Metabolic Profile as a Predictor of Ischaemic Stroke: The Experience of a Rural Hospital in Nigeria

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Abstract

BACKGROUND

The metabolic profile which includes glycated haemoglobin, insulin resistance, pancreatic beta cell function and lipid profile is frequently deranged in acute ischaemic stroke. Stroke is a leading cause of death worldwide and an emerging cause of long-term disability and mortality in Africa. Our study aimed to determine the correlation between the metabolic profile and acute ischaemic stroke in a rural Hospital in Southern Nigeria.

METHODOLOGY

This was a prospective cross-sectional study. Fifty consecutive first-ever ischaemic stroke patients presenting within 72 hours of stroke were matched for age and sex with 3 control groups (49 persons with type 2 diabetes and hypertension, 49 persons with hypertension only and 57 apparently healthy individuals). Blood samples were obtained from all participants to determine glycated haemoglobin, fasting lipid profile, fasting plasma glucose, fasting insulin and C-peptide and random plasma glucose (in stroke cases at presentation). Insulin resistance and pancreatic beta-cell function were determined using the Homeostatic Model Assessment (HOMA). Data were analysed by multivariate and univariate statistics.

RESULTS

One hundred and two (49.8%) males and 103 (50.2%) females participated in the study. The overall mean age of the study participants was 61.6 ± 10.1 years. Compared with the control groups, predictors of acute ischaemic stroke were Fasting insulin (hyperinsulinaemia) [OR (95%CI) = 1.108 (1.043-1.178), p= 0.001], HOMA-β% [OR (95%CI) = 0.994 (0.990-1.001) p=0.006] and total cholesterol [OR (95%CI)= 0.009 (0.001-0.012) p=0.022].

CONCLUSION

In this study, hyperinsulinaemia, impaired beta-cell secretory function (HOMA-β) and elevated total cholesterol were found to be significant risk factors of ischaemic stroke. Hence, the need for regular screening to detect abnormal metabolic profiles and prompt treatment.

Keywords: *C-Peptide, Fasting Insulin, Glycated Haemoglobin, Insulin Resistance, Stroke*

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Introduction

Interrelated metabolic risks which include elevated blood pressure, insulin resistance, chronic hyperglycaemia, abdominal obesity and dyslipidaemia increase the risk of cardiovascular events and cardiovascular morbidity and mortality [1]. Insulin resistance (IR) is a state of reduced insulin sensitivity accompanied by compensatory hyperinsulinaemia [2]. Insulin resistance is an emerging important risk factor for vascular disease that has been associated with an increased risk of myocardial infarction, stroke, and carotid atherosclerosis[1]. The mechanism for the association has been linked with synergism between IR and other cardiovascular risk factors which include dyslipidaemia, hypertension, hypercoagulability, increased platelet reactivity and endothelial dysfunction all of which predispose to atherosclerosis [1].

The worldwide prevalence of IR varies partly due to different methods of assessment of IR. The prevalence of IR varies among different populations, the global prevalence of IR ranges from 15.5% to 46.5% [3,4,5]. Insulin resistance is almost universal in persons with type 2 diabetes (T2DM) but it is also present in more than 50% of patients without diabetes presenting with ischaemic stroke or a transient ischaemic attack (TIA) [6]. Stroke is the most common of the vascular diseases seen in Sub-Saharan Africa and the mortality rate is higher in this region compared to the developed countries of the world [7]. The crude incidence of stroke in Nigeria is 26.0 (12.8-39.0)/100,000 person-years [8]. There is an increasing burden of stroke worldwide and this is largely due to failed management and prevention of modifiable risk factors. Early identification and prevention of modifiable risk factors would reduce the incidence of ischaemic stroke thereby reducing morbidity, and mortality and lower health care expenditure associated with stroke.

Insulin resistance is associated with an increased risk of vascular events. Individuals with IR have elevated levels of plasminogen activator inhibitors and fibrinogen, which enhance the coagulation process and impair fibrinolysis, thus favouring the development of thrombosis [1]. Insulin resistance is also associated with endothelial, vascular smooth muscle, and platelet dysfunction [1,2]. Blood markers of metabolic parameters that influence pathological processes preceding the onset of acute ischaemic strokes such as inflammation, haemostasis and neuronal injury need to be identified [9].

Metabolic syndrome (MS) also known as insulin resistance syndrome comprises cardiovascular risk factors which include DM or glucose intolerance, central obesity, high cholesterol and elevated blood pressure [10]. Type 2 diabetes carries a 2- to 5-fold increased risk of stroke compared with those without diabetes [11,12]. Other risk factors that predispose both T2DM and persons without diabetes to stroke include elevated blood pressure, smoking, advancing age, male sex, atrial fibrillation, hyperglycaemia, elevated total cholesterol, decreased HDL, elevated triglycerides, obesity, and sedentary lifestyle [12].

Cardiovascular disease previously considered rare in Africa is becoming increasingly prevalent probably owing to the adoption of the western lifestyle and the growing prevalence of DM and pre-diabetes [7]. Stroke carries a significant economic, social, and medical challenge to the patient, relatives, physician, and society.

Biomarkers can be used as screening tools in the prevention of stroke, this is important for the clinician, patient and researchers. Furthermore, establishing the correlation between the metabolic profile and acute ischaemic stroke will provide research-based data

for recommending intensive screening programs and improvement on treatment guidelines to reduce the prevalence of stroke. The study aimed to determine the correlation between the metabolic profile and acute ischaemic stroke in a rural setting.

Methodology

Study design, setting and population

This was a prospective study conducted at Irrua Specialist Teaching Hospital, Edo State, Nigeria. Fifty patients, 26 males and 24 females who were consecutively admitted between August 2015 and March 2016 with a diagnosis of a first-ever acute ischaemic stroke were made clinically using the updated definition of stroke [13] and confirmed by brain Computer Tomography scan (CT) at the Emergency ward.

The sample size was calculated using the prevalence of stroke from a previously published hospital-based research on stroke [14]. The control groups were age and sex-matched volunteers from the out-patient clinics, using a case-control ratio of 1:3. These comprised a set of 49 persons with T2DM and hypertension without previous vascular event, another set of 49 with hypertension but without diabetes or previous vascular event while the third set of 57 persons were apparently normal individuals. Patients with a history of pregnancy, liver or kidney failure and those who were on insulin therapy were excluded from the study. A summary of the recruitment of subjects for the study is shown in figures 1 and 2 in the appendix.

Data were collected on age, alcohol intake, smoking, and health history. A comprehensive physical examination was conducted to document each patient's clinical features this included: pulse rate and blood pressure (blood pressure of the right arm was measured by a mercury sphygmomanometer after 10 minutes of rest), weight, height, waist circumference, and hip circumference. Evaluation of the National Institutes of Health Stroke Scale (NIHSS) was done for stroke patients at admission.

Clinical laboratory analyses

Blood glucose estimation was determined by the Trinder reaction using the glucose oxidase method [15]. Fasting insulin concentrations were determined using a commercial enzyme-linked immunosorbent assay (ELISA), a solid phase two-site enzyme immunoassay based on the sandwich technology using Accubind kit® (Monobind Inc; Lake Forest, CA, USA). C-peptide determination was an ELISA kit based on the principle of competitive binding. Glycosylated haemoglobin (Hba1C) was estimated using the NycoCard® HbA1c analyzer system which is an automated boronate affinity assay.

Analytical variable specification

Hypertension was defined as sustained BP readings of systolic BP ≥ 140 or diastolic BP ≥ 90 mmHg or a history of antihypertensive medication use. Central (abdominal) obesity was defined as a waist circumference ≥ 94cm for males and ≥80cm for females (IDF values for Sub-Saharan Africa) [16]. Admission hyperglycaemia in stroke patients was defined as random plasma glucose greater than 7.8mmol/l (140mg/dl). Acute stroke management guidelines are silent on the definition of hyperglycaemia in stroke but recommended that blood glucose be maintained in a range of 7.8 to 10mmol/l (140 to 180 mg/dl) [17]. Pre-existing diabetes was defined as a history of diabetes or HbA1c ≥ 6.5% on admission [18]. The presence of insulin resistance using fasting insulin (FI) was defined using values within the top quartile of the healthy control participants' values (>9.4 µIU/ml) as a cut-off. Impaired fasting C-peptide was defined as (<2.1ng/ml), (values less than 2 standard deviations below the mean derived from the healthy control participants). The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) is defined as the product of fasting

plasma insulin (µU/ml) and fasting plasma glucose (mmol/l), divided by 22.5 [19]. HOMA-IR values within the top quartile were the cut-off for insulin resistance as reported in previous studies [20,21]. C-peptide- Modified HOMA index {HOMA-IR (CP) }= (1.5 + FPG) x fasting serum C-peptide) divided by 2800 [19,21,22]. The HOMA-IR values have been shown to correlate well with values obtained using the "gold standard" clamp technique [19]. Pancreatic beta cell function was determined by using the HOMA-ß % index calculated as the product of 20 and fasting plasma insulin (µIU/ml) divided by FPG (mmol/l) minus 3.5. A score of <100% was defined as impaired pancreatic beta cell function [20].

Ethical considerations

Ethical clearance was obtained from the Institutional Ethics Committee and informed written consent was obtained from all participants or proxies.

Data analysis

Statistical analysis was done using the Statistical Package for Social Sciences, SPSS version 23. Summary data were presented as mean, standard deviation, confidence intervals, proportions, charts, tables and figures.

Table 1:
Sociodemographic Characteristics of the Study Population

	Stroke (n=50)	**T2DM (n=49)**	**Hypertension (n=49)**	**Healthy control (n=57)**	**Total (n=205)p**	**χ^2,**
Gender						
Male	26 (12.7%)	25 (12.2%)	24 (11.7%)	27(13.1%)	102 (49.8%)	2.99,
Female	24 (11.7%)	24 (11.7%)	25 (12.5%)	30 (14.6%)	103 (50.2%)	0.89
Age grp (yrs)						
30-39	1	1	1	1	4 (1.9%)	4.39,
40-49	3	4	2	6	15 (7.4%)	0. 99
50-59	15	15	16	19	65 (31.7%)	
60-69	18	13	17	17	65 (31.7%)	
≥ 70	13	16	13	14	56 (27.3%)	
Educational status						
No education	20	10	8	12	50(24.4%)	19.84,
Primary	8	8	12	18	46(22.4%)	0.02
Secondary	13	10	14	7	44 (21.5%)	
Tertiary	9	10	15	20	65(31.7%)	
Occupation						
Trading	18	13	10	13	54(26.3%)	13.04,
Civil servant	9	21	26	29	85 (41.5%)	0.71
Pensioner	10	7	6	6	29 (14.1%)	
Farming	6	4	4	4	18 (8.8%)	
Others	7	4	3	5	19 (9.3%)	
Alcohol intake						
Never	30	33	37	42	142(69.3%)	24.06,
Past	8	9	7	12	36(17.6%)	0.01
Current	12	7	5	3	27(13.2%)	
Cigarette smoking						
Never	43	43	41	49	176(85.9%)	11.13,
Past	3	5	4	5	17 (8.3%)	0.08
Current	4	1	4	5	12 (5.9%)	

Note*:* no education - no formal education; age grp- age group; yrs- years.

Means and proportions were calculated for the clinical, anthropometric and biochemical variables and the significance of any intergroup differences between the 4 study groups was tested using the One-way analysis of variance (One-way ANOVA) for means and Chi-square for proportions. The biochemical indices of the study participants are summarized in Table 2. There were significant differences in the means of biochemical variables among the four study groups ($p < 0.05$) except for the C-peptide and LDL.

The four study groups differed significantly in the value of their mean HbA_{1c} ($p=0.001$), with the T2DM group having the highest mean while the healthy control group had the lowest mean HbA_{1c}. The mean HbA_{1c} in the stroke cases was 6.65±2.10. There were significant differences in insulin resistance measured by fasting insulin, HOMA-IR and HOMA-IR(CP) across the study group ($p<0.05$). The mean HOMA-IR and HOMA-IR(CP) in the stroke cases were 2.73 ± 2.90 and 1.05 ±0.69 respectively. There were significant differences in the means of the HOMA-ß% among the four study groups, with the healthy control group having the highest beta cell secretory function while the T2DM group had the lowest. Impaired beta-cell function (defined as HOMA-β < 100%) was present in 27 (54%) of the stroke cases. There were significant differences in the means of TC, TG and HDL among the four study groups ($p < 0.05$), however, there was no significant difference in the mean LDL across the study groups.

There were significant differences in fasting insulin in the four groups studied ($p = 0.003$), T2DM and stroke cases had higher percentages (28.6% and 24%) of hyperinsulinaemia compared with hypertension and healthy control group with percentage values of 14.3% and 8.8% respectively.

Table 2:
Comparison of Means of Metabolic Indices across the Study Participants

Variable	Stroke (n=50)	T2DM (n=49)	Hypertension (n=49)	Healthy control (n=57)	F	p-value
HbA_{1c} (%)	6.65±2.10	7.75±1.55	5.54±0.72	5.25±0.50	35.89	0.001
FPG (mmol/l)	6.07±2.08	7.55±3.71	4.92±0.62	4.87±0.59	19.61	0.001
FI (μIU/ml)	9.77±9.16	7.25±5.74	5.25±3.31	2.97±3.21	32.71	0.001
C-peptide (ng/ml)	4.04±3.02	1.51±1.38	4.26±1.77	5.86±1.46	2.88	0.210
HOMA-IR	2.73±2.90	2.33±1.89	1.14±0.69	1.64±0.70	15.79	0.001
HOMA-IR(CP)	1.05±0.69	1.47±0.44	0.73±0.39	0.47±0.44	12.63	0.001
HOMA-β (%)	73.46±24.76	63.39±28.43	96.05±23.97	113.77±17.70	45.26	0.001
TC (mmol/l)	4.87±0.04	4.67±0.97	4.85±0.91	4.35±0.79	3.69	0.013
TG (mmol/l)	1.15±0.47	0.90±0.46	1.06±0.40	1.02± 0.32	2.59	0.022
HDL (mmol/l)Male Female	1.13± 0.27 1.12±0.27	1.19 ± 0.17 1.25±0.17	1.16 ± 0.18 1.28±0.19	1.20 ± 0.17 1.30±0.15	1.60 5.75	0.028 0.001
LDL (mmol/l)	3.03±0.83	2.87±0.81	3.11±0.91	2.62±0.63	2.75	0.301

Note: F= One-way ANOVA. (C-peptide- connecting peptide; FI- fasting insulin; FPG- fasting plasma glucose; HDL- high-density lipoprotein cholesterol; HbA1c- glycated haemoglobin, HOMA-ß- homeostatic model assessment of pancreatic beta-cell secretion, HOMA-IR, homeostatic model assessment of insulin resistance using fasting insulin; HOMA-IR (CP), homeostatic model assessment of insulin resistance using c-peptide; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride).

The four groups significantly differed in insulin resistance indices assessed by HOMA-IR and HOMA-IR (CP) $p<0.05$, with the T2DM group having the highest percentages of 79.6% and 63.6% while the healthy control had the lowest percentages of 5.3% and 3.5% respectively. Proportions of insulin resistance indices are illustrated in Table 3.

The mean SBP, DBP, and MAP were 171.7±28.1, 100.0±18.4, and 123.9±20.2 mmHg, respectively. Forty-seven (94%) of the stroke participants presented with elevated blood pressure (≥ 140/90 mmHg). Thirty-seven (78.7%) were previously diagnosed to be hypertensive, 25 (67.6%) of them had discontinued treatment while 12 (32.4%) were on treatment for hypertension. Ten patients (21.3%) were previously undiagnosed before the onset of stroke (Table 4).

Twenty-six per cent of the stroke patients presented with an altered level of consciousness (GCS≤13/15). The mean NIHSS score was 11.2±5.9 (range: 3-30); using the NIHSS to assess stroke severity at presentation, 6 (12%) patients had a minor stroke (NIHSS score 0-4); 32 (64%) patients had a moderate stroke (NIHSS score 5-14); 7 (14%) had moderate to severe stroke (NIHSS score 15-19) while 5 (10%) patients had a severe stroke (NIHSS score ≥ 20).

The metabolic indices of stroke patients are illustrated in Table 4. The mean ± SD of random plasma glucose of stroke patients at presentation was 8.1mmol/l ± 3.3 (range 4.5-23.6mmol/l).

Table 3:
Frequency of Insulin Resistance in Study Participants

Insulin Index	Resistance	Stroke N=50	T2DM N=49	Hypertension N=49	Healthy control N=57	χ^2, p-value
FI (μIU/ml)	Normal	38 (76%)	35 (71.4%)	42 (85.7%)	52 (91.2%)	
	Abnormal	12 (24%)	14 (28.6%)	7 (14.3%)	5 (8.8%)	8.75, 0.003
HOMA-IR	Normal	34 (68%)	10 (20.4%)	45 (91.8%)	54 (94.7%)	
	Abnormal	16 (32%)	39 (79.6%)	4 (8.2%)	3 (5.3%)	15.79, 0.001
HOMA-IR(CP)	Normal	35 (70%)	18 (36.7%)	44 (89.8%)	55 (96.5%)	
	Abnormal	15 (30%)	31 (63.3%)	5 (10.2%)	2 (3.5%)	6.22, 0.001
C-peptide(ng/ml)	Normal	29 (58%)	8 (16.3%)	45 (91.8%)	54 (94.7%)	
	Abnormal	21 (42%)	41 (83.7%)	4 (8.2%)	3 (5.3%)	13.77, 0.060

Note*:* C-peptide – connecting peptide; FI- fasting insulin; HOMA-IR, homeostatic model assessment of insulin resistance using fasting insulin; HOMA-IR (CP), homeostatic model assessment of insulin resistance using c-peptide.

Table 4:
Description of Clinical Characteristics and Metabolic Indices in Stroke Participants

Clinical characteristics	Mean±SD	Range
Blood Pressure		
Admission SBP (mean±SD), mmHg	171.7±28.1	100-230
Admission DBP(mean±SD), mmHg	100.0±18.4	40-130
Admission MAP(mean±SD), mmHg	124.0±20.2	68-157
Admission NIHSS		
Admission NIHSS score (mean±SD)	11.2±5.9	3-30

Elevated RPG (≥7.8mmol/l) was seen in 23(46%) stroke cases at presentation, of which 11(47.8%) patients were previously diagnosed with diabetes, 3 (13%) patients were previously undiagnosed before the onset of stroke but had both elevated RPG and HbA1c while 9 (39.1%) patients had 'stress induced' hyperglycaemia as their RPG was elevated at presentation but their HbA_{1c} (<6.5%) and subsequent fasting blood glucose during admission were within normal limits.

Glycated haemoglobin was normal in 36 (72%) of stroke patients. To assess the metabolic indices with independent risk for ischaemic stroke multivariate regression analysis was conducted using a best-fit model. Fasting insulin (hyperinsulinaemia) was a predictor for acute ischaemic stroke versus healthy control (OR(95%CI) = 1.108 (1.043-1.178) p= 0.001), HOMA-β% was protective for ischaemic stroke versus controls (OR(95%CI) = 0.994 (0.990-1.001) p=0.006. Also, total cholesterol was a predictor of acute ischaemic stroke versus controls (OR(95%CI)= 1.982 (2.101-1.012), p=0.022. Table 5 shows the multiple regression analysis of metabolic indices.

Discussion

There is a growing body of evidence that abnormal metabolic indices which include insulin resistance, impaired pancreatic beta cell function and abnormal fasting lipid profile are risk factors for acute ischaemic stroke. There is a paucity of knowledge on the effect of metabolic indices on acute ischaemic stroke and the frequency of insulin resistance and pancreatic beta cell secretory function in stroke, as this has not been extensively studied in our environment.

Table 5:
Multiple Regression Analysis of Metabolic Indices

Metabolic indices	Cut-off value		Normal (%)	Abnormal (%)
Waist circumference	< 94 in ♂		18 (36%)	8 (16%)
(cm)	<80 in ♀		8 (16%)	16 (32%)
Waist hip ratio	0.90 in ♂	0.85 in ♀	3 (6%)	23 (46%)
			3 (6%)	21 (42%)
RBG at presentation (mmol/l)	≥ 7.8		27 (54%)	23 (46%)
HbA_{1c} (%)	6.5		36 (72%)	14 (28%)
FI(μIU/ml)	9.4		38 (76%)	12 (24%)
C-peptide (ng/ml)	2.1		29 (58%)	21 (42%)
HOMA-IR	2.2		34 (68%)	16 (32%)
HOMA-IR (CP)	1.3		35 (70%)	15 (30%)
HOMA-**ß** %	100		23 (46%)	27 (54%)
TC)(mmol/l)	5		31 (62%)	19 (38%)
TG (mmol/l)	3.75		41 (82%)	9 (18%)
LDL (mmol/l)	3.25		24 (48%)	26 (52%)
HDL (mmol/l)	>1 in ♂	>1.25 in ♀	18 (36%)	8 (16%)
			7 (14%)	17 (34%)

Note: ♂- male; ♀- female; C-peptide- connecting peptide; DBP- diastolic blood pressure; FI- fasting insulin; FPG- fasting plasma glucose; HDL- high-density lipoprotein cholesterol; HbA1c- glycated haemoglobin, HOMA-*ß*, homeostatic model assessment of beta cell secretory function; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-IR (CP), homeostatic model assessment of insulin resistance using c-peptide; MAP-mean arterial pressure; NIHSS- National Institute of Health Stroke Score; SBP-systolic blood pressure; TC- total cholesterol; TG, triglyceride.

The knowledge of the role of insulin resistance, dyslipidaemia and beta cell function could reinforce the institution of effective preventive and management plans. In this study, the frequency of insulin resistance in the stroke participants was moderated high and was determined by fasting insulin, C-peptide and HOMA-IR were 24%, 42% and 32% respectively. Earlier researchers reported a higher value of insulin resistance (50%) in persons presenting with ischaemic stroke and TIA [6]. Our finding may be due to different indices used to assess insulin resistance and difference in ethnicity of the study population.

There was a significant difference in the mean values of fasting insulin, C-peptide, HOMA-IR, HbA1c and HDL between the stroke group and hypertension group ($p \leq 0.05$). Pancreatic beta-cell function (HOMA- ß%) was impaired in slightly higher than half of the stroke cases. In this study, after controlling for confounders, the independent predictors of risk of ischaemic stroke were fasting insulin and HOMA-ß% while HbA1c and HOMA-IR (CP) did not seem to significantly predict the risk of developing stroke. An earlier report showed that pancreatic beta-cell dysfunction as measured by HOMA-ß% was a significant predictor of incident cardiovascular events and mortality after controlling for other confounders [23].

In the same context, findings from the IRIS trial (Insulin Resistance Intervention after Stroke) demonstrated that improving insulin sensitivity can prevent cardiovascular events including stroke in individuals with insulin resistance [20]. In contrast to an earlier report from a population-based study on the risk of stroke in non-diabetic elderly persons, fasting insulin and HOMA-IR levels were not associated with ischaemic stroke and haemorrhagic stroke after adjusting for multiple confounders [24]. The difference in findings may be due to differences in the age of the study population and ethnicity. Insulin resistance might be important in the pathological mechanism that results in ischaemic stroke, however, this conclusion needs further confirmation in larger studies.

Table 5:
Multiple Regression Analysis of Stroke Predictors

Variables	Odds ratio	95% CI	B	p-value
FPG (mg/dl)	0.024	0.010 - 0.040	0.998	0.320
CP (ng/ml)	0.089	0.048 - 0.193	1.191	0.235
FI (µIU/ml)	1.108	1.043 - 1.178	0.103	0.001*
HOMA-IR	0.091	0.084 - 0.099	0.168	0.867
HOMA-IR(CP)	0.500	0.250 - 0.751	0.988	0.324
HOMA-**ß**%	0.994	0.990 - 1.002	-9.918	0.006*
HbA1c (%)	0.079	0.025 - 0.108	1.234	0.219
TC	1.982	2.101 - 1.012	2.313	0.022*
TG	0.012	0.004 - 0.020	0.476	0.634
HDL	0.017	0.019 - 0.004	-1.272	0.205
LDL	0.114	0.124 - 0.100	0.211	0.833

Note: p value< 0.05 (significant predictors of acute ischaemic stroke); 95% CI- 95% confidence interval; CP- connecting peptide; FI- fasting insulin; FPG- fasting plasma glucose; HDL – high-density lipoprotein cholesterol; HbA1c- glycated haemoglobin, HOMA-ß - beta cell function; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-IR (CP), homeostatic model assessment of insulin resistance using c-peptide.

If the association between fasting insulin levels and ischaemic stroke is established, the need for therapeutic interventions that prevent or reverse insulin resistance might reduce the incidence of stroke. Furthermore, IR has also been reported to influence stroke outcomes. Calleja *et al* [25] reported that IR increased the risk of ischaemic stroke and contributed to persistent arterial occlusions and worse long-term outcomes after acute ischaemic stroke intra-arterial thrombolysis (reperfusion therapy). This may be explained by the hypothesis that hyperinsulinaemia results in a pro-thrombotic and pro-inflammatory state that is characterized by derangement in endogenous fibrinolysis [1].

Diabetes mellitus was seen in 28% of the cohort, a proportion close to this was reported in previous studies from Nigeria [14,26]. Diabetes mellitus is a major risk factor for the development of atherosclerosis and the excess risk of stroke in patients with DM is reported to be four times higher when compared with normal individuals in the general population [14].

Dyslipidaemia was seen in slightly higher than half (54%), and elevated TC was a significant predictor of ischaemic stroke (OR (95%CI)= 0.009 (0.001-0.012) p=0.022). This is similar to earlier reports that showed that an elevated lipid profile is associated with an increased risk of ischaemic stroke [27].

Waist circumference and waist-to-hip ratio did not seem to significantly predict stroke. This is in contrast to an earlier report which demonstrated that central obesity as determined by WC and WHR was associated with incident lacunar infarcts [28]. The difference in result may be due to the larger population size studied in the earlier work and variation in ethnicity.

Concerning stroke severity, this study showed a mean admission NIHSS score of 11.2±5.9 and a median score of 10. A large proportion had a moderate stroke (74%). This is similar to reports from previous studies [29,30]. Higher admission NIHSS scores have been associated with higher mortality after acute ischaemic stroke [29].

The 30-day case fatality rate in this study was 8% which is in agreement with earlier researchers [31]. However, higher rates were reported by earlier studies [14,29], the inclusion of haemorrhagic stroke which has a worse outcome is most likely the reason for the higher case fatality rates reported in these studies. In our environment stroke-related death is underestimated, as some patients may die before reaching the hospital or may seek alternative medicine. Mortality rates provide better estimates of deaths due to stroke, but this is best assessed in community-based multi-centre studies.

Strengths and Limitations

This study looked at IR using different indices which have not been well studied in stroke patients in Sub-Saharan Africa population. We estimated IR using HOMA-IR, which is frequently used in clinical studies and preferred to oral glucose tolerance test (OGTT). An advantage of HOMA-IR is that it can be performed in the acute phase of stroke as it is not contra-indicated in patients with severe stroke who may be unconscious or have bulbar palsy and are unable to swallow, hence OGTT may be detrimental. Insulin resistance in this study was derived from insulin resistance indices using hormonal-based methods rather than the hyperinsulinaemic euglycaemic clamp method which is considered the gold standard.

The insulin resistance indices used however have been shown to have a good correlation with the hyperinsulinaemic euglycaemic clap method. Also, Insulin sensitivity may be transiently impaired after a stroke due to acute-phase reaction. It would have been better to repeat fasting samples 2 weeks post-stroke and the average value used to assess the metabolic effect, but this could not be done due to logistics.

Conclusion

In summary, our study gives further insight into the metabolic profile in acute ischaemic stroke. Insulin resistance and impaired pancreatic beta cell function (HOMA-ß) are fairly common in acute ischaemic stroke. Insulin resistance, impaired beta-cell secretory function (HOMA-ß<100%) and elevated total cholesterol were found to be significant risk factors of ischaemic stroke in this study. The physiological relevance of this association needs to be explored in further studies. It is imperative to emphasize the need for regular screening to detect abnormal metabolic profiles and prompt treatment.

Recommendations

1) Insulin resistance is common among persons with ischaemic stroke. Therefore IR should be assessed and treated in routine clinical practice as its treatment will prevent ischaemic stroke.
2) Impaired beta cell secretory function is a predictor of stroke. Screening and prompt treatment of persons with impaired beta cell function should be included as an important strategy in stroke prevention.
3) Further research, involving multi-centre studies of the African population by evaluating the use of beta-cell function, insulin resistance and lipid profile for the assessment of the risk of ischaemic stroke and their effect on stroke outcome should be carried out in the future.

Abbreviations

BMI: Body Mass Index;
C-peptide: Connecting Peptide;
CT scan: Computer Tomography scan;
ELISA: Enzyme-Linked Immunosorbent Assay;
CVD: Cardiovascular Disease;
FPG: Fasting Plasma Glucose,
HbA1c: Glycated Haemoglobin;
HDL: High-Density Lipoprotein,
HOMA-β%: Homeostatic Model Assessment of Beta Cell Secretory Function;
HOMA-IR: Homeostatic Model Assessment of Insulin Resistance;
HOMA-IR (CP): Homeostatic Model Assessment of Insulin Resistance using C-peptide;
IDF: International Diabetes Federation;
IR: Insulin Resistance;
LDL: Low-Density Lipoprotein;
MS: Metabolic Syndrome;
NIHSS: National Institute of Health Stroke Scale Score;
T2DM: Type 2 Diabetes Mellitus;
TIA: Transient Ischaemic Attack;
WHO: World Health Organisation.

Competing Interest

The authors declare that they have no known competing interests.

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Appendix 1: Figure 1

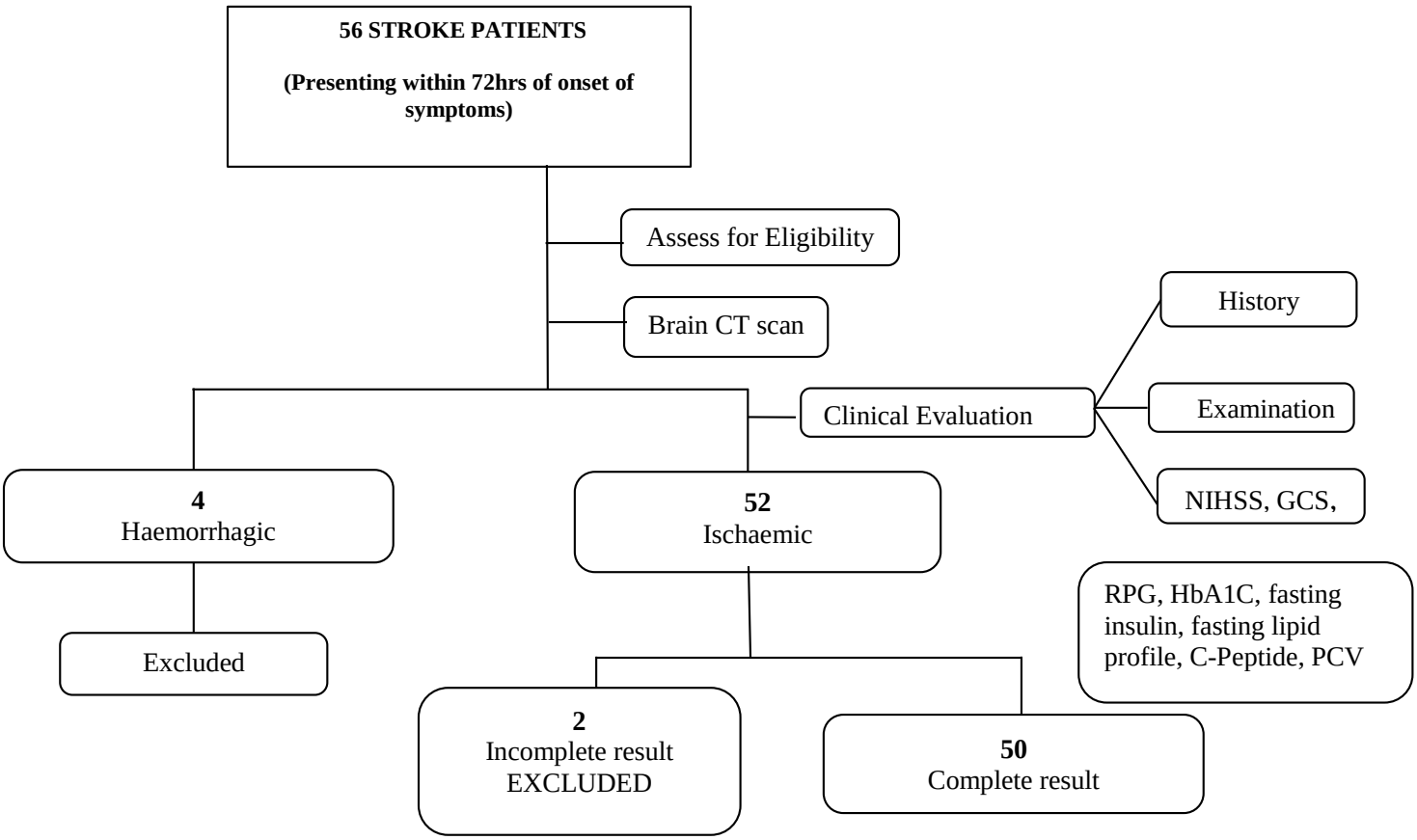

Figure 1:
Flow Chart for Stroke Patient

Note: Out of the 56 stroke patients recruited for the study, 6 subjects were excluded, 4 had a haemorrhagic stroke and 2 had incomplete results. **(** Brain CT Scan- Brain computer tomography scan; C-Peptide- Connecting Peptide; GCS-Glasgow coma score; HbA_{1C}-glycated haemoglobin; NIHSS- National Institute of Health Stroke Scale; FBC-full blood count; RPG-Random Plasma Glucose).

Appendix 2: Figure 2

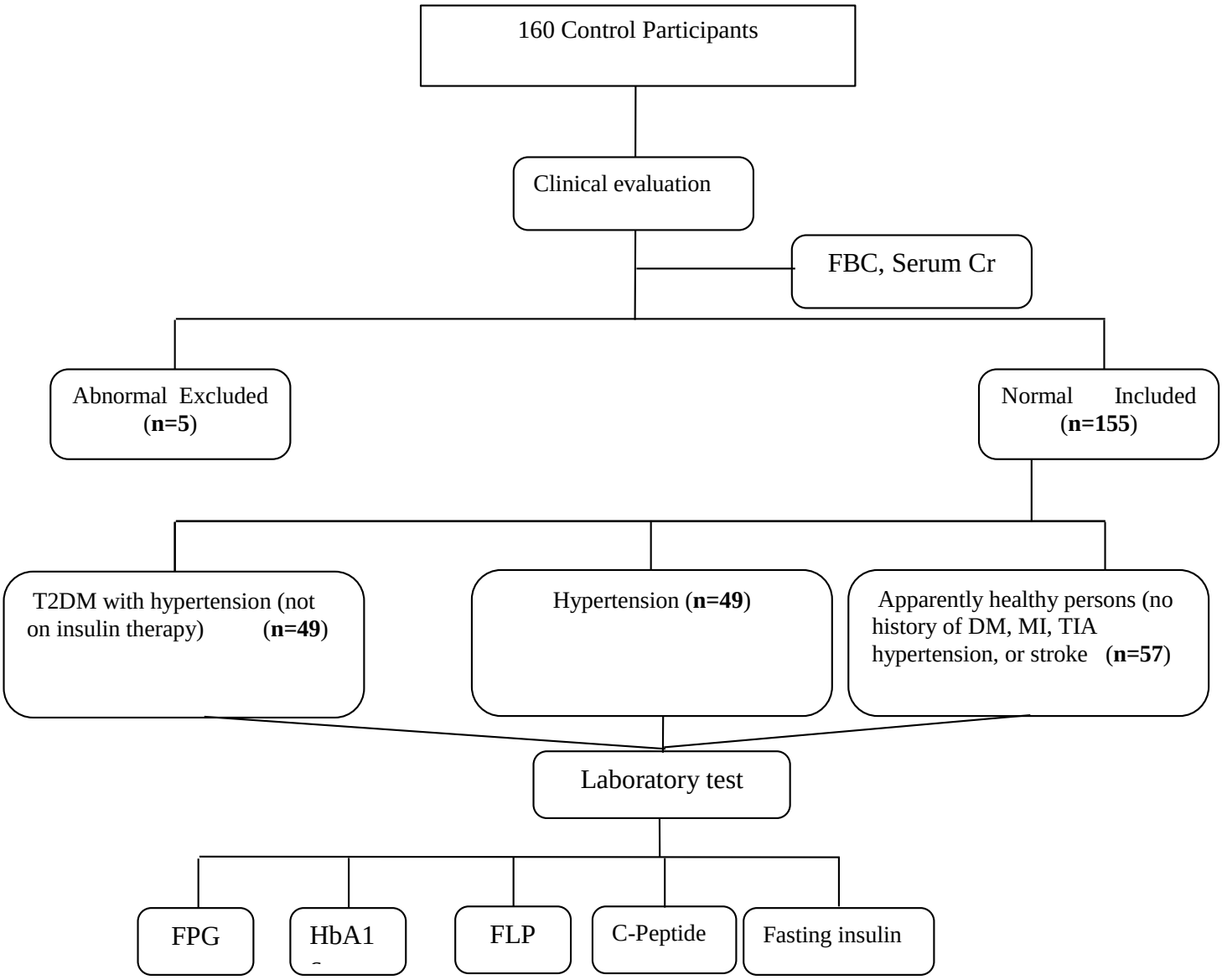

Figure 2:
Flow Chart for Control Participants

Note: Out of the 160 control participants recruited for the study, 5 were excluded for being anaemic. (C-Peptide-Connecting Peptide; FLP-Fasting lipid profile; FPG-Fasting Plasma Glucose; FLP-Fasting lipid profile; HbA_{1C}-Glycated Haemoglobin; MI-Myocardial infraction; T2DM-type 2 diabetes; TIA-Transient ischaemic attack; PCV-Packed Cell Volume; Serum Cr- Serum creatinine.