

INDONESIAN JOURNAL OF
**CLINICAL PATHOLOGY AND
MEDICAL LABORATORY**

Majalah Patologi Klinik Indonesia dan Laboratorium Medik

EDITORIAL TEAM

Editor-in-chief:

Puspa Wardhani

Editor-in-chief Emeritus:

Prihatini

Krisnowati

Editorial Boards:

Maimun Zulhaidah Arthamin, AAG Sudewa, Rahayuningsih Dharma, Mansyur Arif, July Kumalawati, Nurhayana Sennang Andi Nanggung, Aryati, Purwanto AP, Jusak Nugraha, Sidarti Soehita, Endang Retnowati Kusumowidagdo, Edi Widjajanto, Budi Mulyono, Adi Koesoema Aman, Uleng Bahrin, Ninik Sukartini, Kusworini Handono, Rismawati Yaswir, Osman Sianipar

Editorial Assistant:

Dian Wahyu Utami

Language Editors:

Yolanda Probohoesodo, Nurul Fitri Hapsari

Layout Editor:

Akbar Fahmi

Editorial Adress:

d/a Laboratorium Patologi Klinik RSUD Dr. Soetomo Jl. Mayjend. Prof. Dr Moestopo 6-8 Surabaya, Indonesia
Telp/Fax. (031) 5042113, 085-733220600 E-mail: majalah.ijcp@yahoo.com, jurnal.ijcp@gmail.com
Website: <http://www.indonesianjournalofclinicalpathology.or.id>

Accredited No. 36a/E/KPT/2016, Tanggal 23 Mei 2016

INDONESIAN JOURNAL OF
**CLINICAL PATHOLOGY AND
MEDICAL LABORATORY**

Majalah Patologi Klinik Indonesia dan Laboratorium Medik

CONTENTS

RESEARCHS

Molecular Aspect Correlation between Glycated Hemoglobin (HbA1c), Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) on Type 2 Diabetes Mellitus (T2DM) <i>(Aspek molekuler Hubungan Kadar Hemoglobin Terглиkasi (HbA1c), Prothrombin Time (PT) dan Activated Partial Thromboplastin Time (APTT) di Diabetes Melitus Tipe 2)</i> Indranila KS	1-6
Platelet-Lymphocyte Ratio (PLR) Markers in Acute Coroner Syndrome <i>(Platelet Lymphocyte Ratio (PLR) Sebagai Petanda Sindrom Koroner Akut)</i> Haerani Harun, Uleng Bahrn, Darmawaty ER	7-11
The Mutation Status of Kras Gene Codon 12 and 13 in Colorectal Adenocarcinoma <i>(Status Mutasi Gen Kras Kodon 12 dan 13 di Adenocarcinoma Colorectal)</i> Gondo Mastutik, Alphania Rahniayu, Anny Setijo Rahaju, Nila Kurniasari, Reny P'tishom	12-17
Creatine Kinase Related to the Mortality in Myocardial Infarction <i>(Creatine Kinase terhadap Angka Kematian di Infark Miokard)</i> Liong Boy Kurniawan, Uleng Bahrn, Darmawaty Rauf, Mansyur Arif	18-21
Application of DNA Methylation on Urine Sample for Age Estimation <i>(Penggunaan Metilasi DNA Dalam Perkiraan Umur Individu di Sampel Air Kemih)</i> Rosalinda Avia Eryatma, Puspa Wardhani, Ahmad Yudianto	22-26
Lipid Profile Analysis on Regular and Non-Regular Blood Donors <i>(Analisis Profil Lipid di Pendoror Darah Reguler dan Non-Reguler)</i> Waode Rusdiah, Rachmawati Muhiddin, Mansyur Arif	27-30
Percentage of CD3 ⁺ T Lymphocytes Expressing IFN- γ After CFP-10 Stimulation <i>(Persentase Limfosit T-CD3⁺ yang Mengekspresikan Interferon Gamma Setelah Stimulasi Antigen CFP-10)</i> Yulia Nadar Indrasari, Betty Agustina Tambunan, Jusak Nugraha, Fransiska Sri Oetami	31-35
Characteristics of Crossmatch Types in Compatibility Testing on Diagnosis and Blood Types Using Gel Method <i>(Ciri Inkompatibilitas Uji Cocok Serasi Metode Gel terhadap Diagnosis dan Golongan Darah)</i> Irawaty, Rachmawati AM, Mansyur Arif	36-41
Diagnostic Values of Mycobacterium Tuberculosis 38 kDa Antigen in Urine and Serum of Childhood Tuberculosis <i>(Nilai Diagnostik Antigen 38 kDa Mycobacterium tuberculosis Air Kemih dan Serum di Tuberkulosis Anak)</i> Agustin Iskandar, Leliawaty, Maimun Z. Arthamin, Ery Olivianto	42-49
Erythrocyte Indices to Differentiate Iron Deficiency Anemia From β Trait Thalassemia <i>(Indeks Eritrosit Untuk Membedakan Anemia Defisiensi Besi Dengan Thalassemia β Trait)</i> Yohanes Salim, Ninik Sukartini, Arini Setiawati	50-55

HbA1c Levels in Type 2 Diabetes Mellitus Patients with and without Incidence of Thrombotic Stroke (Kadar HbA1c Pasien Diabetes Melitus Tipe 2 Dengan dan Tanpa Kejadian Strok Infark Trombotik) Dafina Balqis, Yudhi Adrianto, Jongky Hendro Prayitno	56–60
Comparative Ratio of BCR-ABL Genes with PCR Method Using the Codification of G6PD and ABL Genes in Chronic Myeloid Leukemia Patients (Perbandingan Angka Banding Gen BCR-ABL Metode PCR Menggunakan Baku Gen Glucosa-6-Phosphate Dehidrogenase dan Gen Abelson Kinase di Pasien Chronic Myeloid Leukemia) Tonggo Gerdina Panjaitan, Delita Prihatni, Agnes Rengga Indrati, Amaylia Oehadian	61–66
Virological and Immunological Response to Anti-Retroviral Treatment in HIV-Infected Patients (Respons Virologis dan Imunologis Terhadap Pengobatan Anti-Retroviral di Pasien Terinfeksi HIV) Umi S. Intansari, Yunika Puspa Dewi, Mohammad Juffrie, Marsetyawan HNE Soesatyo, Yanri W Subronto, Budi Mulyono	67–73
Comparison of sdLDL-C Analysis Using Srisawasdi Method and Homogeneous Enzymatic Assay Method on Hypertriglyceridemia Condition (Perbandingan Analisa sdLDL-C metode Srisawasdi dan Homogeneous Enzymatic Assay di Kondisi Hipertrigliseridemia) Gilang Nugraha, Soebagijo Poegoeh Edijanto, Edhi Rianto	74–79
Pattern of Bacteria and Their Antibiotic Sensitivity in Sepsis Patients (Pola Kuman dan Kepekaan terhadap Antibiotik di Pasien Sepsis) Wahyuni, Nurahmi, Benny Rusli	80–83
The Correlation of Naive CD4 ⁺ T Lymphocyte Cell Percentage, Interleukin-4 Levels and Total Immunoglobulin E in Patients with Allergic Asthma (Kenasaban antara Persentase Sel Limfosit T-CD4 ⁺ Naive dengan Kadar Interleukin-4 dan Jumlah Immunoglobulin E Total di Pasien Asma Alergi) Si Ngr. Oka Putrawan, Endang Retnowati, Daniel Maranatha	84–89
LITERATURE REVIEW	
Antibiogram (Antibiogram) Jeine Stela Akualing, IGAA Putri Sri Rejeki	90–95
CASE REPORT	
Pancreatic Cancer in 31 Years Old Patient with Normal Serum Amylase Level (Kanker Pankreas di Pasien Usia 31 Tahun Dengan Kadar Amilase Serum Normal) Melda F. Flora, Budiono Raharjo, Maimun Z. Arthamin	96–101

Thanks to editors in duty of IJCP & ML Vol 23 No. 1 November 2016

Kusworini Handono, Prihatini, Purwanto AP, July Kumalawati, Jusak Nugraha, Ida Parwati,
Adi Koesoema Aman, Edi Widjajanto, AAG. Sudewa, Nurhayana Sennang AN

RESEARCH

HbA1C LEVELS IN TYPE 2 DIABETES MELLITUS PATIENTS WITH AND WITHOUT INCIDENCE OF THROMBOTIC STROKE

(Kadar HbA1c Pasien Diabetes Melitus Tipe 2 dengan dan Tanpa Kejadian Strok Infark Trombotik)

Dafina Balqis¹, Yudhi Adrianto², Jongky Hendro Prayitno³

ABSTRAK

Strok saat ini menjadi salah satu penyebab utama kematian global. Hubungan antara kejadian strok dengan diabetes telah lama diketahui. Kontrol gula darah, yang dipantau melalui kadar HbA1c, telah menunjukkan hubungan dengan strok dan penyakit kardiovaskular lain. Kajian ini untuk menentukan perbedaan kadar HbA1c antara pasien diabetes melitus tipe 2 dengan dan tanpa kejadian strok infark trombotik. Metode penelitian yang digunakan adalah analisis retrospektif menggunakan rekam medis pasien selama 3,5 tahun. Penelitian ini mengumpulkan data kadar HbA1c dari 443 pasien diabetes melitus tipe 2 kemudian membandingkan rerata kadar HbA1c antara pasien diabetes mellitus tipe 2 dengan kejadian strok trombotik (n=74) dan tanpa kejadian strok trombotik (n=369). Perbandingan tingkat HbA1c juga dilakukan secara terpisah antara laki-laki dan perempuan. Kajian ini menemukan rerata kadar HbA1c yang tinggi di kedua kelompok sampel (10,49%±2,53% untuk kelompok dengan kejadian strok infark trombotik dan 10,44%±2,8% untuk kelompok tanpa kejadian strok infark trombotik) dengan perbandingan sarana $p>0,05$. Perbandingan yang dilakukan secara terpisah di laki-laki dan perempuan juga menunjukkan hasil yang sama dengan $p>0,05$. Sebagai simpulan, kadar HbA1c di kedua kelompok penelitian sama-sama tinggi dan tidak ada perbedaan bermakna kadar HbA1c yang ditemukan di pasien dengan diabetes tipe 2 dengan dan tanpa kejadian strok trombotik.

Kata kunci: Stroke, diabetes melitus, HbA1c, penyakit kardiovaskular

ABSTRACT

Stroke has been stated as one of the leading cause of mortality globally. Association between the incidence of stroke with diabetes have long known. Specifically, duration of diabetes and glycemic control, which monitored through HbA1c levels, has shown it's relation with incidence of stroke and other cardiovascular diseases. This study is to determine the difference of HbA1c levels between type 2 diabetes mellitus patients with and without the incidence of thrombotic stroke. The method used in this study is analytic retrospective using patients' medical records for 3.5 years. This study collected data of HbA1c levels from 443 type 2 diabetes mellitus patients then compared means of HbA1c levels between type 2 diabetes mellitus patients with incidence of thrombotic stroke (n=74) and without incidence of thrombotic stroke (n=369). The comparison of HbA1c levels were also done separately between males and females. This study found the average HbA1c levels were high on both sample groups (10.49%±2.53% for group with incidence of thrombotic stroke and 10.44%±2.8% for group without incidence of thrombotic stroke) with comparison of means $p>0.05$. Comparison which done separately on males and females also showed similar results with $p>0.05$. In conclusion, HbA1c levels in both study groups were equally high and there was no significant difference in HbA1c levels found in patients with type 2 diabetes with and without incidence of thrombotic stroke.

Key words: Stroke, diabetes mellitus, HbA1c, cardiovascular disease

¹ Student of Faculty of Medicine, Airlangga University, Surabaya, Indonesia. Email: dafina.balqis-12@fk.unair.ac.id

² Department of Neuro-imaging and Neuro-intervention, Division of Neurology Dr. Soetomo General Hospital, Surabaya, Indonesia

³ Department of Center of Diabetes and Nutrition Dr. Soetomo General Hospital, Surabaya, Indonesia

INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disease mainly characterized by hyperglycemia condition. Metabolic deregulation associated with diabetes can cause secondary pathophysiology on various organ systems, causing various complications.¹ In vascular system, diabetes can give microvascular complications, such as peripheral vascular disorders, nephropathy, neuropathy, and diabetic retinopathy, as well as macrovascular complications, such as coronary heart disease and stroke.^{2,3}

Diabetes Mellitus, moreover, has been declared as one of the risk factors for stroke.⁴ Stroke is a clinical disorder characterized by a decrease in neurological function that occurs suddenly at intervals of 24 hours. This is caused by the resistance of blood flow to the brain,⁵ leading to the death of cells in the tissues involved.⁶ Stroke, consequently, is a common cause of death in the world and the leading cause of death in many countries in Southeast Asia.^{7,8} In Indonesia, there were 300 of the 100,000 deaths caused by stroke⁸ with the incidence of stroke per 1000 people.⁹

Chronic hyperglycemia that occurs in people with diabetes, furthermore, can induce bad adaptation to the endothelium, thus contributing in the development of atherosclerosis in macrovascular complications. Some of the key mechanisms that have a role in the occurrence of atherosclerosis as the effects of hyperglycemia are an increased flow of glucose in the polyol pathway, AGE formation, activation of protein kinase C (PKC) and oxidative stress.¹⁰

In addition, HbA1c reflects the mean of plasma glucose level for 2–3 months.³ HbA1c is a superior parameter in diagnosing and monitoring the blood glucose of patients with DM.¹¹ Glycated hemoglobin together with the duration of diabetes and hypertension is positively associated with arterial stiffness in atherosclerosis.¹² Thus, this research aimed to determine differences in HbA1c levels among patients with type 2 diabetes mellitus with and without thrombotic infarct stroke.

METHODS

This research was a retrospective analytical study using secondary data from medical records. Data used was collected from Lamongan Muhammadiyah Hospital, which has had an integrated medical record system. Thus, all medical records of patients in this hospital were completely recorded in accordance with

the medical record number, so the data collection could be facilitated easily.

The number of population selected for this research was 2494 patients with type 2 diabetes as recorded in 3.5 years, ie from January 2012 to June 2015. The entire population was then filtered with several inclusion criteria. First, the patients had to be aged between 45–80 years old. Second, the patients had to have complete data of age, blood pressure, lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) and HbA1c. The age range of 45–80 years had been selected since it is more common in male patients up to 80 years and then becomes equally prevalent in male and female patients who suffer the first ischemic stroke. The sharp decline in the prevalence of diabetes in male patients is after the age of 70 years old, whereas in female patients the prevalence declines after the age of 80 years.¹³ The rest of the samples was filtered by excluding patients who were anemic, so the final number of the samples were 443 people. These samples were then divided into two groups, namely type 2 diabetes patients with stroke and type 2 DM patients without stroke.

HbA1c levels used for the group with the incidence of thrombotic infarct stroke in this research were HbA1c levels when stroke attack and HbA1c levels prior the stroke. Meanwhile, HbA1c levels used for the group without thrombotic infarct stroke were the

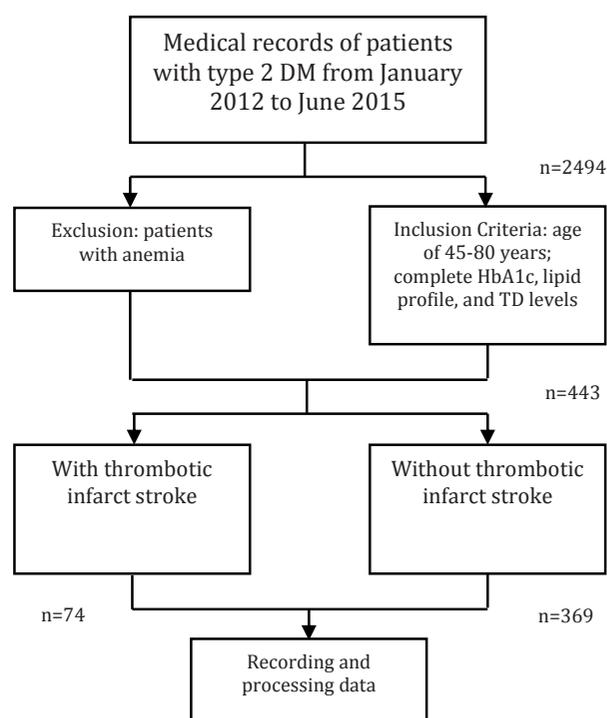


Figure 1. Schematic of sampling.

last HbA1c levels. The entire samples of HbA1c levels then were determined by *chromatography based HPLC assay* in the laboratory of Muhammadiyah Hospital, Lamongan.

Finally, all data taken from samples were presented descriptively. Next, a normality test, Kolmogorov-Smirnov test was conducted. A homogeneity test then was also performed using Lavene test on the entire samples. After having found that HbA1c variables were normally distributed and had a homogeneous variance, a comparison test. The t test was conducted using two independent samples.

RESULTS AND DISCUSSION

The number of samples was 443 patients with type 2 diabetes. Those samples were divided into two groups, type 2 diabetes patients with thrombotic infarct stroke (n=74) and type 2 diabetes patients without thrombotic infarct stroke group (n=369). Characteristics of the samples are shown in Table 1 and 2.

Table 1. Characteristics of the research sample group with thrombotic infarct stroke

The research sample group with thrombotic infarct stroke		
Variables	Data Convergence	Normality
Age (years)	57.03±7.94	p>0.05
HbA1c (%)	10.49±2.53	p>0.05
Systolic BP (mmHg)	167.61±33.45	p>0.05
Diastolic BP (mmHg)	90.28±18.46	p>0.05
Total Cholesterol (mg/dL)	213.29±59.37	p>0.05
HDL- Cholesterol (mg/dL)	35.67±7.96	p>0.05
LDL- Cholesterol (mg/dL)	133.72±47.02	p>0.05
Triglyceride (mg/dL)	176.5 (Median) 124 (Mode)	p>0.05

Table 2. Characteristics of the research sample group without thrombotic infarct stroke

The research sample group without thrombotic infarct stroke		
Variables	Data Convergence	Normality
Age (years)	56.36±6.74	p<0.05
HbA1c (%)	10.44±2.8	p>0.05
Systolic BP (mmHg)	150.14±34.41	p<0.05
Diastolic BP (mmHg)	84.88±18.15	p<0.05
Total Cholesterol (mg/dL)	199.76±67.29	p<0.05
HDL- Cholesterol (mg/dL)	34.97±13.06	p>0.05
LDL- Cholesterol (mg/dL)	122.97±52.11	p>0.05
Triglyceride (mg/dL)	187 (Median) 234 (Mode)	p<0.05

The homogeneity of the samples then was examined in each variable using Lavene test. The entire sample showed a homogenous variance in HbA1c variables with p=0.154 (p>0.05). Meanwhile, the variables of HDL cholesterol and triglycerides showed non-homogeneous data (p<0.05).

The mean of HbA1c levels in type 2 diabetes patients with stroke incidence was 10.49±2.53, while the mean in type 2 diabetes patients without stroke was 10.44±2.8. The results of t-test on two independent samples showed no significant difference in HbA1c between the group of type 2 diabetes patients with thrombotic infarct stroke and the group of type 2 diabetes patients without thrombotic infarct stroke (p=0.871). Similar results were also obtained in two independent samples after t test was performed separately on the samples of male patients (p=0.617) and female patients (p=0.409). The mean HbA1c levels in both male and female patients can be seen in Figure 2.

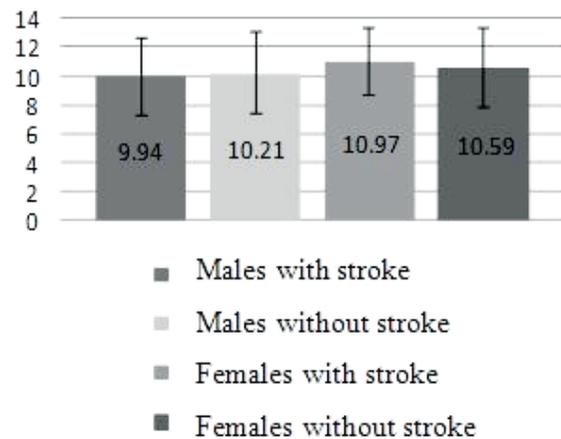


Figure 2. The mean of HbA1c levels in the research samples based on sex.

These results are supported by the results of *Veterans Affairs Diabetes Trial (VADT)* stating that intensive glucose control could not lower the incidence of cardiovascular disease in 1791 people with type 2 diabetes mellitus.¹⁴ However, after the results of the study were reviewed together with the various results of other studies, it can be concluded that tight blood sugar control for many years can reduce the risk of cerebrovascular disease.¹⁵

The insignificant comparative results of HbA1c levels is also incompatible with a large observational research showing the increased risk of progressive on the incidence of cardiovascular disease, stroke, coronary heart disease and total mortality due to

elevated levels of HbA1c.¹⁶ It is also contrary to a theory stating that uncontrolled hyperglycemia-marked with high HbA1c levels-may increase the incidence of cardiovascular disease. Chronic hyperglycemia can increase AGE levels in the circulation and trigger a variety of signaling processes in the body. Vascular conditions, such as arterial stiffness and adhesion as well as platelet aggregation caused by AGEs can lead to stroke, myocardial infarction, heart failure and entirely death.¹⁰

If the characteristics of the samples were observed, furthermore, it is known that there was no difference in the two groups since a variety of other independent variables can lead to stroke, such as blood pressure samples. Low blood pressure (<110/65 mmHg) or high one (\geq 160/100 mmHg) is known to be associated with the incidence of stroke in patients with type 2 diabetes mellitus.¹⁷ In both groups, the mean of systolic BP reached more than 160 mmHg, positively associated with the incidence of stroke.

Additionally, the lipid profile of the research samples may also affect the incidence of stroke in patients with type 2 diabetes mellitus patients. Type 2 diabetes mellitus patients commonly experience diabetic dyslipidemia characterized by elevated levels of triglycerides, reduced levels of HDL and increased sdLDL that can cause endothelial dysfunction and thickening of the tunica media.^{6,18} Non-HDL cholesterol levels, on the other hand, are associated with an increased risk of stroke incidence and mortality related to diabetes.¹⁹ Summary of various researches suggests that decreased levels of LDL cholesterol in patients with type 2 diabetes may reduce the risk of stroke.¹⁵

The results of this research showed that there was no difference in the mean of HbA1c levels between in type 2 diabetes mellitus patients with thrombotic infarct stroke and in type 2 diabetes mellitus patients without thrombotic infarct stroke. This comparison was conducted since there was a difference in the incidence of stroke between male and female patients. The incidence of stroke was higher in male patients with type 2 diabetes than in female ones. These results differ from prospective studies suggesting a positive correlation between levels of HbA1c and the risk of stroke in female patients with type 2 diabetes mellitus.²⁰ The increased risk of stroke and cardiovascular disease in female patients with diabetes is expected because of the tendency for them to reach the high Body Mass Index (BMI) triggering diabetes.²¹

Nevertheless, this research still has some limitations, including the design of research using secondary data. Medical records had made the

researchers less flexibility in choosing the samples due to limited knowledge of the written data. Therefore, it was too hard to maximize the homogeneity of the samples. This research also had not collected data on the genetic history of cardiovascular disease, smoking and BMI yet, which could also be able to determine the incidence of cardiovascular complications in patients with type 2 DM.³

In addition, the results of this research still have not paid attention to the patient's history of various antidiabetic treatment, anti-hypertensive drugs, or drugs for dyslipidemia. The effect of those various therapies actually can also affect the incidence of cardiovascular disease in diabetes patients.^{15,22}

Taking a level of HbA1c, not the average one, furthermore, can also influence the absence of differences in levels of HbA1c in both groups. This value could be obtained when the patient was first diagnosed, so the value was likely to be high. Similarly, a research conducted by Litwak, *et al*² with large samples used only one value of HbA1c to predict the incidence of complications of diabetes. Macrovascular complications actually will occur once faced with high HbA1c levels for many years.² Hence, for similar further research, it would be better if the blood sugar control variables are obtained through the mean of HbA1c levels since fluctuations in levels of HbA1c can be potential predictors of cardiovascular disease incidence.²³

CONCLUSION AND SUGGESTION

In conclusion, the results of this research show that there is no difference in HbA1c levels between type 2 diabetes patients with thrombotic infarct stroke and type 2 diabetes patients without thrombotic infarct stroke. The mean of HbA1c levels in both groups is equally high. Similar results are also found in a separate test between male and female genders. This research also finds that the incidence of thrombotic infarct stroke as one of the macrovascular complications of type 2 diabetes does not only rely on blood sugar control, but also other factors affecting endothelial dysfunction, such as lipid profile and blood pressure.

However, this research still has not directly compared a wide range of other risk factors affecting endothelial dysfunctions. Thus, further researches are needed to compare the various other risk factors in order to provide complete information about the variables that need to be controlled by the patients to prevent complications.

Finally, this research indicates that type 2 diabetic patients in have high HbA1c levels. Therefore, medical apparatus must conduct further efforts to improve patients' adherence to have routine treatment and take regular medication to control their blood sugar levels.

REFERENCES

1. Fauci WA, Braunwald E, Kasper D, Hauser S, Longo D, Jameson J. Harrison principle of internal medicine. 18thEd., New York, Mcgraw-Hill Companies Inc. 2012; 2305.
2. Litwak L, Goh SY, Hussein Z, Malek R, Prusty V, Khamseh ME. Prevalence of diabetes complications in people with type 2 diabetes mellitus and its association with baseline characteristics in the multinational A lchieve study. *Diabetology & metabolic syndrome*. 2013; 5(1): 1.
3. American Diabetes Association. Standards of medical care in diabetes—2015 abridged for primary care providers. *Clinical Diabetes*. 2015; 33(2): 97–111.
4. Banerjee C, Moon YP, Paik MC, Rundek T, Mora-McLaughlin C, Vieira JR, Sacco RL, Elkind MS. Duration of Diabetes and Risk of Ischemic Stroke The Northern Manhattan Study. *Stroke*. 2012; 43(5): 1212–7.
5. Hall JE. Guyton and Hall Textbook of Medical Physiology. 12th. Philadelphia, Pennsylvania, Elsevier Saunders, 2011; 691.
6. D'Souza A, Hussain M, Howarth FC, Woods NM, Bidasee K, Singh J. Pathogenesis and pathophysiology of accelerated atherosclerosis in the diabetic heart. *Molecular and cellular biochemistry*. 2009; 331(1-2): 89–116.
7. G. A. Donnan, M. Fisher, M. Macleod and S. M. Davis. *Stroke*. The Lancet. 2008; 371(9624): 1612–23.
8. Hoy DG, Rao C, Hoa NP, Suhardi S, Lwin AM. Stroke mortality variations in South-East Asia: empirical evidence from the field. *International Journal of Stroke*. 2013 Oct 1; 8(A100): 21–7.
9. Wijaya AK. Pathophysiology Stroke Non-Hemorrhagic Et Causa Thrombus. *E-Jurnal Medika Udayana*. 2013; 2(10): 1652-66.
10. Kumar V, Abbas AK, Fausto N, Aster JC. Robbins and Cotran Pathologic Basis of Disease. Philadelphia, Pennsylvania, Elsevier Health Sciences, 2014; 493–5.
11. Tankova T, Chakarova N, Dakovska L, Atanassova I. Assessment of HbA1c as a diagnostic tool in diabetes and prediabetes. *Acta diabetologica*. 2012; 49(5): 371–8.
12. Chen Y, Huang Y, Li X, Xu M, Bi Y, Zhang Y, Gu W, Ning G. Association of arterial stiffness with HbA1c in 1,000 type 2 diabetic patients with or without hypertension. *Endocrine*. 2009; 36(2): 262–7.
13. Andersen KK, Andersen ZJ, Olsen TS. Age-and Gender-Specific Prevalence of Cardiovascular Risk Factors in 40 102 Patients with First-Ever Ischemic Stroke A Nationwide Danish Study. *Stroke*. 2010; 41(12): 2768–74.
14. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR. Glucose control and vascular complications in veterans with type 2 diabetes. *New England Journal of Medicine*. 2009; 360(2): 129–39.
15. Ergul A, Kelly-Cobbs A, Abdalla M, Fagan SC. Cerebrovascular complications of diabetes: focus on stroke. *Endocrine, metabolic & immune disorders drug targets*. 2012; 12(2): 148.
16. Eeg-Olofsson K, Cederholm J, Nilsson PM, Zethelius B, Svensson AM, Gudbjörnsdóttir S, Eliasson B. New aspects of HbA1c as a risk factor for cardiovascular diseases in type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR). *Journal of internal medicine*. 2010; 268(5): 471–82.
17. Zhao W, Katzmarzyk PT, Horswell R, Wang Y, Johnson J, Cefalu WT, Ryan DH, Hu G. Blood pressure and stroke risk among diabetic patients. *The Journal of Clinical Endocrinology & Metabolism*. 2013; 98(9): 3653–62.
18. Gerber PA, Thalhammer C, Schmied C, Spring S, Amann-Vesti B, Spinaz GA, Berneis K. Small, dense LDL particles predict changes in intima media thickness and insulin resistance in men with type 2 diabetes and prediabetes—a prospective cohort study. *PLoS one*. 2013; 8(8): e72763.
19. Araki A, Iimuro S, Sakurai T, Umegaki H, Iijima K, Nakano H, Oba K, Yokono K, Sone H, Yamada N, Ako J. Non-high-density lipoprotein cholesterol: An important predictor of stroke and diabetes-related mortality in Japanese elderly diabetic patients. *Geriatrics & gerontology international*. 2012; 12(s1): 18–28.
20. Zhao W, Katzmarzyk PT, Horswell R, Wang Y, Johnson J, Hu G. Sex differences in the risk of stroke and HbA1c among diabetic patients. *Diabetologia*. 2014; 57(5): 918–26.
21. Peters SA, Huxley RR, Sattar N, Woodward M. Sex differences in the excess risk of cardiovascular diseases associated with type 2 diabetes: potential explanations and clinical implications. *Current cardiovascular risk reports*. 2015; 9(7): 1–7.
22. Hewitt J, Castilla Guerra L, Fernández-Moreno MD, Sierra C. Diabetes and stroke prevention: a review. *Stroke research and treatment*. 2012; 2012.
23. Bouchi R, Babazono T, Mugishima M, Yoshida N, Nyumura I, Toya K, Hayashi T, Hanai K, Tanaka N, Ishii A, Iwamoto Y. Fluctuations in HbA1c are associated with a higher incidence of cardiovascular disease in Japanese patients with type 2 diabetes. *Journal of diabetes investigation*. 2012; 3(2): 148–55.