ACTA MEDICA SALINIANA

ORIGINAL PAPERS

PLASMA HISTONE DEACETYLASE ACTIVITIES, LIPID PROFILE, AND GLYCATED HAEMOGLOBIN LEVELS AS INDICATOR OF GLYCEMIC CONTROL IN TYPE 2 DIABETES MELLITUS

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ISSN 0350-364X

DOI: 10.5457/556

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ABSTRACT

Background: The number of people with Diabetes mellitus (DM) is steadily rising globally and its socio-economic effects extend beyond the individual to affect their families and whole societies.

Aim: This study aimed at determining the Plasma Lipid Profile, Glycated Haemoglobin (HbA_{1C}) and Histone Deacetylase (HDAC) enzyme activities as indicator of Glycaemic control in Type 2 Diabetes mellitus.

Methods: A total of 100 newly diagnosed DM patients and 50 control subjects were recruited. The weight, height, body mass index (BMI), waist circumference (WC), and blood pressure of each participant were determined. Also, fasting plasma glucose (FPG), triglycerides, total Cholesterol (TC), high density lipoprotein (HDLC) and HDAC activities were measured using standard methods. Low density lipoprotein (LDLC) was computed.

Results: A significant increase in mean age, FPG, systolic and diastolic blood pressure, HbA_{1c} total cholesterol, triglyceride, and low density lipoprotein, and HDAC activities; and a decrease in plasma HDLC were observed among the diabetics when compared with the controls. A direct but significant correlation existed between HDAC activities and FPG, WC, and duration of diabetes; and between HbA_{1C} and FBG, TC, LDLC, HDLC, and duration of diabetes; a direct but non-significant correlation existed between HDAC and HbA_{1C}, HDLC; an inverse and significant correlation existed between BMI and TC, Triglyceride and LDLC.

Conclusion: It could be inferred from this study that plasma HDAC activities is di-rectly related to FPG as it was found to increase with increasing FPG, indicating its likely role in metabolism.

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Received:
01.04.2020.

Accepted:
15.11.2022.

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Funding: none

Competing interests: none

Keywords: Diabetes mellitus, histone deacetylase, fasting plasma glucose, glycated haemoglobin, lipid profile.

INTRODUCTION

Metabolic disorders occur when there is alteration in the normal metabolic processes resulting in abnormal biochemical reactions in the body. Diabetes mellitus (DM), as an example of metabolic disorders, is primarily a disorder of glucose metabolism with the affectation of fat and protein metabolism due to abnormal insulin secretion, deficient action of insulin on target tissues, or both [1, 2]. The pathognomonic clinical features of DM are hyperglycemia-induced and resultant complications include ketoacidosis, angiopathy, neuropathy, retinopathy, nephropathy, gangrene, infection, dysfunction and failure of various organs among others [2]. The trend in plasma glucose follows the order of normal (< 6.1mmol/L or < 110mg/dL), impairment (6.1–6.9mmol/L or 110–125mg/dL) and finally diabetes (≥ 7mmol/L or ≥ 126mg/dL) [2]. Oftentimes symptoms may be absent, mild or sufficient enough to cause functional and chronic incipient pathological changes before diagnosis is made. Thus, at diagnosis, evidence of such complications as dyslipidaemia, cataract formation, blurred vision, prolonged wound healing, macrosomia, and furunculosis are seen.

These hyperglycemia-induced complications are preventable by early diagnosis and institution of management to have a good glycemic control, good drug compliance on the part of patients, and use of markers having good predictive qualities for patient monitoring. Such markers include fasting plasma glucose, glycated

haemoglobin (HbA_{1c}) levels, and plasma lipid profile. Glycated hemoglobin level is directly proportional to average blood glucose concentration over the past 2-3 months provided there is a normal hemoglobin concentration and red blood cell survival [3, 4]. High concentrations of HbA_{1c} indicate poor glycemic control and have been associated with cardiovascular disease, nephropathy and retinopathy [4, 5]. Lipid profile is a direct measure of blood cholesterol, triglycerides, and high-density lipoproteins (HDL). Type 2 diabetes is associated with abnormalities in plasma lipid and lipoproteins which include elevated small dense LDL particles, elevated triglyceride levels, and reduced HDL cholesterol [6, 7].

In the recent time, histone deacetylases (HDACs) have been discovered to play important roles in metabolism. The HDACs are involved in glucose homeostasis by modifying histones through acetylation, phosphorylation, methylation and ubiquitination; and transcriptional factors thereby providing a key mechanism for the control of cellular signalling and gene expression and playing a central role in the regulation of glucose metabolism and pathogenesis of DM [8, 9]. This research therefore was aimed at determining the plasma concentration of histone deacetylase activities in type 2 DM and its potential use as marker of glycemic control alongside with lipid profile, and glycated haemoglobin levels.

MATERIALS AND METHODS

Study population and study design

The research was a case-control, cross-sectional comparative studies carried out using 100 newly diagnosed Diabetes Mellitus patients and 50 non-diabetic subjects as control. All participants were attending Ibeju-Lekki General Hospital, Akodo, Lagos State between November 2018 and April 2019. Questionnaires were administered on all participants to obtain socio-demographic information (such as age, sex, occupation and family history of diabetes and hypertension).

Body mass index and waist circumference measurements

The weight of each participant was determined using bathroom weighing scale, the height measured with a stadiometer and body mass index was calculated (BMI = weight (kg)/height (m^2). Waist circumference (WC) was measured to the nearest 0.5 cm using a non-stretchable tape meter around a bare waist while the patient stand with back straight and feet shoulder width (25-30cm) apart. The tape measure was placed directly on the skin halfway between the lowest rib and the top of the hipbone, wrapped parallel to the floor, not twisted all the way around the waist, applied with sufficient tension to conform to the measurement surface and the circumferences measured. The blood pressure was measured in siting position using acous-son sphygmomanometer.

Diabetes was defined as fasting plasma glucose greater than 126mg/dL (7mmol/L) [10, 11]; hypertension defined as systolic and diastolic blood pressure greater than 130mmHg and 80mmHg respectively [11]; obesity was defined as BMI greater than 30 0 kg/m^2 and WC greater than 94cm and 80cm respectively for men and women [12, 13].

Inclusion and exclusion criteria

Included in the study are all newly diagnosed type 2 Diabetes Mellitus patients and non-diabetic subjects consented to be part of the study as test and control respectively. Excluded from the study are known type 2 Diabetes Mellitus patients on antihyperglycemic drugs and subjects with chronic disease condition other than DM, chronic alcoholics, pregnant female and those who did not consented to the study.

Blood sample collection

Ten millilitres (10mL) of blood sample was drawn from the antecubital vein of the arms of each participant using sterile disposable syringe. Five millilitres (5mL) of the drawn blood sample was dispensed into heparinised bottle for lipid profile test and the remaining 5mL was dispensed into K-EDTA bottle for glycated haemoglobin estimation and HDAC assay. This was done for each patient. The blood samples were centrifuged at 5000 rpm for 5 min to obtain the plasma which was stored at -20°C till assayed.

Measurement of biochemical parameters

Fasting plasma glucose (FPG), triglycerides, total Cholesterol, and HDLC were measured using the methods described by Kadish *et al.* (1969) [14], Friedewald (1972) [15], Schettler and Nussel (1975) [16], and Nagele *et al.* (1984) [17]respectively. Plasma LDLC concentration was calculated using the Friedewald (1972) [15] formula. Histone deacetylase activity was determined by colorimetric method using EpiQuik™ HDAC Activity/Inhibition assay kit while glycated haemoglobin was determined by ionic exchange resin method with the use of Semi-auto analyser (Rayto Semi-auto analyser).

Ethical approval

The ethical approval was obtained from the Research Ethical Committee of State Hospital, Ifako-Ijaye, Lagos State, Nigeria with approval number IBLGH/P/MED/7070. Informed consent was also obtained from each participant after explaining to them the procedures involved in the research.

Statistical analysis

The statistical analysis was done using SPSS software version 21.0. Descriptive statistics and bar chart representations were used to describe and represent variables. Student independent t-test was used to compare differences in mean between the two groups. Correlation of obtained parameters among the type 2 diabetes mellitus patients was done using Pearson correlation. The level of statistical significance was set at $p < 0.05$.

RESULT

Figure 1: Sex distribution of the controls and type 2 diabetes mellitus patients

Table 1: Anthropometric features of type 2 diabetes mellitus patients and the controls

Parameters	Controls	Test	t-value	p-value
Age (yr)	39.10±13.5	57.54±15.53	7.152	0.000
Weight (kg)	76.30±17.28	70.19±14.99	2.234	0.027
Height (m)	1.82±0.10	1.74±0.05	6.164	0.000
BMI (kg/m^2)	23.25±5.69	23.03±4.27	0.272	0.786
Waist Circ (cm)	77.55±19.92	79.28±14.28	2.022	0.045

Table 1 above shows a significant increase ($p < 0.05$) in mean age and waist circumference; and a significant decrease ($p < 0.05$) in the weight among the diabetic group. Also, a non-significant increase ($p > 0.05$) in height and BMI was observed among the control group. Values are mean ± Standard deviation (mean ± SD) and statistically significant at $p < 0.05$. BMI = Body mass index.

Table 2: Biochemical parameters of type 2 diabetes mellitus patients and the controls

Parameters	Controls	Test	t-value	p-value
FPG (mg/dL)	79.70±8.64	187.25±79.9	9.474	0.000
Systolic (mmHg)	107.0±11.11	134.75±18 .92	9.566	0.000
Diastolic (mmHg)	72.0±7.55	79.90±5.77	7.105	0.000
HbA_{1C} (%)	5.48±0.29	7.98±2.26	7.774	0.000
T. Chol (mg/dL)	124.90±25.66	119.81±40.33	0.813	0.417
Trig (mg/dL)	89.10±40.43	81.30±24.36	1.470	0.144
HDL (mg/dL)	42.00±6.51	46.34±19.82	1.506	0.134
LDL (mg/dL)	64.60±14.98	57.99±21.99	1.913	0.058
HDAC (ng/h/mL)	83.70±15.6	132.29±60.99	5.535	0.000

Table 2 above shows a significant increase ($p < 0.05$) in plasma glucose; systolic and diastolic blood pressure; HbA_{1C}; and HDAC activities among the test group. Also, a non-significant increase ($p > 0.05$) was observed in plasma total cholesterol, triglyceride, and LDLC and a decrease in plasma HDLC in the test group. Values are mean ± Standard deviation (mean ± SD) and are statistically significant at $p < 0.05$.

Table 3: Pearson correlation of parameters among type 2 diabetes mellitus patients

	BMI	FPG	WC	Duration	HbA_{1C}	T.Chol	Trig	HDL	LDL	HDAC
BMI	1									
FBS	065 0.432	1								
WC	300 0.000	140 0.087	1							
Duration	005 0.963	427 0.000	116 0.250	1						
HbA_{1C}	-182 0.026	087 0.289	028 0.735	266 0.007	1					
T. Chol	-197 0.016	-296 0.000	-131 0.111	164 0.103	319 0.000	1				

Trig	271 0.001	-250 0.002	-152 0.064	131 0.194	116 0.156	786 0.000	1			
HDL	053 0.522	-018 0.823	026 0.748	345 0.000	203 0.013	784 0.000	375 0.000	1		
LDL	-330 0.000	-397 0.000	-206 0.011	037 0.716	378 0.000	918 0.000	793 0.000	496 0.000	1	
HDAC	-032 0.698	920 0.000	212 0.009	543 0.000	010 0.899	-189 0.002	-186 0.023	072 0.384	-290 0.000	1

Table 3 shows a direct and significant (p = 0.000) correlation between FPG and HDAC activities; HDAC and waist circumference (p = 0.009) and duration of diabetes. A direct but non-significant correlation was observed to exist between HDAC and HbA_{1C}; HDAC and HDLC; and HbA_{1C} and FBG, TC, LDL, and HDL. Also, an inverse and significant correlation exists between BMI and other lipids (total cholesterol, tTriglycerides and LDLC.

DISCUSSION

There is growing evidence that gender differences are particularly relevant in the epidemiology, pathophysiology, severity, management and prognosis of non-communicable endocrine and metabolic diseases such as type 2 DM [18]. However, controversies ensue in the gender distribution of type 2 DM. While Misra and Lager (2009) [19], Marina *et al.* (2013) [20] and Natasha *et al.* (2015) [21] reported higher incidence among female, Aregbesola *et al.* (2016) [22] reported higher incidence among male. Result obtained from this study revealed that 92% (92 out of 100) of the diabetic patients were female while male constituted 8% (8 out of 100) (Figure 1). This corroborates earlier reported higher incidence of type 2 DM among females [19-21, 23]. The observed difference is because gender roles are influenced by a complex interplay between genetic, endocrine, and social factors [24]. Identified risk factors include body mass index; body fat distribution; brown adipose tissue; metabolic syndrome; sex hormones imbalance; pre-diabetes; gestational DM; and consumption of sugar-sweetened beverages, alcohol, and smoking [25].

The relative risk of a raised BMI and obesity tends to be greater in women than in men [21, 26]. The result of anthropometric features of type 2 DM patients and controls shows that the mean age of the test group (57.54±15.53yr) was significantly higher (p < 0.05) than that of the control group (39.10±13.5 yr) (Table 1). The observed mean age of the test group further confirms that the average age of onset of type 2 DM is 45 years [27]. However, type 2 DM has been increasingly reported to occur in children and adolescence due to increasing prevalence of obesity [28]. No significant changes (p > 0.05) were observed in weight, height, BMI and waist circumference (WC) among the two groups. These parameters were within standard range for normal people [29]. Thus, any observed abnormality in lipid pattern in this study is not as a result of obesity but as a result of diabetes.

The pathognomonic features of type 2 DM namely polydipsia, polyuria, polyphagia and weight loss and its complications are reflections of associated hyperglycemic state as indicated by FPG ≥ 126 mg/dL. Result of plasma glucose obtained from this study showed a significantly high value (p < 0.05) among the test group (187.25±79.9) when compared to the controls (79.70±8.64) thereby confirming existence of DM among the test group (Table 2).

Considering the blood pressure, result from this study revealed a significant increase (p < 0.05) in both systolic and diastolic blood pressure among the test group when compared to the controls. This indicates existence of systolic hypertension (systolic blood pressure > 130 mmHg) among the diabetes patience, though the diastolic blood pressure is still normal (< 90 mmHg) [11]. This observation corroborates the earlier work of Olooto *et al.* (2016) [7] and further confirms the co-existence of diabetes and hypertension.

Monitoring glycemic controls among diabetes patients is objectively done by monitoring improvements in clinical conditions of diabetic patients. This could also be achieved biochemically using plasma glucose, HbA_{1C}, and lipid profile. The HbA_{1c} level is directly proportional to average blood glucose concentration over the past 60-90 days. Values are normally < 6% but in poorly controlled diabetes the quantities are much higher with values > 6.5% [2, 30]. Values obtained from this study are 7.98% and 5.48% in the test and control groups respectively. The difference is significant (p < 0.05) and higher values among the test (diabetic patients) show poor glycemic control which is an indication of non-institution of any antihyperglycemic treatment in the test group.

However, lipid profile pattern revealed dyslipidemia and this together with hyperglycemia are the major causes of the various complications such as cardiovascular diseases associated with type 2 DM. Result of lipid profile (total cholesterol, triglyceride, high density lipoprotein and low density lipoprotein) obtained in this study showed an increase in plasma total cholesterol, triglyceride, and low density lipoprotein and a decrease in plasma HDL in the test group when compared to the controls (Table 2). Though the observed values are high they are still within the normal range. These findings contradict the earlier reported presence of dyslipidemia in type 2 DM at diagnosis [7]. The observed absence of dyslipidemia at this stage of the

disease may be a reflection of improvement in awareness of the disease condition among people and also in their attitude towards prompt seeking for medical interventions to their health challenges. Thus, the characteristic diabetic dyslipidemia is not always present at diagnosis but may reflect different metabolic compensations involving carbohydrate, protein and lipid in the course of the disease.

Result of HDAC activities revealed a statistically significant increase ($p < 0.05$) in the activities of the enzyme among the diabetics when compared with the controls. In diabetic hyperglycemia, there is deficiency of glucose as metabolic fuel at the cellular level. Thus, glucagon is released signalling gluconeogenesis and glycogenolysis up-regulation in the liver. Increase cellular metabolism requires corresponding increase in glucagon secretion and that of HDAC activities. Plasma level of HDAC activities therefore objectively measures the degree of cellular glucose uptake and improvement in hyperglycemic state.

On correlating plasma glucose with markers of glycemic control, there is a direct and significant ($p = 0.000$) correlation between FPG and HDAC activities (Table 3). This is similar to the work done by Sathishkumar *et al.* (2016) [31]. This implies that as blood glucose concentration increases, HDAC activities also increases and vice versa. Also, HDAC shows a direct and significant correlation with waist circumference ($p = 0.009$) and duration of diabetes. A direct but non-significant correlation was observed to exist between HDAC and HbA_{1C}; and HDAC and HDL. On the other hand, it shows an inverse and significant correlation with BMI and other lipids (TC, Trig and LDL). Meanwhile, HbA_{1C} demonstrate direct correlations with FBG, TC, LDL, HDL, and with duration of diabetes. This is similar to the findings of some researchers in which HbA_{1C} level showed positive correlation with TC, LDL-C and HDL-C in diabetic patients [32-34].

CONCLUSION

Since HDAC was the major biomarker used in comparing other already established biomarkers (Lipids, FBG, and HBA1c) in this study, the inference from this study therefore is that plasma HDAC activities is directly related to FPG as it was found to increase with increasing FPG, indicating its role in metabolism. Therefore, targeting HDAC as a measure of glycemic control will assist in the management of patients with type 2 DM and improve their quality of life.

REFERENCES

1. Amballi AA, Kayode BO, Odusan OO, Oritogun KS, Olooto WE, Olawale OO et al. Cortisol and Electrolyte Levels in Type 2 Diabetic Patients Attending a State University Teaching Hospital, Ogun State, Nigeria. International Journal of Biomedical and Health Sciences 2018;14(2):51-58
2. World Health Organisation. Classification of Diabetes Mellitus, 2019.
3. Nathan DM, Turgeon H, Regan S. Relationship between glycated haemoglobin levels and mean glucose levels over time. Diabetologia 2007;50:2239-2244.
4. Sultanpur CM, Deepa K, Kumar SV. Comprehensive review on hba1c in diagnosis of diabetes mellitus. International Journal of Pharmaceutical Sciences Review and Research 2010;3(2):119-122.
5. World Health Organization. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus: Abbreviated Report of a WHO Consultation, 2011.
6. Susanti E, Donosepoetro M, Patellong I, and Arif M. Differences between several atherogenic parameters in patients with controlled and uncontrolled type 2 Diabetes Mellitus, Medical Journal of Indonesia 2012;19(2):103-108.
7. Olooto WE, Ifabumuyi AT, Odusan O, Olawale OO. Plasma Micronutrients (magnesium, zinc, selenium) Status and Lipid Profile among adults with Type 2 Diabetes Mellitus in Sagamu, Southwestern Nigeria.Annals of Health Research 2016;2(2):105-112.
8. Berger SL. Histone modifications in transcriptional regulation. Current Opinion in Genetics and Development 2002;12:142–148.
9. Xiaojie W, Xinbing W, Qi P, Fan Y. Histone deacetylases and their inhibitors: molecular mechanisms and therapeutic implications in diabetes mellitus. Acta PharmaceuticasinicaB 2012;2(4):387-395.
10. American Diabetes Association Standards of Medical Care in Diabetes, Diabetes Care 2017;40(1):S1–S2.
11. American Heart Association. Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, 2017.
12. World Health Organization. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. The Lancet 2004;157-163.
13. Canadian Diabetes Association. Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada provides a guideline for waist circumference targets on based gender and ethnicity, 2013.
14. Kadish AH, Little RI. and Sternberg JC. A newnand rapid method for the determination of glucose by measurement of rate of oxygen consumption, Clinical Chemistry, 1969;14:116-118.
15. Friedewald, WT, Levy RI and Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge, Clinical Chemistry 1972;18:499-502.
16. Schettler G and Nussel E. Colorimetric determination of Cholesterol, Arh Med Soz Med Prav Med 1975;10:55.
17. Nagele U, Hagele EO, and Sauer G. Reagent fot enzymatic determination of serum otal triglycerides with improved lypholytic efficiency, Journal of Clinical Chemistry and Clinical Biochemistry 1984;22:165-174.
18. Kautzky-Willer A, Harreiter J, Pacini G. Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus. Endocrine Reviews2016;37(3):278–316.
19. Misra R, Lager J. Ethnic and gender differences in psychosocial factors, glycemic control, and quality of life among adult type 2 diabetic patients. Journal of Diabetes Complications 2009;23(1):54–64.
20. Marina S, Christine AS, Vallabh OS, Andrew SN, Francesca T, David SK et al. Prevalence of Diabetes Is

Higher Among Female than Male Zuni Indians. Diabetes Care 2003;26(1):55-60.

21. Sobers-Grannum N, Murphy MM, Nielsen A, Guell C, Samuels TA, Bishop L et al. Female gender is a social determinant of diabetes in the Caribbean: a systematic review and meta-analysis. PLoS One 2015;10(5):e0126799.
22. Aregbesola A, Voutilainen S, Virtanen JK, Mursu J, Tuomainen TP. Gender difference in type 2 diabetes and the role of body iron stores. Annals of Clinical Biochemistry 2017;54(1):113-120.
23. Chivese T, Mahmoud W, Magodoro I, Kengne AP, Norris SA, and Levitt NS. Prevalence of type 2 diabetes mellitus in women of childbearing age in Africa during 2000–2016: protocol of a systematic review and meta-analysis. BMJ Open 2016;6:e012255.
24. Geary N. Counterpoint: physiologists should not distinguish "sex" and "gender."American Journal of Physiology Regulatory, Integrative and Comparative Physiology 2010;298:R1702–R1704.
25. Esayas H, Hiroshi Y, Leo K, Atsuko A. Differences by sex in the prevalence of diabetes mellitus, impaired fasting glycaemia and impaired glucose tolerance in sub-Saharan Africa: a systematic review and meta-analysis. Bulletin of the World Health Organization 2013;91:671-682D.
26. Abdullah S, Goblan A, Mohammed A, Alfi A, Muhammad Z. (2014). Mechanism linking diabetes mellitus and obesity. Diabetes, Metabolic Syndrome and Obesity 2014;7:587–591.
27. American Diabetes Association. Standards of Medical Care in Diabetes, Diabetes Care 2019;42(1):S1-S2.
28. Thomas R. Type 2 diabetes mellitus in children and adolescents. World Journal of Diabetes 2013;4(6):270–281.
29. Kolimechkov S, Petrov L, Ilinova B, et al. Assessment of the physical development of pre-school and primary school children practising artistic gymnastics. Journal of Sport Science 2013;4:106-115.
30. Weykamp C, John WG, Mosca A. A Review of the Challenge in Measuring Hemoglobin A1c. Journal of Diabetes Science and Technology 2009;3(3):439-445.
31. Sathishkumar C, Prabu P, Balakumar M, Lenin R, Prabhu D, Anjana RM et al. Augmentation of histone deacetylase 3 (HDAC3) epigenetic signature at the interface of proinflammation and insulin resistance in patients with type 2 diabetes. Clinical epigenetics 2016;8:125.
32. Lu W, Resnick HE, Jablonski KA, Jones KL, Jain AK, Howard WJ et al. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the strong heart study. Diabetes Care 2003;26:16–23.
33. Erciyas F, Taneli F, Arslan B, Uslu Y. Glycemic control, oxidative stress and lipid profile in children with type 1 Diabetes Mellitus. Archives of Medical Research 2004;35:134-140.
34. Ram V, Prajwal G, Pramod R, Prashant R, Khelanand S, Dipendra P et al. Association between glycemic control and serum lipid profile in type 2 diabetic patients: Glycated haemoglobin as a dual biomarker.Biomedical Research 2011;22(3):375-380.