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ASSESMENT OF PLASMA RANDOM BLOOD GLUCOSE AND GLYCATED HAEMOGLOBIN LEVELS IN HYPERTENSIVE SUBJECTS IN SOME HOSPITALS IN ANAMBRA STATE, NIGERIA.

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ABSTRACT

Hypertension is an important and major global public health problem.This study is designed to assess plasma random blood glucose and glycated hemoglobin levels in hypertensive (non-diabetic) subjects in some hospitals in Anambra state, Nigeria. A total of 80 subjects were recruited (40 non-diabetic hypertensive and 40 normotensive non-diabetic who served as the control group). Blood samples were collected from the non-diabetic hypertensive subjects as well as the control group. Plasma random blood glucose levels were estimated by the Glucose Oxidase Method while glycated hemoglobin levels were determined using spectrophotometric method. The mean glycated haemoglobin (Hb/Ac) and plasma random blood glucose (RBG) levels in non-diabetic hypertensive subjects were significantly higher when compared to control group (p=0.000). The correlation of plasma RBG levels and Hb1Ac to diastolic blood pressure (DBP) in non-diabetic hypertensive subjects were not significantly different when observed among the group (p>0.05). However, a positive weak correlation was observed in the mean Hb1Ac (r=0.045) of the non –diabetic hypertensive. In contrast, no significant difference was observed in the correlation of plasma

RBG levels and Hb1Ac to systolic blood pressure (SBP) in non-diabetic hypertensive subjects ($p>0.05$). Interestingly, the mean plasma RBG and Hb1Ac levels did not differ significantly when compared among different age groups in non-diabetic hypertensive subjects ($p>0.05$). Moreover, the mean plasma RBG levels and Hb1Ac in non-diabetic hypertensive subjects taking antihypertensive medication and those not taking medication were not significantly ($p>0.05$) different when compared among the groups ($p>0.05$). Therefore, it was observed that non-diabetic hypertensive subjects are at risk of developing diabetes as their diastolic blood pressure increases in the near future.

KEY WORDS: Hypertension, Diabetes, non-diabetic hypertensives, **S**ystolic blood pressure (SBP), Diastolic blood pressure, Age, Glycated haemoglobin (Hb/Ac), Random blood glucose (RBG).

INTRODUCTION

Hypertension, also known as High Blood pressure (HBP), is a common, important and major global public health problem (Wolf – Maier *et al*., 2003). Black individuals have a higher prevalence and incidence of hypertension than white persons (Brown, 2006). Blood pressure is the force exerted by the blood against the walls of blood vessels, and the magnitude of this force depends on the cardiac output and the resistance of the blood vessel (George, 2015). Blood pressure is expressed by two measurements; the systolic and diastolic pressures (CDCP, 2015). Normal blood pressure at rest is within the range of 100–140 millimeters mercury (mmHg) systolic and 60–90 mmHg diastolic (Giuseppe *et al*., 2013). Blood pressure is said to be high if the resting blood pressure is persistently at or above 140/90 mmHg for most adults (Poulter *et al.*, 2015). Hypertension can be caused by family history of heart disease, stress, high fat, high sodium diet, sedentary life style, advanced age, obesity, smoking, too little potassium or vitamin D, chronic diseases like kidney disease, diabetes and sleep apnea. It have been discovered as the major risk factor for kidney failure, diabetes, and cardiovascular disorders such as stroke, heart failure, peripheral artery disease, coronary heart disease, ischemic heart disease and heart attack (Lewington *et al*., 2002). According to Kearney *et al.,* (2005) by 2025 about 75% of the world hypertensive population will be in developing countries. In Nigeria for example it is the number one risk factor for stroke, heart failure, ischemic heart disease, and kidney failure. With an increasing adult population as well as rising prevalence of hypertension, Nigeria will experience economic and health challenges due to the disease if the tide is not arrested.Hypertension is a common condition

which usually co-exists with diabetes mellitus (DM) and aggravates DM complications as well as cardiovascular morbidity and mortality. Hypertension is associated with bad prognosis when it is associated with DM, male sex, older age, obesity, hypercholesterolemia, black race, smoking and excessive alcohol intake and lack of exercise (Williams, 2001).

Random plasma glucose otherwise called casual blood glucose measures blood glucose regardless of when last an individual ate. Although the most widely accepted glucose base criteria diagnosis is fasting plasma glucose (FPG)126mg/dl or 2 hours plasma glucose, 200mg/dl during an oral glucose tolerance test (OGTT) on more than one occasion (WHO, 2006). Random testing is useful because glucose levels in healthy individuals do not vary widely throughout the day. In a patient with classic symptoms of diabetes, single random plasma glucose 200mg/dl is considered diagnostic (American Diabetes Association, 2010).

Glycated hemoglobin (HbA_{1c}), a marker of chronic hyperglycemia, is the standard measure for monitoring glucose control in diabetic patients and recently was recommended for use in the diagnosis of diabetes (ADA, 2010; WHO, 2011). HbA1c is a measure of the beta-N-1-deoxy fructosyl component of hemoglobin (Miedema, 2005).Elevated HbA_{1c} strongly predicts the development of diabetes (Sevin *et al.*, 2010; Heianza *et al*., 2011) and is independently associated with cardiovascular outcomes even in individuals without a diabetes diagnosis (Adams *et al*., 2009; Sarwar *et al*., 2010).HbA1c reflects the average plasma glucose control over a period of 2-3 months therefore effectively used as a marker for evaluating glucose level (Hasan *et al*., 2004). It is the non-enzymatic binding of hemoglobin with glucose (Akinloye *et al*., 2007; Manjunatha *et al*., 2011).

There is high frequency of co-occurrence of diabetes and hypertension all over the world. Such association results in higher rate of cardiovascular complications. Several studies have shown that raised blood pressure is more prevalent in people with diabetes than in the general population (HDSG, 1993; Cowie *et al*., 1995). Hence, information gotten from this study could help clinicians or health professionals in the diagnosis, management and treatment of non-diabetics hypertensive patients, thereby helping to curb or prevent the development of diabetes in the near future.

MATERIALS AND METHODS

Study site

This research was done in Nnamdi Azikiwe University Teaching Hospital (NAUTH), Mercy Specialist Hospital, Nnewi North L.G.A, Diocesan Hospital, Amichi Nnewi South L.G.A, and Ifebi Medical Center Akwa, Anambra state, Nigeria.

Study Design

This a case control study designed to assess the plasma random blood glucose and glycated haemoglobin levels in hypertensive subjects in some hospitals in Anambra State, Nigeria. A total of 113 subjects were randomly recruited for this study. This includes 60 known non-diabetic hypertensive subjects and 53 apparently healthy subjects (control subjects). A well-structured questionnaire was used to obtain data such as age, presence of any other form of complication and lifestyle of the subjects which will be used as overall index of eligibility. Thereafter, Five (5) ml of fasting venous blood was collected and dispensed into appropriate anticoagulant containers. The sample for random blood glucose (2mls) was dispensed into fluoride oxalate anticoagulant container, and properly mixed with the anticoagulant. The remaining 3mls was dispensed into an EDTA anticoagulant container for glycated haemoglobin estimation and was properly mixed with the anticoagulant. Thereafter, biochemical parameters were assayed using standard laboratory methods. RBG was estimated using glucose oxidase method as described by Bergmeyer and Bernt, (1974), whereas, glycated haemoglobin estimation was done using spectrophotometeric.

Ethical issues and approval

Before the commencement of this study, an ethical approval was obtained from the ethics committee of Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, Anambra State, Nigeria. Informed consent of subjects were sought and obtained also.

Inclusion criteria and Exclusion criteria

Known hypertensive non - diabetic subjects were included for the study while non hypertensive subjects and Diabetic subjects were excluded from the study.

Statistical Analysis

Statistical package for social science (SPSS version 20) was employed in the analysis of the data collected. The results for parameters studied were expressed as mean standard deviation

and compared between the groups using student's t- test and ANOVA, with level of significance set at $p<0.05$. Correlation of parameters was done using Pearson's correlation.

RESULTS

The mean glycated haemoglobin (HbAc) and the mean random blood glucose levels (RBG) in non-diabetic hypertensive subjects were significantly ($p<0.05$) higher when compared to those of apparently healthy subjects (control group), (table 1).

Table 1: Comparison of plasma random blood glucose and glycated haemoglobin levels in non-diabetic hypertensive subjects and control group.

Parameters	Non-Diabetic Hypertensive N=40	Control N=40	T-Value	P-Value
RBG	5.50 ± 0.91	4.51 ± 1.93	4.852	**0.000****
HbAC	11.32 ± 1.17	6.98 ± 7.59	18.261	**0.000****

***Statistically significant at p<0.05.**

The mean plasma RBG levels and HbAc were not significantly ($p>0.05$) different when observed among different age groups (40 years and above) in non-diabetic hypertensive subject (table 2).

Table 2: Comparison of plasma random blood glucose and glycated haemoglobin levels among different age groups in non-diabetic hypertensive subjects (Mean±STD).

Parameters	41-50 Years N=9	51-60 Years N=11	61-70 Years N=10	>70 Years N=10	F-Value	P-Value
RBG	5.93 ± 0.80	5.27 ± 1.08	5.86 ± 0.56	4.99 ± 0.87	2.800	0.054
Hb1AC	11.90 ±0.53	10.58 ±1.44	11.38 ±1.21	11.54 ±0.90	2.621	0.066

***Statistically significant at p<0.05.**

Again, the mean plasma RBG levels and HbAc in non-diabetic hypertensive subjects taking antihypertensive medication and those not taking medication were not significantly ($p>0.05$) different when observed among the groups (table 3).

Table 3: Comparison of plasma random blood glucose and glycated haemoglobin levels in non-diabetic hypertensive subjects taking antihypertensive medication and those not taking medication (MEAN±STD).

Parameters	YES N=36	NO N=4	T-Value	P-Value
RBG	5.53 ± 0.90	5.23 ±1.10	0.624	0.536
Hb1AC	11.24 ± 1.19	12.03 ± 0.63	-1.288	0.206

***Statistically significant at p<0.05.**

The mean correlation of plasma RBG levels and HbAc to systolic blood pressure (SBP) in non-diabetic hypertensive subjects were not significantly (p>0.05) different when observed among the group (table 4).

Table 4: Correlation of plasma random blood glucose and glycated haemoglobin levels and SBP and DBP in non-diabetic hypertensive subjects.

Parameters	RBG		Hb1AC	
	r-VALUE	P-VALUE	r-VALUE	P-VALUE
SBP	-0.076	0.643	0.210	0.193
DBP	0.170	0.293	0.319	**0.045****

***Statistically significant at p<0.05.**

More so, the mean correlation of plasma RBG levels and HbAc to diastolic blood pressure (DBP) in non-diabetic hypertensive subjects were not significantly (p>0.05) different when observed among the group. Expect a positive weak correlation observed in the mean Hb1Ac (r=0.045) of the non –diabetic hypertensive (table 4 and fig 1).

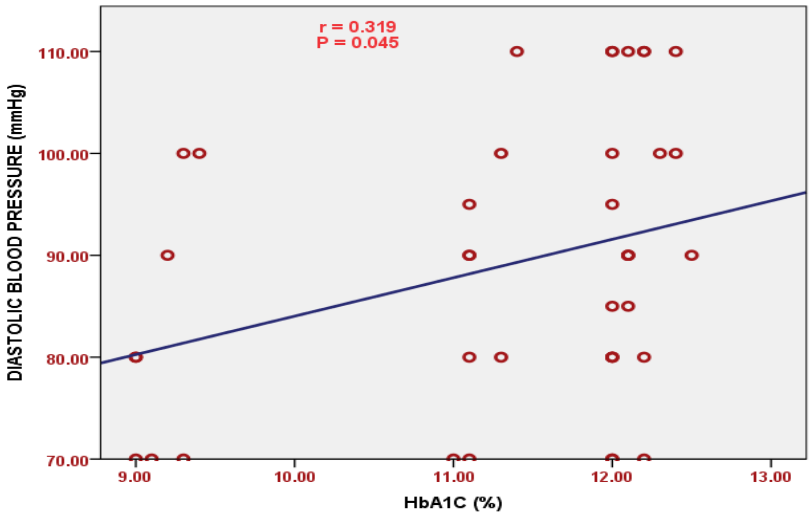

Fig 1: Correlation of plasma glycated haemoglobin levels (HbA1c) and DBP in non-diabetic hypertensive subject.

DISCUSSION

Hypertension is a growing epidemic affecting an important percentage of the population(Kearney *et al*., 2005). Hypertensive patients have increased risk for the development and progression of both microvascular and macrovascular complications. As a result the need for a comprehensive management of high blood pressure is essential.

In the present study, the mean glycated haemoglobin (11.32 ± 1.17) and the mean random blood glucose levels (5.50 ± 0.91) in non-diabetic hypertensive subjects were significantly ($p<0.05$) higher when compared to those of apparently healthy subjects (control group). Anital *et al*.,(2015) reported similarly a significantly high ($p <0.0001$) mean glycated hemoglobin level of 6.44 ± 1.20 in the hypertensive group and c 4.59 ± 1.48 in the control group. In his study, about 40% of the hypertensive group compared to 60% of the control group were found to have HbA1c in the range of prediabetics. This significant increase may be as a result that hypertension is associated with increased HbA1c level, because of the tendency of cardio-metabolic risk factors to cluster, particularly with central adiposity. Increased glycation of proteins may be found in non-diabetic hypertensive subjects, as a result that lipid peroxidation plays a role in glycation of hemoglobin and plasma protein. This is because one of the end product of lipid peroxidation malondialdehyde increases the glycation of haemoglobin and the production of fructosamine. Elevated serum glucose levels may be associated with low HDL levels even during antihypertensive therapy, independent of the potential impact of treatment with losartan vs atenolol, HCTZ and statins, and of other potential factors that could influence glucose levels. Low HDL may stimulate the development of abnormal glucose tolerance and provide insights into the relationship between low HDL and development of diabetes. Elevated HbA1c levels may be associated with the development of retinopathy and as well as other complications.

In this study, the correlation of glycated hemoglobin levels to diastolic blood pressure (DBP) in non-diabetic hypertensive subjects showed a significant positive weak relationship, ($r = 0.045$) and but not significant with SBP. Similarly, Connor *et al.*, (2015) in his study; meta-analysis assessing the link between blood pressure and risk of diabetes, found that a higher diastolic blood pressure of 10mmHg was associated with a 52% higher risk of diabetes (HR 1.52; 95% CI 1.51 to 1.54). Sandra *et al*., (2016), in their study also reported that systolic blood pressure (SBP), diastolic blood pressure (DBP) and a higher HbA when compared with the control children and adolescents in multiple regression to predict

alterations in DBP from HbA adjusted for age, disease duration, and body mass index demonstrated a positive relationship with DBP ($P < 0.05$) and any 1% increase in HbA was found to be associated with 1.73 mmHg increase in DBP and no significant correlation with SBP. The effect DBP on HbA1c may be as a result of resistance to insulin action on glucose uptake in peripheral tissues which is a common underlying mechanism in hypertension and diabetes.

Furthermore, the mean glycated haemoglobin levels and plasma random blood glucose in the non-diabetic hypertensive subjects taking medication and that of those not taking medication were not significantly different ($p > 0.05$). Verdecchia *et al.,* (2004) and Almgren *et al.,* (2007), in contrast reported a minimum, increase in the glycemic level of hypertensive patients taking antihypertensive medication and Barzilay *et al.,* (2006) similarly reported as in this study that; this glycemic increase is independent of the type of antihypertensive therapy. The difference in the reports from this studies, results from the fact that various classes of antihypertensive drugs have different effects on blood glucose metabolism. Certain agents have been associated with insulin resistance and diabetes mellitus, which are independent predictors of cardiovascular morbidity. Antihypertensive drugs induce glycemic defects via various mechanisms such as; effects on peripheral blood flow, effects on the insulin receptor, effects on the liver and effects on insulin release. Indeed, antihypertensive agents, such as β-blockers and thiazide diuretics have been associated with negative effects on blood glucose in contrast to other classes, such as angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACE-I) which have been associated with beneficial effects on glucose homeostasis. Calcium channel blockers (CCBs) have an overall neutral effect on glucose metabolism. Improved peripheral blood flow to skeletal muscles is thought to facilitate glucose disposal to the tissues. In this way, medications such as alpha-blockers, which promote peripheral vasodilation, may improve insulin sensitivity and glucose uptake. Through the same mechanism, ACEIs or ARBs may improve insulin sensitivity by reducing angiotensin II-mediated vasoconstriction and/or increasing vasodilators such as bradykinin, prostaglandins or nitric oxide.

Conversely, medications that reduce peripheral blood flow could direct blood away from sites of glucose uptake, reducing glucose disposal. Non-selective beta-blockers limit peripheral blood flow by reducing cardiac output, a beta-1-mediated effect, and preventing peripheral vasodilation, a beta-2-mediated effect (Pollare *et al.,*1989). Beta-blockers with intrinsic

sympathomimetic activity are less likely than non-selective agents to reduce peripheral blood flow because of neutral or stimulatory effects on beta-2 receptors. Therefore, these agents may have a reduced impact on glucose disposal and insulin sensitivity compared with non-selective beta-blockers. Cardio-selective beta-blockers are also less likely to reduce peripheral blood flow than non-selective agents; however, cardio-selective beta-blockers still exhibit some glycemic adverse effects. In support of the blood flow hypothesis, is the observation that reduced capillary density in skeletal muscle places individuals at a greater risk for beta-blocker-induced glycemic effects. Insulin sensitivity may also be altered through effects on the insulin receptor or downstream signalling. Although few studies have directly examined changes to the insulin receptor, it appears that some antihypertensive agents may modify its activity. Hypokalemia can be linked to reduced insulin-receptor sensitivity, but this theory has not been consistently supported (Helgeland *et al.*,1994; Reneland *et al.*,2000). Various antihypertensive agents could alter glucose transport proteins (GLUT 1 and GLUT 4), tyrosine kinase activity, or insulin receptor binding affinity. However, more information is needed to evaluate these effects.

Two other potential sources of altered glucose control include hepatic insulin resistance and impaired insulin release. It has been suggested that thiazide diuretics promote hepatic insulin resistance, resulting in continued hepatic glucose production despite rising serum glucose or insulin level. Although this effect has been observed with high-dose thiazide diuretics, it is less apparent with lower doses (12.5 mg to 25 mg of hydrochlorothiazide daily) used in current practice. Inhibition of insulin release can lead to hyperglycemia, and beta-blockers have long been considered to inhibit insulin release through pancreatic beta-receptor blockade. Similarly, diuretic therapy has also been associated with impaired insulin release through depletion of serum potassium. However, because insulin levels are higher than normal in most patients with diabetes, this mechanism is unlikely to be of major importance. Based on the already existing postulate, theories and findings on the adverse effect and benefits of some types of antihypertensive agents, the reason for the mean glycated haemoglobin levels and plasma random blood glucose levels in the non-diabetic hypertensive subjects taking medication in this study not being significant, may be an indication that these hypertensive subjects uses antihypertensive agents which favours glucose metabolism.

The study done by Gary *et al.,(*2006) reported that the correlation coefficients between age and plasma glucose levels in fasting, 2-hour post-prandial, and random group of patients were

0.159, 0.169, and 0.114, respectively (adjusted for body mass index, smoking, and gender; all *P* values <0.001). Fasting and random plasma glucose level increased by 0.15 mmol/L, while 2-hour post-prandial plasma glucose level increased by 0.26 mmol/L per decade-increase in age. In this present study, the mean random blood glucose levels and glycated hemoglobin in contrast were not significantly different when observed among different age groups (40 years and above) in non-diabetic hypertensive subject (p> 0.05). The difference between the two results may be as a result of analytical error. It may also be as a result of increase in the utilization of glucose in the body which may be due to increase demand on the utilization of ATP in the body due to environmental factors.

CONCLUSION

From the evaluations made in this study, non-diabetic hypertensive subjects are at risk of developing diabetes in future. Glycated hemoglobin is associated with slightly raise diastolic blood pressure. Therefore, non-diabetic hypertensives are at high risk of developing diabetes as their diastolic blood pressure increases.

RECOMMENDATION

Constant monitoring of blood pressure and blood glucose level through routine check- up is recommended for the non-diabetic hypertensive and normotensive non-diabetics to avoid the development of diabetics and its horrible complication.

REFERENCES

1. Adams, R.J., Appleton, S.L., Hill, C.L. Independent association of HbA(1c) and incident cardiovascular disease in people without diabetes. *Obesity (Silver Spring) 2009;* 17: 559–563.
2. Akinloye, O.A., Adaramoye, O.A., Akinlade, K.S., Odetola, A.A., Raji, A.A. Relationship between Fasting Plasma Glucose and Glycated Haemoglobin in Adult Diabetic Nigerians. *African Journal of Biomedical Research 2007*; 10(2): 127-32.
3. Almgren, T., Wilhelmsen, L., Samuelsson, O., Himmelmann, A., Rosengren, A. and Andersson, O.K. Diabetes in treated hypertension is common and carries a high cardiovascular risk: Results from a 28-year follow-up. *Journal of* Hypertension, 2007; 25: 13117.
4. American diabetes Association Diagnosis and classification of diabetes mellitus. *Diabetes care*; 2010; 33(1): 62 –69.

5. Barzilay, J.I., Davis, B.R. and Cutler, J.A. ALLHAT Collaborative Research Group. Fasting glucose levels and incident diabetes mellitus in older nondiabetic adults randomized to receive 3 different classes of antihypertensive treatment: A report from the Antihypertensive and Lipid- Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Archives Internal Medicine*, 2006; 166: 2191- 2201.
6. Brown, M.J. Hypertension and ethnic group. *British Medical Journal*. 2006; 332(7545): 833-836.
7. Center for Disease Control and prevention (2015). "*High Blood Pressure Fact Sheet*". *Journal of Hypertension*, 1995; 25(3): 305-313.
8. Connor, A., Emdin, H., Simon, G., Anderson, Mark, W. and Kazem, R. Usual blood pressure and risk of new-onset diabetes. *Journal of the American College of Cardiology*, 2015; 66(14): 1552–1562.
9. Cowie, C.C., Harris, M.I. Physical and metabolic characteristics of persons with diabetes. In: Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennett PH, editors. Diabetes in America. 2nd. Washington DC: National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases., 1995.
10. Executive summary standards of medical care in diabetes. *Diabetes care*; 2010; 33(l): 4.
11. Gary, T. C., Hendena, P. S. W., Joyce, S. F. T., Effect of Age on Plasma Glucose Levels in Non-diabetic Hong Kong Chinese. Croatian Medical Journal; 2006; 47(5): 709-713
12. George B. Merck Manual, professional edition, edited by Robert Porter et al., published online at merck manuals.com by Merck & Co. Overview of hypertension. Hypertension and Diabetes overview". *Medical journal of Australia., 2015.*
13. George, B. Overview of hypertension, Merck *Manual*, professional edition, edited by Robert Porter et al., published online at merckmanuals.com by Merck & Co. Hypertension and Diabetes overview". *Medical journal of Australia*., 2015.
14. Giuseppe, Mancia., Fagard, R., Narkiewicz, K., Redon, J., Zanchetti, A., Bohm, M., Christiaens, T., Cifkova, R., De Backer, G., Dominiczak, A., Galderisi, M., Grobbee, D.E., Jaarsma, T., Kirchhof, P., Kjeldsen, S.E., Laurent, S., Manolis, A.J., Nilsson, P.M., Ruilope, L.M., Schmieder, R.E., Sirnes, P.A., Sleight, P., Viigimaa, M., Waeber, B., Zannad, F., Redon, J., Dominiczak, A., Narkiewicz, K. and Nilsson, P.M. ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *European Heart Journal, 2013;* 34(28): 2159–2219.

15. Hasan, Z.U., Zia, S., Maracy, M. Baseline disease knowledge assessment in patients with type 2 diabetes in a rural area of northwest of Pakistan. *Journal of Pakistan Medical Association*; 2004; 54: 67-72.
16. Heianza, Y., Hara, S., Arase, Y. HbA1c 5·7–6·4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study. *Lancet*; 2011; 378: 147–155.
17. Helgeland, A., Leren, P., Foss, O. P., Hjermann, I., Holme, I., Lund-Larsen, P. G., Serum glucose levels during long-term observation of treated and untreated men with mild hypertension. The Oslo study. *Americal Journal of Medicine*. 1994; 76: 802–805.
18. Hypertension in Diabetes Study Group HDS I: prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardio-vascular and diabetic complications. *Journal of Hypertension*; 1993; 11: 309–317.
19. Kearney, P. M., Whelton, M., Reynolds, K., Muntner, p., whelton, P. K., The Global burden of hypertension: analysis of world wide data. *The Lancet*; 2005; 365: 217-223.
20. Lewington, S., Clarke, R., Qizilbash, N., Peto, R. and Collins, R. Age –specfici relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *The Lancet;* 2002; 360(9349): 1903-1913.
21. Manjunatha, G.B.K., Bhavna, N., Sarsina, D.O., Sathisha, T.G., Shivashanker, Devaki, R.N. Relation of calculated HbA1c with fasting plasma glucose and duration of diabetes. International Journal of Applied Biology and Pharmaceutical Technology; 2011; 2(2): 58-61.
22. Miedema, K. Standardization of HbA1c and Optimal Range of Monitoring. *Scandinavian Journal of Clinical and Laboratory Investigation,* 2005; 240: 61–72.
23. Pollare, T., Lithell, H., Selinus, I., Berne, C., Sensitivity to insulin during treatment with atenolol and metoprolol: A randomised, double blind study of effects on carbohydrate and lipoprotein metabolism in hypertensive patients. *British Medical Journal.* 1989; 298: 1152–1167.
24. Poulter, N.R., Prabhakaran, D. and Caulfield, M. *Hypertension*., 2015.
25. Reneland, R., Alvarez, E., Andersson, P. E., Haenni, A., Byberg, L., Lithell, H., Induction of insulin resistance by beta-blockade but not ACE-inhibition: Long-term treatment with atenolol or trandolapril. *Journal of Human Hypertension*. 2000; 14: 175–180.
26. Sandra de Oliveira, Dahan da Cunha Nasciment, Ramires, A. T., Samuel Lima de Oliveira, Ivo Vieira de Sousa Neto, Roberta Kelly Menezes Maciel Falleiros, Leonardo, G.M., Hermelinda, C.P., James, W.N., Guilherme, B.P., & Jonato, P. Elevated glycated

hemoglobin levels impair blood pressure in children and adolescents with type 1 diabetes mellitus. *Diabetology & Metabolic Syndrome*, 2016; 8: 4.

27. Sarwar, N., Aspelund, T., Eiriksdottir, G. Markers of dysglycaemia and risk of coronary heart disease in people without diabetes: Reykjavik prospective study and systematic review. *PLoS Medicine*; 2010; 7: e1000278.
28. Selvin, E., Steffes, M.W., Zhu, H. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *New England Journal of Medicine*; 2010; 362: 800–811.
29. The international expert committee international expert committee report on the A1c assay in the diagnosis of diabetes *Diabetes care*; 2009; 32: 1327-1334.
30. Verdecchia, P., Reboldi, G., Angeli, F. Adverse prognostic significance of new diabetes in treated hypertensive subjects. *Hypertension*; 2004; 43: 963-999.
31. Williams, G. H. Hypertensive Vascular Disease. *Harrison's Principles of internal medicine. 15th Ed.* 2001; 1414-1429.
32. Wolf –Maier, K., Cooper, R.S., Banegas, J. S., Giampaolis, Hense, H. W., Roffres, M., Kastarinen, M., Poulter, N., Primatesta, P. and Rodriguez – Artalejo, F. Hypertension Prevalence and blood pressure levels in 6 European countries, Canada, and the united states *jama.jama. network.com/.../jouornal.aspx*; 2003; 289: 2363-2369.
33. World Health Organization Definition and Diagnosis* of Diabetes Mellitus and intermediate Hyperglycermia: Report of a WHO // DF consuitation., 2006.
34. World Health Organization Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus: Abbreviated Report of a WHO Consultation. Geneva, World Health Org. (Report no. WHO/NMH/CHP/CPM/11.1)., 2006.