

HYPERTENSION AND METABOLIC SYNDROME: IMPACT OF CLUSTERING OF HYPERTENSION IN SUBJECTS WITH METABOLIC SYNDROME

Sikandar Hayat Khan¹, Farooq Ahmad Khan², Amir Ijaz³,
Abdus Sattar⁴, Mohammad Dilawar⁵, Rizwan Hashim⁶

ABSTRACT

Objective: To compare insulin resistance between hypertensive and non-hypertensive subjects.

Methodology: It is a comparative cross-sectional study which was carried out between April 2004 to March 2006 at department of chemical pathology and endocrinology, Armed Forces Institute of Pathology, Rawalpindi. A total of sixty-three subjects with metabolic syndrome were selected as per the criteria of National Cholesterol Education Program, Adult Treatment Panel III (NCEP, ATP III) from a target population diagnosed to have impaired glucose regulation at AFIP, along with forty-seven age and sex-matched controls. Insulin resistance was calculated by the method of HOMA-IR, using the formula of Mathew's et al. Blood pressure was measured as per recommendations of JNC7 report on prevention, detection, evaluation and treatment of high blood pressure.

Results: The difference for hypertension for diastolic blood pressure between subjects with and without metabolic syndrome were found to be significant [Metabolic syndrome: 86.79 mm of Hg (95 % CI: 83.75-89.84), Age and sex matched controls: 80.21(95 % CI: 76.80-83.62) ($p < 0.05$). However the difference for systolic blood pressure were not found to be significant between the two groups ($p = 0.860$). Hypertensive individuals had higher HOMA-IR [(n=33): 2.87 (95 % CI: 2.37-3.05)] than non-hypertensive [(n=30): 1.76(95 % CI: 1.53-2.05)] ($p < 0.05$). The effect of obesity as determined by waist circumference between patients with and without hypertension remained significant ($p < 0.05$)

Conclusion: Hypertensive individuals have higher insulin resistance than subjects without hypertension. Thus it is recommended that vigorous search be made to diagnose insulin resistance in subjects diagnosed to have hypertension, and to demonstrate other components of metabolic syndrome.

KEY WORDS: Homeostasis Model Assessment for Insulin Resistance, Hypertension, Metabolic syndrome, National cholesterol education program, Adult treatment Panel-III.

Pak J Med Sci October - December 2007 (Part-II) Vol. 23 No. 6 903-908

1. Sikandar Hayat Khan,
 2. Farooq Ahmad Khan,
 3. Amir Ijaz,
 4. Abdus Sattar,
 5. Mohammad Dilawar,
 6. Rizwan Hashim
- 1-6: Department of Chemical Pathology & Endocrinology,
Armed Forces Institute of Pathology, Rawalpindi.

Correspondence

Dr. Sikandar Hayat Khan,
Pathologist PNS Rahat, Greater Karsaz Area,
Ibrahim Rehmat Ullah Road, Karachi - Pakistan.
E-mail: sik_cpssp@yahoo.com

* Received for Publication: June 13, 2007

* Revision Accepted: August 30, 2007

INTRODUCTION

“Metabolic syndrome” constitute the clustering of clinical and biochemical risk factors, which has been termed significant in the future causation of coronary artery and stroke related diseases.¹⁻³ The clinical parameters included in the diagnostic criteria for metabolic syndrome include the measures of obesity like waist circumference, waist to hip ratio or body mass index and hypertension.⁴ While the biochemical risk factors associated with insulin

resistance include impaired glucose regulation, dyslipidaemias and according to some authorities microalbuminuria.^{5,6} According to this concept, it has been hypothesized that hypertension is an important component of this syndrome.^{7,8} "Whether hypertension has underlying insulin resistance" is yet not completely understood. There are four controversies to appreciate: Firstly, hypertension like other measures of insulin resistance syndrome has also been termed as a distinct entity, and treatment approaches have been varying and often includes the use of drugs like thiazides as the front line and first treatment which may aggravate the associated metabolic components like impaired glucose regulation and dyslipidaemias.^{9,10} Secondly the rapidly expanding pandemic of hypertension mostly includes subjects with essential hypertension, where no cause is found in majority of the patients.^{11,12} Here insulin resistance may be the probable reason and can become a target for interventional strategies in future.¹³ Thirdly, the relative pattern, prevalence and other characteristics of hypertension have been documented to have regional, racial and social differences and thus requires locally available data for conclusions.¹³⁻¹⁵

Lastly the clinical confusion becomes more highlighted once the available literature search yields varying conclusions about association of hypertension with metabolic syndrome.^{15,16} Hence this study was planned to assess the differences for insulin resistance between subjects with and without hypertension.

SUBJECTS AND METHODS

This cross-sectional study was conducted at the department of chemical pathology and endocrinology, Armed Forces Institute of Pathology between April 2004 to January 2006. A total of sixty-three subjects with metabolic syndrome as per NCEP, ATP III criteria were selected from a target population of impaired glucose regulation who presented for evaluation at AFIP. Forty-seven age and sex-matched controls were also included in the study. The details of data collection procedure were as;

Firstly selection of subjects from a target population of impaired glucose regulation (plasma glucose fasting= 5.6 to 6.9 mmol/L or 2 hour OGTT results between 7.8 to 11.0 mmol/L) was carried out. These subjects were provisionally considered for further study. Subjects who were receiving treatment for diabetes mellitus, hypertension, ischaemic heart disease and any other ailment were excluded from the study.

Finally selected individuals were asked to report for sampling in medical fasting state, after brief explanation of the necessary requirements for medical fasting and study. On day of reporting, formal consent was signed. This was followed by detailed history, examination and collection of blood for plasma glucose, triglycerides and HDL-cholesterol and insulin. Blood pressure was measured as per the guide lines of "The Seventh Report of the Joint National Committee on prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7).¹⁷ Blood pressures were measured twice during the procedure and the mean reading of the two were recorded for the study. Plasma glucose was analyzed using GOD-PAP method on Selectra-2. Serum triglycerides and HDL-c were analyzed using GPO-PAP and indirect phospho-tungstic acid method respectively. All of these above methods are in accordance with NCEP, ATP III specifications. Serum insulin was measured using chemiluminescence's technique on Immulite 1000. HOMA-IR was used as a marker for measuring insulin resistance and the calculations were made as per the method of Mathew's et al as:¹⁸

$$\text{HOMA IR} = \frac{\text{Fasting serum insulin} \times \text{Fasting plasma glucose}}{22.5}$$

Statistical Analysis: All data were entered into SPSS- version 15. Descriptive statistics in terms of mean and SD were calculated for all demographic and biochemical details. Independent sample t-test was applied to measure the degree of significance of systolic and diastolic blood pressure between subjects with and without metabolic syndrome. To know the

Table-I: Clinical characteristics of subjects

Parameter	Healthy Controls (n=63)	Metabolic Syndrome (n=47)	Significance
	Mean + (95 % CI)	Mean + (95 % CI)	
Age (Years)	46.28(44.32-48.24)		0.103
Waist circumference(cm)	90.30(88.12-92.65)	96.10(94.21-98.01)	<0.001
Diastolic blood pressure (mm Hg)	80.21(76.80-83.62)	86.79(83.75-89.84)	<0.05
Systolic blood pressure (mm Hg)	118.6(112.37-122.87)	121.5(114.54-124.36)	0.860

effect of various confounding factors like age, urbanization and educational status, a univariate GLM Generalized Linear Model) was employed keeping the diastolic blood pressure as dependent variable. A p-value of <0.05 was considered as significant.

RESULTS

The clinical profiles of patients are shown in Table-I. The diastolic and systolic blood pressures were higher in subjects with metabolic syndrome in comparison to age and sex matched controls ($p < 0.05$ and $p = 0.860$); however statistical significance was not reached in case of systolic blood pressure (Fig-1 & 2). Hypertensive individuals irrespective of their inclusion in metabolic syndrome, were found to have higher insulin resistance [(n=33): 2.87 (95 % CI: 2.37-3.05)] than non-hypertensive individuals[(n=30): 1.76(95 % CI: 1.53-2.05)] ($p < 0.001$), as Fig-3. The general linear model showed the effect of urbanization, sex, age and education to be non-significant in the development of diastolic blood pressure (Table-II).

Waist circumference was used as a marker of obesity, which demonstrated significant differences between subjects with and without hypertension (Fig-4).

DISCUSSION

The recorded blood pressures were higher in subjects with NCEP defined metabolic syndrome as compared to age and sex-matched controls. This finding suggests that hypertension is an important factor in the overall development of the phenotype “metabolic syndrome”, with underlying “insulin resistances” as an etiology. These findings are in accordance with the works of Cordero et al and Zavaroni et al.^{20,21} However reviewing the literature there are few studies which show contrasting results to ours. Almeida-Pititto et al have shown no link between hypertension and metabolic syndrome, but this particular study was carried out in specific cohort of “Japanese-Brazilian women” and leptin was used as a marker of insulin resistance which is not a direct measure of insulin resistance.¹⁵ Moreover, many

Table-II: Univariate General linear model showing the regression analysis for diastolic blood pressure as the dependent variable.

Dependent Variable: Diastolic blood pressure						
Source	Type III Sum of Squares	df	Mean Square	F	Sig.	
Corrected Model	1909.797 ^a	6	318.30	2.160	0.053	
Intercept	13004.807	1	13004.81	88.247	0.000	
sex	611.060	3	203.69	1.382	0.252	
age	497.741	1	497.74	3.378	0.069	
education	78.244	1	78.24	0.531	0.468	
urbanization	196.033	1	196.03	1.330	0.251	
Error	15768.492	107	147.37			
Total	823575.000	114				
Corrected Total	17678.289	113				

^a R Squared = 0.108 (Adjusted R Squared = 0.058)

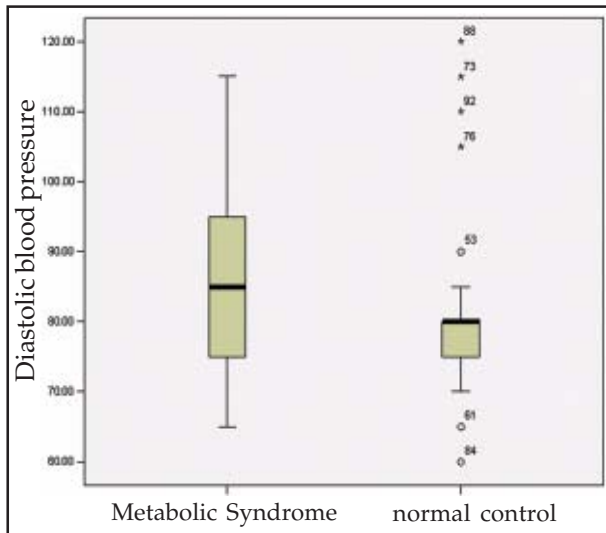


Fig-1: Diastolic blood pressure between subject with and without metabolic syndrome ($p < 0.05$)

other studies have highlighted the role of ethnicity, environmental and community based difference in the development of hypertension and insulin resistance.¹⁴

The type of hypertension most strongly associated with insulin resistance in our study was diastolic one; systolic blood pressure also remained higher in subjects with metabolic syndrome, but statistical significance was not reached. Reasons to these differences could be manifold. First of all, systolic and diastolic blood pressures both signify different disease processes leading to one common outcome i.e.,

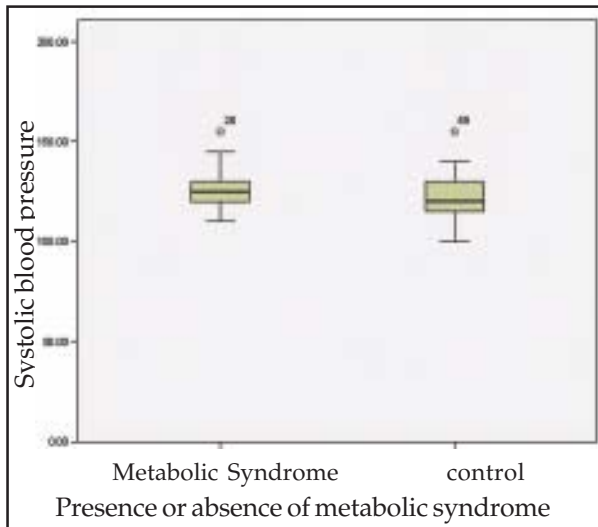


Fig-2: Systolic blood pressure between subjects with and without metabolic syndrome ($p=0.860$)

hypertension. Diastolic blood pressures are more representative of fluid overload state, probably secondary to increased sodium resorption and excessive myogenic vasoconstriction due to medullary NO production.²² While the systolic blood pressure deals more with the compliance of vasculature, which has also been shown to be related with the ongoing process of ageing.²³ The higher diastolic blood pressure may indicate early onset of changes linked to mild fluid overload state and over the ensuing years may convert into full blown hypertension. Secondly, the differences demonstrated in our study can be attributed to our population characteristics. As the body appearances

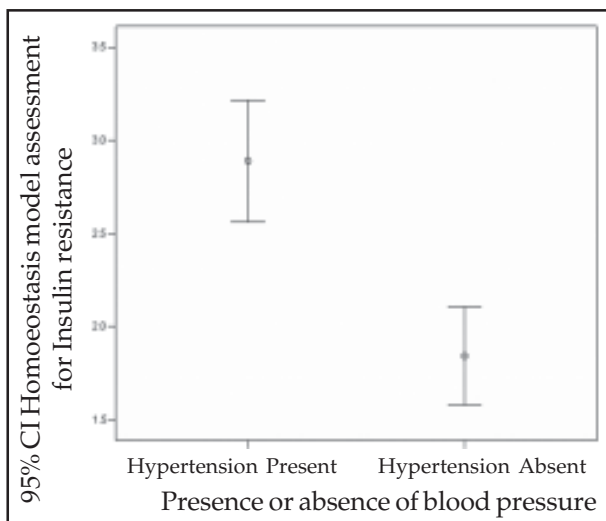


Fig-3: Difference in insulin resistance between subjects with and without hypertension ($p < 0.001$)

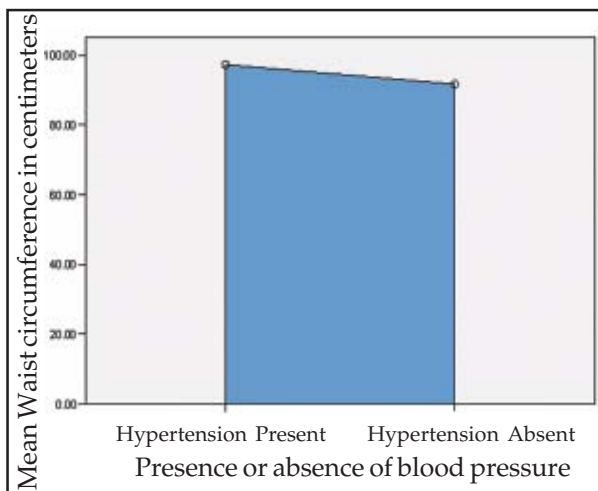


Fig-4: Effect of obesity (waist circumference) on hypertension ($p < 0.05$)

and frames can vary, so does the endogenous metabolism. These types of differences have been highlighted in many regional and western studies for both hypertension and insulin resistance.^{24,25} However, detailed epidemiological workup is required to augment this finding. Thirdly, the definition of metabolic syndrome incorporates clustering of various other clinical and metabolic risk factors and hypertension may not be the sole performer; other factors have their own role to play. This particular study was aimed just to show the link between hypertension and insulin resistance; "how much role does it have?" requires a risk stratification and quantification approach. Recently Macchai et al have categorized each risk as per its magnitude in the overall development of insulin resistance.²⁶ This approach may become a future for metabolic risk stratification. Fourthly systolic hypertension is usually associated with elderly populace, due to progressive decrease in compliance of blood vessels. The age range in our study was between 41 to 47 years, while most of the studies showing higher day time systolic blood pressures were carried out in comparatively elderly subjects.^{27,28} Moreover, there are studies available in literature which have shown positive correlation between age and systolic blood pressure.²⁹ Lastly there are few recent studies which have shown day time diastolic blood pressures to be superior to systolic blood pressures in terms of its correlation with insulin resistance.³⁰

There are few limitations to our study: the sample mainly constituted an urbanized population, so a real contrast between urbanized and non-urbanized population can not be made. However sedentary life styles and intake of refined dietary products have also been shown to contribute in the development of both hypertension and insulin resistance.³¹ So urbanization has to go hand on hand with insulin resistance and hypertension. Secondly, type-II errors may remain a possibility that some of the significance between the samples may have been missed like for systolic blood pressure; but as per statistical recommendations a sample size of thirty is fair enough to prove or dis-

prove a hypothesis. Lastly there are several strategies to diagnose insulin resistance, NCEP, ATP III criteria remains most "in use" method. The concept of 24 hour blood pressure monitoring may appear a better determinant of hypertension;³² however neither the JNC-7 recommendations suggest, nor the present clinical practice has adopted this method of identifying hypertension.

The study may have enormous clinical implications. Out of all the metabolic diseases, hypertension is one of those entities where more than 90 % patients don't have a specific etiopathogenetic mechanism and labeled as "essential". Insulin resistance as shown by our study may become a future target for not only diagnosis but may also establish itself as an area for intervention and monitoring. Thus every effort must be made to measure insulin resistance and identify other metabolic clustering in subjects diagnosed to have hypertension.

CONCLUSIONS

Hypertensive individuals have higher insulin resistance than subjects without hypertension. Thus it is recommended that vigorous search be made to diagnose insulin resistance in subjects diagnosed to have hypertension and to demonstrate other components of metabolic syndrome. Moreover, further clinical, epidemiological and physiological workup is necessary to characterize various pathogenetic mechanisms involved in the development of hypertension in our society.

REFERENCES

1. Zarich SW. Cardiovascular risk factors in the metabolic syndrome: impact of insulin resistance on lipids, hypertension, and the development of diabetes and cardiac events. *Rev Cardiovasc Med* 2005;6(4): 194-205.
2. Cheal LK, Abbasi F, Lamendola C, MC Laughlin T, Reaven MG, Ford SE. Relationship to insulin Resistance of the Adult Treatment Panel III Diagnostic Criteria for Identification of the Metabolic Syndrome. *Diabetes* 2004; 53: 1195-1200.
3. Grundy MS. Etiology of the Metabolic Syndrome-Reply. *JAMA* 2004; 291 (12): 1444.
4. Pausova Z. From big fat cells to high blood pressure: A pathway to obesity-associated hypertension. *Curr Opin Nephrol Hypertens* 2006; 15(2):173-8.

5. Lorenzo C, Okoloise M, Williams K, Stern MP, Haffner SM; San Antonio Heart Study. The metabolic syndrome as predictor of type 2 diabetes: the San Antonio heart study. *Diabetes Care* 2003; 26(11):3153-9.
6. Ford ES, Giles WH. A comparison of the prevalence of the metabolic syndrome using two proposed definitions. *Diabetes Care* 2003; 26(3):575-81.
7. Fujiwara T, Saitoh S, Takagi S, Takeuchi H, Isobe T, Chiba Y, et al. Development and progression of atherosclerotic disease in relation to insulin resistance & hyperinsulinemia. *Hypertens Res* 2005; 28(8):665-70.
8. Liese AD, Mayer-Davis EJ, Chambless LE, Folsom AR, Sharrett AR, Brancati FL, et al. Elevated fasting insulin predicts incident hypertension: the ARIC study. *Atherosclerosis Risk in Communities Study Investigators. J Hypertens* 1999; 17(8):1169-77.
9. Ernsberger P, Koletsky RJ. Metabolic effects of anti-hypertensive agents: Role of sympathoadrenal and renin-angiotensin systems. *Naunyn Schmiedeberg's Arch Pharmacol* 2006; 373(4):245-58.
10. Scheen AJ. Prevention of type 2 diabetes mellitus through inhibition of the Renin-Angiotensin system. *Drugs* 2004; 64(22):2537-65.
11. Cordero Fort A, Moreno Arribas J, Alegria Ezquerro E. Is essential hypertension essentially metabolic? *Med Clin (Barc)* 2006; 127(18):705-8.
12. Srinivasan SR, Myers L, Berenson GS. Changes in metabolic syndrome variables since childhood in prehypertensive and hypertensive subjects: the Bogalusa Heart Study. *Hypertension* 2006; 48(1):33-8.
13. Velarde G, Berk BC. Role of hypertension in the metabolic syndrome: who is affected? *Curr Hypertens Rep* 2005; 7(6):418-26.
14. Monsalve MV, Thommasen HV, Pachev G, Frohlich J. Differences in cardiovascular risks in the aboriginal and non-aboriginal people living in Bella Coola, British Columbia. *Med Sci MoInt* 2005; 11(1): CR21-8.
15. Almeida-Pititto B, Gimeno SG, Freire RD, Ribeiro-Filho FF, Ferreira SR. Leptin is not associated independently with hypertension in Japanese-Brazilian women. *Braz J Med Biol Res* 2006; 39(1):99-105.
16. Cabezas-Cerrato J, Garcia-Estevéz DA, Araujo-Vilar D. Lack of association between both insulin resistance and plasma insulin levels with blood pressure values in essential hypertension. *Horm Metab Res* 1997; 29:561-5.
17. Toft I, Bona KH, Jenssen T. Insulin resistance in hypertension is associated with body fat rather than blood pressure. *Hypertension* 1998; 32:115-22.
18. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. Seventh report of the joint National Committee Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; 42: 1206-52.
19. Matthews DR, Hosker JP, Rudenski AS, Naylor GA, Treacher DF, Turner RL. Homeostasis model assessment: insulin resistance and b-cell function from plasma glucose insulin concentrations in man. *Diabetologia* 1985;28: 412-9.
20. Cordero A, Laclaustra M, Leon M, Grima A, Casanovas JA, Luengo E, et al. Prehypertension is associated with insulin resistance state and not with an initial renal function impairment: A Metabolic Syndrome in Active Subjects in Spain (MESYAS) Registry Substudy. *Am J Hypertens* 2006; 19(2):189-96.
21. Zavaroni I, Ardigo D, Zuccarelli A, Pacetti E, Piatti PM, Monti L, et al. Insulin resistance/compensatory hyperinsulinemia predict carotid intimal medial thickness in patients with essential hypertension. *Nutr Metab Cardiovasc Dis* 2006; 16(1):22-7.
22. Fujiwara K, Hayashi K, Matsuda H, Kubota E, Honda M, Ozawa Y, et al. Altered pressure-natriuresis in obese Zucker rats. *Hypertension* 1999;33(6):1470-5.
23. De Castro Ra, Moncau Je, Marcopito Lf. Hypertension prevalence in the city of Formiga, MG, Brazil. *Arq Bras Cardiol* 2007; 88(3):334-9.
24. Ghosh R. Microlevel determinants of blood pressure among women of two ethnic groups in a periurban area of Kolkata city, India. *Am J Hum Biol* 2007;19(3):409-15.
25. Ruijge JB, Assendelft WJ, Dekker JM, Kostense PJ, Heine RJ, Bouter LM. Insulin and risk of cardiovascular disease: A meta-analysis. *Circulation* 1998;97:996-1001.
26. Macchia A, Levantesi G, Borrelli G, Franzosi MG, Maggioni AP, Marfisi R, et al. A clinically practicable diagnostic score for metabolic syndrome improves its predictivity of diabetes mellitus: the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)-Prevenzione scoring. *Am Heart J* 2006;151(3):754.
27. Anan F, Yonemochi H, Masaki T, Takahashi N, Fukunaga N, Teshima Y, et al. High-density lipoprotein cholesterol and insulin resistance are independent and additive markers of left ventricular hypertrophy in essential hypertension. *Hypertens Res* 2007;30(2):125-31.
28. Anan F, Takahashi N, Ooie T, Yufu K, Saikawa T, Yoshimatsu H. Role of insulin resistance in nondipper essential hypertensive patients. *Hypertens Res* 2003; 26:669-76.
29. Kusuma YS, Babu BV, Naidu JM. Group and sex-specific effects of age, body composition and pulse rate on blood pressure variability in some cross-cultural populations of Visakhapatnam District; South India. *J Cardiovasc Risk* 2001;8:337-47.
30. Afsar B, Sezer S, Elsurer R, Ozdemir FN. Is HOMA index a predictor of nocturnal nondipping in hypertensives with newly diagnosed type 2 diabetes mellitus? *Blood Press Monit* 2007;12:133-9.
31. Mohan V, Shanthirani S, Deepa R, Premalatha G, Sastry NG, Saroja R; Chennai Urban Population Study (CUPS No. 4). Intra-urban differences in the prevalence of the metabolic syndrome in southern India — the Chennai Urban Population Study (CUPS No.4). *Diabet Med* 2001;18:280-7.
32. Birkenhager AM, van den Meiracker AH. Causes and consequences of a non-dipping blood pressure profile. *Neth J Med* 2007; 65:127-131.