The impact of non-compliance with the therapeutic regimen on the development of stroke among hypertensive men and women in Gaza, Palestine

Bernhard T. Baune, *MD, MPH,* ***Yousef I. Aljeesh,*** *Dr.Ph, MPH,* ***Ralf Bender,*** *PhD.*

ABSTRACT

Objective: Hypertension and stroke are 2 major public health problems worldwide. Several biological and non-biological risk factors for stroke have been identified in the past. Little is known regarding risk factors for stroke among the Arabic population in Gaza. To identify potential risk factors we investigated compliance with the therapeutic regimen and life style factors which may increase the risk for stroke.

Methods: To research this study question, a pair matched case control study was conducted in Gaza Strip (Shefa Hospital, Nasser Hospital, Khan Younis Hospital, and related primary health care clinics) in 2001 (from January through to December) among 112 patients, who had been hospitalized for acute stroke and history of hypertension, and 224 controls with history of hypertension from primary health care clinics.

Results: Conditional logistic regression models show significant associations between stroke and medication not taking as prescribed (odds ratio (OR)=6.07; 95% confidence interval (CI)=1.53, 24.07), using excessive salt at meals (OR=4.51; 95% CI=2.05, 9.90), eating diet high in fat (OR=4.67; 95% CI=2.09, 10.40), and high levels of stress (OR=2.77; 95% CI=1.43, 5.38). No significant association between smoking and the development of stroke (OR=2.12; 95 CI 0.82, 5.51) was found. Regular physical exercise was a protective factor (OR=0.26; 95% CI=0.12, 0.57).

Conclusion: Our results on risk factors for stroke confirm several other studies. In future programs on health promotion among hypertensive men and women in Gaza these modifiable risk factors could be addressed by health education strategies.

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Hypertension is worldwide a public health problem affecting 20% of the adult population, responsible for over 70% of stroke in women and 40% in men and the single most important potent risk factor for stroke.[1-7] Hypertension is one of the main causes which contribute to disability, health care costs, and stroke mortality.[8,9] Stroke, a possible consequence of hypertension, often leads to death and disability.[4,10-12] In developing countries, stroke remains a major public health problem.[12] In Gaza Strip and West Bank cerebro-vascular diseases are the second leading cause of death of the total cardiovascular disease mortality (35% in Gaza Strip, and 27.5% in West Bank). The mortality rate among

From the Department of Psychiatry and Psychotherapy (Baune), University of Muenster, Muenster, Department of Medical Biometry, Epidemiology and Informatics (Bender), Johannes-Gutenberg-University of Mainz, Mainz, *Germany*. Department of Nursing (Aljeesh), Faculty of Nursing, The Islamic University of Gaza, Gaza, *Palestinian Authority*.

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Address correspondence and reprint request to: Dr. Bernhard T. Baune, Senior Lecturer and Consultant Psychiatrist, Department of Psychiatry and Psychotherapy, University of Muenster, Albert-Schweitzer-Street 11, D-48129 Muenster, *Germany*. Tel. +49 (251) 8356638. Fax. +49 (251) 8356612. E-mail: bbaune@uni-muenster.de

people of 60-years of age and over is highest in patients with cerebro-vascular disease (15.2%), in comparison to hypertension (11.3%), malignant neoplasm (9.1%), diabetes mellitus (5.3%), and renal failure (3.2%).[13] Non-compliance to the therapeutic regimen is a potential risk factor for stroke in hypertensive patients. Further potential risk factors for stroke are obesity, high cholesterol, smoking, and alcohol consumption.[14-18] Physical activity is found to be a significant protective factor in men, but not in women.[19] No data are available to estimate the impact of these risk factors among the Palestinian population in Gaza Strip.

A case control study was carried out in Gaza Strip to investigate whether a significant association exists between non-compliance with the therapeutic regimen (such as usage of anti-hypertensive medication, dietary restrictions in sodium and fat, implementation of weight reduction and exercise program, regular follow up health care, and smoking) and the development of stroke among hypertensive patients.

Methods. A one to two matched case control study was carried out. The case group consists of 112 subjects with stroke and history of hypertension only, and the control group consists of 224 subjects with hypertension only. Cases and controls were matched by age, sex, starting point of therapeutic regimen, time of hypertension and enrollment location of hospital related health care clinics. For each case 2 identical controls were recruited to detect small differences between the 2 groups[20] and to compensate potential loss of controls. To test feasibility, validity and reliability of the instrument a small scale study was carried out by using a small sample consisting of 10 cases of stroke with history of hypertension (5 males and 5 females), and 20 patients with hypertension only as a control group. Minor adjustment of the questionnaire was carried out. Cases and controls were recruited from the same geographical area in Gaza Strip.[20,21] Three main hospitals in Gaza Strip (Shefa, Nasser, and Khan Younis Hospital) and the geographically and administratively related primary health care clinics were pinpointed for the selection of the study population. The population under study consists of patients aged between 35 and 69-years. Both, cases and controls had received antihypertensive pharmaceutical treatment for at least one year before enrollment into the study. A physician made a diagnosis of stroke or hypertension, or both. Hypertension was defined when the threshold levels of 140mm Hg systolic and 90 mm Hg diastolic were reached. Further grading into mild, moderate, severe hypertension was not made. A computed tomography head scan had been carried out in patients with stroke. Both groups were selected only, if a history of other physical diseases (diabetes, myocardial infarction, atrial fibrillation, pulmonary edema, asthma) was excluded. Sixty-eight (38%) out of 180 selected cases were excluded from the study: 19 (28%) died after first stroke; 18 (26%) had a second stroke; 7 subjects (10%) were over 69-years old; 10 (15%) participated in the pilot study; 7 (10%) patients had no computer tomography (CT) head scan; 4 (6%) refused to participate in the study; 3 (4%) patients started their therapeutic regimen less than one year. Patients participating in the pilot study and test-retest study were excluded to reduce response bias. All available discharge data of patients from the selected hospitals were screened for cases. Patients who had been hospitalized for acute stroke and history of hypertension between 1 January and 31 December 2001 were defined as cases (N=180). According to exclusion criteria, 68 (38%) cases were excluded. In total 112 (62%) cases were ultimately selected from the registers. The diagnosis of stroke was confirmed by a physician and a head CT scan was performed. Stroke was defined as "a sudden loss of brain function resulting from disruption of the blood supply to a part of the brain".[14] Controls were defined as having hypertension only, without history of stroke. Controls were selected from the same primary health care clinics where cases used to receive follow up appointments for hypertension on primary health care level before hospital admission due to the development of stroke.

The questionnaire has been developed from 2 sources. The first part, which deals with personnel, (age, sex, address, marital status, number of children), medical, and socio-economic status, was developed by ourselves, and the second part, which deals with therapeutic regimen (anti-hypertensive medications, dietary restriction of sodium and fat, weight reduction, exercise program, follow up health care) has been adopted from a medical-surgical book.[14] The third part of the questionnaire deals with psychological and environmental stressors, which have been adopted from a psychometric questionnaire (SCL-90).[22] A certified translation of the questionnaire from English into Arabic language was performed twice independently and the results were checked for inconsistencies. To enhance the validity of the instrument, an examination of face and content validity was carried out by submitting the questionnaire to experts. To enhance the reliability of the instrument, a pilot-study was undertaken and a test-retest. The therapeutic regimen was defined as a plan that deals with different methods of treatment and healing, particularly the use of drugs, diet restrictions, weight loss or reduction, exercise program, and follow up health care in the cure of disease.[23] Compliance was defined as the extent to

Table 1 - Gender and age distribution among case and control study.

Variables	Case group (N=112)		Control group (N=224)	
Gender				
Female	54	(48.2)	108	(48.2)
Male	58	(51.8)	116	(51.8)
Total	**N=112**	**(100)**	**N=224**	**(100)**
Age				
<40	3	(2.7)	6	(2.7)
40-45	18	(16.1)	36	(16.1)
46-51	32	(28.6)	64	(28.6)
52-57	32	(28.6)	64	(28.6)
58-63	27	(24)	54	(24)
64-69				
Total	**N=112**	**(100)**	**N=224**	**(100)**

Table 2 - Education and average income in dollars among case and control group.

Education and Income	Case group (N=112)		Control group (N=224)		Pearson's Chi-square test *p* value
Level of education					
No education	67	(59.8)	84	(37.5)	
Primary school	11	(9.8)	29	(12.9)	
Preparatory school	8	(7.1)	44	(19.6)	
Secondary school	15	(13.4)	41	(18.3)	0,003
University degree	10	(8.9)	25	(11.2)	
Other	1	(0.9)	1	(0.4)	
Total	**N=112**	**(100)**	**N=224**	**(100)**	
Average income per month US$					
<200 US$	48	(42.9)	101	(45.1)	
200-350 US$	29	(25.9)	76	(33.9)	
360-550 US$	29	(25.9)	39	(17.4)	
560-750 US$	6	(5.4)	8	(3.6)	0,183
>750 US$		-		-	
Total	**N=112**	**(100)**	**N=224**	**(100)**	

which the patients follow medical advice.[24] Stress was regarded as high when probands ranked high on a sum score of scales for 5 different psychological factors (criticism, loneliness, nervousness, paranoia, social phobia). Stroke was defined as "a sudden loss of brain function".[14,25] Frequency tables were calculated to describe cases and controls regarding sex, age, socio-economic factors and factors of non-compliance with the therapeutic regimen. To test proportions the chi-square test was used. To examine the associations between explanatory variables and stroke, conditional logistic regression was used to test the following potential explanatory variables: 1. Anti-hypertensive medication, 2. Usage of salt, 3. Usage of fat, 4. Weight reduction, 5. Physical exercise, 6. Follow-up health care, 7. Current smoking, 8. High level of stress.

A significance level at a=0.05 for removing an explanatory variable from the model was used. Odds ratios of the final model based upon the backward selection were calculated with the SAS procedure PHREG. For all other statistical procedures statistical package social sciences statistical software was used.

Results. **Table 1** shows both gender and age distribution among the case and control groups. The gender and age proportion among cases and controls is identical due to matching by age and sex. Males (51.8%) are only slightly more frequent than female in the study population (48.2%). Among the registered patients none was younger than 40-years and none older than 69-years of age. Two larger age groups (52-57-years; 58-63-years) accounted for 57% of the age distribution. The elder probands (64-69-years) showed a proportion of 24%. Probands aged 45-years old or younger were the smallest group in the study. The distribution of educational qualifications and of average monthly income stratified by case status is presented in **Table 2**. The level of education was significantly different between cases and controls (p=0.003, **Table 2**). Probands from the control group were generally higher qualified than probands from the case group, which is most prominent if probands were not formally qualified (no education). Whereas nearly 60% of patients with stroke (cases) present without a formal qualification, only a little more than one third (37.5%) among the control group is formally not qualified. The average monthly income in US$ indicates a financially underprivileged population under study: more than 75% of the probands had a monthly income of 350 US$ or less. The average monthly income among the study population was distributed without statistically significant differences between case and control group (**Table 2**). Factors of compliance and non-compliance with the therapeutic regimen and life style factors among the case and control group are presented in **Table 3**. Potential risk factors are listed in the left column. Patients answered questions with either "yes" or "no". Alternative answers are classified as factors of compliance or non-compliance with the therapeutic regimen. The distribution is stratified for cases and controls. Results show that more than 50% of cases were compliant with the therapeutic regimen regarding medication and regular health care follow ups only. Almost two thirds of the cases were neither smoker (64.3%) nor had high levels of stress (61.6%). In contrast, the control group shows a

Table 3 - Frequencies of factors of compliance and non-compliance with the therapeutic regimen and life style factors among case and control group.

Case status	Case group (stroke) (N=112)		Control group (non-stroke) (N=112)	
Therapeutic regimen and life style	**Factors of compliance**	**Factors of non-compliance**	**Factors of compliance**	**Factors of non-compliance**
Anti-hypertensive medication	Yes	No	Yes	Yes
Taking medications as prescribed	84 (75)	28 (25)	214 (95.5)	10 (4.5)
Diet	No	Yes	No	Yes
Using excessive salt	46 (41.1)	66 (58.9)	182 (81.3)	42 (18.8)
Eating diet high in fat	42 (37.5)	70 (62.5)	165 (73.7)	59 (26.3)
Weight reduction	Yes	No	Yes	No
Involvement in regular program of weight reduction	4 (3.6)	108 (96.4)	35 (15.6)	189 (84.4)
Exercise program	Yes	No	Yes	No
Involvement in regular program of physical exercise	18 (16.1)	94 (83.9)	109 (48.7)	115 (51.3)
Follow up health care	Yes	No	Yes	No
Regular follow up clinic or physician appointment	70 (62.5)	42 (37.5)	187 (83.5)	37 (16.5)
Stress level	No	Yes	No	Yes
High level of stress	69 (61.6)	43 (38.4)	142 (63.4)	82 (36.6)
Smoking	72 (64.3)	40 (35.7)	176 (78.6)	48 (21.4)

Table 4 - Results of a multiple conditional logistic regression model considering main effects only (no interactions).

Variable	β	SE	*p* value	OR	LL	UL
Medication (as prescribed)	1.80387	0.70263	0.0102	6.073	1.532	24.071
Salt (diet)	1.50678	0.40114	0.0002	4.512	2.056	9.905
Fat (diet)	1.54128	0.40876	0.0002	4.671	2.096	10.407
Physical exercise	-1.31138	0.38561	0.0007	0.269	0.127	0.574
Smoking	0.75479	0.48591	0.1203	2.127	0.821	5.513
High level of stress	1.02225	0.33769	0.0025	2.779	1.434	5.388

OR - odds ratio, LL - lower level, UL - upper level

different pattern. The majority of controls were compliant with the therapeutic regimen except in the areas of weight reduction (84.4%) and exercise program (51.3%) where more than half of the controls showed non-compliant behavior.

The results of a multiple conditional logistic regression model containing statistical significant main effects only are shown in **Table 4**. Significant risk factors for stroke were excessive usage of salt (OR=4,512), excessive usage of fat (OR=4.671), high level of stress (OR=2.779) and medication not taken as prescribed (OR=6.073). Regular physical exercise (OR=0.269) was found to be a protective factor. Smoking (OR=2.127) is not a significant risk factor for stroke, if regarded as main effect only.

Discussion. In this case control study potential risk factors among the therapeutic regimen and life style factors for the development of stroke were focussed. Certain risk factors for the development of stroke were identified. Despite its strengths, the study has some limitations such as possible recall bias, information bias, classification bias and selection bias. The capacity to remember facts and incidents of one year before stroke might be affected by the stroke itself, which may lead to a recall bias. To minimize recall bias information was obtained from both family and patients especially in stroke patients who were unable to communicate verbally with the interviewers. If necessary, we had the patient's file or chart in case of ambiguous information. As information is self reported regarding fat and salt diet, medication, health care follow up, exercise, and smoking information bias could have occurred. We tried to minimize this problem by increasing the reliability of the data

using test retest methods in the early stage of the study. Due to missing information regarding the level of blood pressure upon the systolic and diastolic thresholds we could not control this potential misclassification bias. As an effect of misclassification more probands with mild hypertension could have been in the control group than in the case group and more probands with severe hypertension in the case group than in the control group. The fourth bias is a potential selection bias happening during the selection of cases from hospital wards and via medical records. To control a selection bias, patients' names were obtained twice, independently from the disease registry office, and from the ward where the patient was admitted. Subsequently, every patient was included once only. In addition we compared the background characteristics and matching variables of the case and control groups to control for selection and matching bias among both groups during the study.

The age distribution of the study population showed more than 50% of the cases being between the ages of 52-63-years which indicates a higher proportion of stroke patients in the older age groups. This could be explained by selection bias in the hospitals and does not reflect the real incidence and prevalence of stroke in the Palestinian population. Thus, results can not be generalized for the Palestinian population. The Palestinian Annual Report in 1997 noticed the highest incidence of stroke in the age group 52-63-years and older age. According to the life expectancy in Palestine in 1997, which was 69-years for males and 71-years for females, the most frequent age group (52-63-years) of the cases suffering from stroke in our study represents the older age group of the Palestinian population.[13]

The study population had an average monthly income of 350 in US$ or less. Differences between cases and controls were statistically not significant. This financially and economically underprivileged population under study may reflect the economic situation as a whole and the level of individual income in Palestine. The actual unemployment rate in Gaza Strip is estimated to 53%, and the percentage of Palestinians living below the poverty line is 64%. In contrast to the most recent situation, a smaller proportion of the population (21%) was living below the poverty line.[26,27] The World Bank reported by the beginning of May 2001, that the GDP per capita was reduced by approximately 10% in 2002 compared to 1999.[28] The economic situation of the study population in Gaza Strip is comparable to mean level of income in Palestine. The poor economic situation in Palestine may have an indirect effect on stroke by increasing psychological and environmental stress, which in turn may increase blood pressure and lead to stroke development especially among hypertensive patients. A multiple conditional logistic regression model showed several significant risk factors for stroke. Patients with hypertension plus stroke and not taking the medication as prescribed, eating excessive salt, usage of high fat in meals, smoking and having high levels of stress supposed to have a higher risk for stroke than patients with hypertension only who are compliant with the provided therapeutic regimen. Other studies emphasize the importance of anti-hypertensive medication in order to control blood pressure and to reduce the incidence of stroke. Collins and MacMahon have reported that a mean decline of 5-6 mm Hg in diastolic blood pressure for 5 years led to 38-42% reductions in stroke incidence.[26,29] In addition, anti-hypertensive medication is very important to decrease the mortality rate of hypertensive complications such as stroke.[19,30]

In contrast to findings of other studies the factors weight reduction and regular follow up health care did not account for a lower risk of stroke in our study.[30,31] These 2 potential risk factors were excluded statistically from the model by the backward selection process. We found physical exercise to be a protective factor. Several studies reported that physical activity decreases the risk for thromboembolic stroke among older non-smokers, and reduces the risk of cerebral hemorrhage.[16,19,31] The association between smoking and development of stroke (OR=2.127; 95% CI: 0.821, 5.513) was not significant. Donnan et al[32] found in another case control study a significant odds ratio of 5.2 for smokers compared to non-smokers for the presence of transient ischemic attack. The interpretation of the significant association between high level stress (HLS) and development of stroke in our model (OR=2.779; 95% CI: 1.434, 5.388) leads to at least 2 different interpretations. On the one hand this is generally consistent with previous studies, which have reported that treatment of hypertension shall be started with non-pharmacological therapy through a modification of lifestyle, such as a reduction of stress.[16] On the other hand, our result contrasts other studies, where little medical evidence is found for stress as a major cause of stroke. Most strokes occur in people who are not under great stress.[32]

Our findings support several other studies on risk factors for stroke. Further studies are needed to confirm our results in the Palestinian population. Health education programs aiming at the prevention of hypertension and stroke should focus on medication, diet restrictions, physical exercise and stress.

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