By analyzing, one can get the blood glucose details of the tissue penetration depth of the photons [43]. The influence of any optical inhomogeneity (structural or rapid metabolic changes) in the tissue layers could easily be detected by this technique.

Transillumination of different patient blood glucose concentration of fasting and post Parandial are shown In figure.3. The corresponding transillumination voltage of fasting and post Parandial blood glucose are tabulated in Table I. Blood was collected from 133 subjects and corresponding transillumination was noted were BGL(PP) is blood glucose level of post Parandial in milligram per deci-liter, BGL(F) is blood glucose level of fasting in milligram per deci-liter, BGL(PPT) is blood glucose level of post Parandial transilluminated voltage in milli-voltage , BGL(FTV) is blood glucose level of fasting transilluminated voltage in milli-voltage.

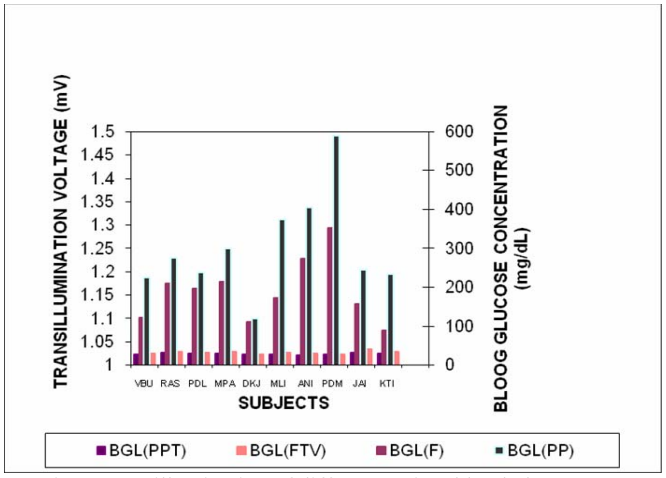

Fig. 3.Transillumination of different patient blood glucose concentration

TABLE I SUMMARY OF THE MEASURED RESULTS OF THE RIGHT COMMON CAROTID OF THE VOLUNTEERS

Subjects	BGL(F)	BGL(FTV)	BGL(PP)	BGL(PPT)
V. BALU(VBU)	122	1.0247	226	1.0237
RASU(RAS)	209	1.0278	275	1.0258
P. DHANABAL(PDL)	196	1.0268	238	1.0248
M. PARIMALA(MPA)	215	1.0287	300	1.0257
D. KAVIN RAJ(DKJ)*	112	1.0228	120	1.0228
M. LAKSHMI(MLI)	173	1.0267	374	1.0237
A. NAGAKAKSHMI (ANI)	274	1.0248	404	1.0218
P. DANABAKIYAM(PDM)	352	1.0238	589	1.0228
J. ANJALI DEVI (JAI)	157	1.0347	245	1.0258
K. THULASIMANI(KTI)	89	1.0287	234	1.0248

(*Normal healthy Subject)

The signals collected from the index finger match well with the theoretical concept and with functional aspects, which is influenced by the distribution of cells in the tissue.

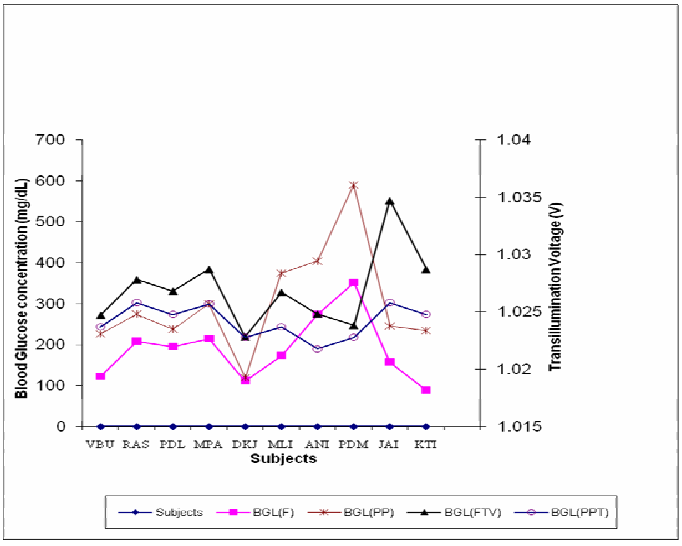

Fig. 4. Study of Blood Glucose Level and its corresponding transillumination at fasting and post Parandial conditions.

The corresponding transillumination voltages at fasting and post parandial conditions are plotted. Thus here the alteration of absorption is indirectly proportional to the transillumination signal. The blood glucose concentration was analyzed by glucose oxidize method and its corresponding transillumination was noted from the above figure.4.

VII. CONCLUSION AND FUTURE WORK

The maximum scattered signal at 29^0 & 337^0 and transilluminated signal at $167^0$was obtained according to anisotropy factor that was selected for further study. The transillumination and blood glucose concentration at fasting and post Parandial conditions of individual subjects are compared and found that transillumination is inversely proportional to the concentration of blood glucose. The difference in glucose concentration between fasting and post Parandial is correlated with transillumination and found a linear relationship between them.

Management of diabetes mellitus is mainly based on the continuous analysis of blood glucose level. Existing methods to estimate the blood glucose level need patient preparation, regent preparation, piercing the skin, pricking the vein, sophisticated instruments and skilled technicians. The results presented here indicate the ability of non invasive technique to measure the relative changes of blood flow according to the blood glucose concentration. We demonstrated and proved the different ratio which influences the blood glucose concentration according to our non invasive technique.

Despite the encouraging preliminary results, more measurements are required to further test the system and estimate the sensitive and accuracy. Moreover, further development of the theoretical model that correlates the measured optical signal is required. It will potentially lead to a better noninvasive blood glucose measurement using optical parameters.

Thus, there is a continuing need for improved low-cost noninvasive analytical instruments and methods that would provide essentially the same accuracy as conventional invasive blood glucose test. Our method will fulfill the need for a durable, cost-effective, and environmentally conscious nondisposable apparatus for measuring blood glucose.

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