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PREVALENCE OF PERIPHERAL VASCULAR DISEASE IN CHRONIC ALCOHOLICS AS MEASURED BY ANKLE TO BRACHIAL INDEX

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ABSTRACT: The ankle-brachial pressure index (ABI), which is the ratio of ankle to brachial systolic blood pressure, is the golden standard for the diagnosis of peripheral arterial disease (PAD) and is a highly specific method for the assessment of vascular risk in otherwise asymptomatic patients. ABI value of individual with daily alcohol level >60g/d was significantly lower consumption of less than 60g/d had an inverse association with peripheral atherosclerosis whereas consumption of 60 g/d or more had a positive association. Studies have shown the sensitivity of ABPI is 90% with a corresponding 98% specificity for detecting hemodynamically significant (Serious) stenosis >50% in major leg arteries, defined by angiogram. **AIMS AND OBJECTIVES:** To determine the prevalence of peripheral vascular disease in chronic alcoholics using ankle to brachial index and to compare the values of ankle brachial index in chronic alcoholics with age and sex matched healthy controls. **MATERIALS AND METHODS:** In the present study, 50 cases consuming more than 60gm of absolute alcohol per day for more than 12 months attending outpatient department and admitted were enrolled. 50 age and sex matched healthy controls who have never consumed alcohol (never drinkers) were also enrolled. After taking detailed history using Doppler ultrasound blood flow detector mean systolic pressure in upper limb and lower limb was calculated and then the mean ABI was calculated. This value was then compared with variables like LDL levels, Triglycerides levels, age, clinical symptoms of PVD, alcohol consumption amount and duration. **RESULTS:** It was observed that mean ABI was significantly lower (<0.9) in 11(22%) cases and majority of them were between age group of 41-50 years. Of these only 7(14%) showed clinical symptoms of PVD. The prevalence of PVD was 66% in those who consumed 61-70 grams alcohol per day for around 6-10 years. Results were found to be statistically significant. **CONCLUSION:** This study was able to establish a direct association between peripheral vascular disease (ABI<0.9) and alcohol consumption above 60gms/day for more than 1yr duration. Chronic alcoholics with peripheral vascular disease also had increased level of HDL and LDL cholesterol.

KEYWORDS: Peripheral Vascular Disease, Chronic Alcoholic, Ankle to Brachial Index.

INTRODUCTION: The ankle-brachial pressure index (ABI), which is the ratio of ankle to brachial systolic blood pressure, is the golden standard for the diagnosis of peripheral arterial disease (PAD) and is a highly specific method for the assessment of vascular risk in otherwise asymptomatic patients.¹ The American Heart Association (AHA) Prevention Conference V suggested that the ABI is a strong and independent risk factor for cardiovascular mortality and recommended it be used to detect subclinical disease in the prevention of cardiovascular mortality and stroke.^{2,3} ABI value <0.9 is widely acknowledged to indicate an abnormally low level¹ and several studies have shown that a low ABI was an independent predictor of increased risk of fatal myocardial infarction⁴ and increased risk of cardiovascular disease (CVD) mortality.⁵ And the ABI provides a simple measurement that can be

performed in primary care settings without expensive or elaborate equipment or extensive training or experience.⁶

Many studies indicated that excessive alcohol intake may result in poor health outcome, especially cardiovascular disease^{7,8} but moderate drinking was associated with cardiovascular protective effects.^{9,10}

A significant increase in ABI occurs with daily alcohol consumption up to 60g. But the ABI value of individual with daily alcohol level >60g/d was significantly lower than those never drink or than those with daily alcohol level <60g/day. Alcohol consumption was associated with peripheral atherosclerosis, and consumption of less than 60g/d had an inverse association with peripheral atherosclerosis whereas consumption of 60g/d or more had a positive association.

Alcohol Equivalents:

1. Whisky 60ml = 20g.
2. Wine 100ml = 10g.
3. Beer 250ml = 10g.

A Doppler ultrasound blood flow detector, commonly called Doppler Wand or Doppler probe, and a sphygmomanometer (Blood pressure cuff) are usually needed. The blood pressure cuff is inflated proximal to the artery in question. Measured by the Doppler wand, the inflation continues until the pulse in the artery ceases. The blood pressure cuff is then slowly deflated. When the artery's pulse is re-detected through the Doppler probe the pressure in the cuff at that moment indicates the systolic pressure of that artery.

The higher systolic reading of the left and right arm brachial artery is generally used in the assessment. The pressures in each foot's posterior tibial artery and dorsalis pedi artery are measured with the higher of the two values used as the ABI for that leg.¹¹

$$ABPI = P_{Leg} / P_{Arm}.$$

Where P_{Leg} is the systolic blood pressure of dorsalis pedis or posterior tibial arteries and P_{Arm} is the highest of the left and right arm brachial systolic blood pressure.

The ABPI test is a popular tool for the non-invasive assessment of PVD. Studies have shown the sensitivity of ABPI is 90% with a corresponding 98% specificity for detecting hemodynamically significant (Serious) stenosis >50% in major leg arteries, defined by angiogram.¹²

However, ABPI has known Issues: ABPI is known to be unreliable on patients with arterial calcification (hardening of the arteries) which results in less or incompressible arteries,¹³ as the stiff arteries produce falsely elevated ankle pressure, giving false negatives.¹⁴ This is often found in patients with diabetes melitus¹⁵ (41% of PAD patients have diabetes¹⁶), renal failure or heavy smokers. ABPI values < 0.9 & >1.3 should be investigated further.

AIMS AND OBJECTIVE:

1. To determine the prevalence of peripheral vascular disease in chronic alcoholics using ankle to brachial index.
2. To compare the values of ankle brachial index in chronic alcoholics with age and sex matched healthy controls.

MATERIAL AND METHODS: In the present study, 50 cases consuming more than 60gm of absolute alcohol per day for more than 12months attending outpatient department and admitted in department

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of medicine of Sri Guru Ram Das institute of Medical Sciences and Research Amritsar, were enrolled. 50 age and sex matched healthy controls who have never consumed alcohol (Never drinkers) were also enrolled for the study.

The study was conducted after approval of ethical committee and obtaining informed consent from patient or relative.

The cases were worked up according to the proforma with detailed history and general physical examination with particular reference to vascular system of the limbs.

Inclusion Criteria:

1. All the patients with H/O chronic alcoholism aged more 40 years.

Exclusion Criteria:

1. Subjects with previous h/o cardiovascular events such as myocardial infarction, Transient Ischemic Attacks (TIA) and heart failure.
2. Patients with h/o Diabetes Mellitus-2.
3. Chronic Smokers.

To assess the drinking status of the study population, four questions were asked as follows:

1. Prior to this study, have you ever drunk alcoholic beverages?
2. In the 12 months before the date of this study, did you drink alcoholic beverages?
3. On a day when you do drink alcohol, how many drinks/how much alcohol do you usually have?
4. How often do you have a drink containing alcohol, per week?

The persons who answered “no” to both the first question and the second question were classified as never- drinkers. The persons who answered “yes” to the first question and “no” to the second question were classified as former drinkers. The persons who answered “yes” to both the first question and the second question were defined as current drinkers. The amount of alcohol consumed per day was calculated from the average number of alcoholic beverages consumed. The ankle brachial pressure index (Which has been described as a risk factor for cardiovascular disease) of the controls (Never drinkers) and those who have consumed more than 60g of alcohol per day was measured using the Doppler ultrasound blood flow detector. The ankle brachial pressure index was calculated as follows:

- Systolic pressure in right brachial artery.
- Systolic pressure in left brachial artery.
- Mean value of the arterial pressure of arm (P_{Arm}).
- Systolic pressure in right dorsalis pedis artery.
- Systolic pressure in left dorsalis pedis artery.
- Systolic pressure in right posterior tibial artery.
- Systolic pressure in left posterior tibial artery.
- Mean value of the arterial pressure of leg (P_{Leg}).
- Mean Ankle Brachial Index= $\text{Mean } P_{Leg} / \text{Mean } P_{Arm}$.

ABPI value	Interpretation
Above 1.2	Abnormal Vessel

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	hardening from PVD
1.0 - 1.2	Normal range
0.9 - 1.0	Acceptable
0.8 - 0.9	Some arterial disease
0.5 - 0.8	Moderate arterial disease
Under 0.5	Severe arterial disease
The values of the ankle brachial pressure index thus measured were grouped as follows:	

The results were tabulated and statistically analysed using SPSS version 19.

RESULTS:

Fig. 1: Distribution of study subjects according to peripheral vascular disease and age.

The chi-square statistic is 7.6856. The P-Value is 0.052976. The result is not significant at $p < 0.05$.

Fig. 2: Distribution of study CONTROLS according to peripheral vascular disease and age.

The chi-square statistic is 7.4468. The P-Value is 0.058941. The result is not significant at $p < 0.05$.

Fig. 3: Distribution of study subjects according to peripheral vascular disease and presence of clinical symptoms.

The Chi-square statistic is 28.8584. The P value is 0. This result is significant at $p < 0.05$.

Fig. 4: Distribution of study controls according to peripheral vascular disease and presence of clinical symptoms.

The Chi-square statistic is 0.4352. The P value is 0.509447. This result is not significant at $p < 0.05$.

Fig. 5: Distribution of study subjects according to peripheral vascular disease and LDL.

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The Chi-square statistic is 10.8844. The P value is 0.00097. This result is significant at $p < 0.05$.

Fig. 6: Distribution of study controls according to peripheral vascular disease and LDL.

The Chi-square statistic is 3.1853. The P value is 0.074305. This result is not significant at $p < 0.05$.

Fig. 7: Distribution of study subjects according to peripheral vascular disease and Triglycerides.

The Chi-square statistic is 9.1837. The P value is 0.002442. This result is significant at $p < 0.05$.

Fig. 8: Distribution of study controls according to peripheral vascular disease and Triglycerides.

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The Chi-square statistic is 0.5195. The P value is 0.471036. This result is not significant at $p < 0.05$.

AMOUNT IN GRAMS	PVD (ABI<0.9)		TOTAL
	PRESENT	ABSENT	
61-70	2(18.1%)	31(79.4%)	33(66%)
71-80	5(45.4%)	7(17.9%)	12(24%)
81-90	2(18.1%)	1(2.5%)	3(6%)
91-100	2(18.1%)	0(0.0%)	2(4%)
TOTAL	11(100%)	39(100%)	50(100%)

Table 1: Distribution of study subjects according to peripheral vascular disease and amount of alcohol consumed

The chi-square statistic is 18.1695. The P-Value is 0.000406. The result is significant at $p < 0.05$.

DURATION IN YEARS	PVD (ABI<0.9)		TOTAL
	PRESENT	ABSENT	
1-5 YEARS	3 (27.2%)	28 (71.7%)	31 (62%)
6-10 YEARS	8 (72.7%)	11 (28.2%)	19(38%)
TOTAL	11 (100%)	39(100%)	50(100%)

Table 2: Distribution of study subjects according to peripheral vascular disease and years of alcohol consumption

The Chi-square statistic is 7.2188. The P value is 0.007214. This result is significant at $p < 0.05$.

FIG. 9: Distribution of ABI in CASES and with respect to presence of clinical symptoms.

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The Chi-square statistic is 0.2878. The P value is 0.591629. This result is not significant at $p < 0.05$.

Fig. 10: Distribution of ABI in CASES and with respect to presence of clinical symptoms:

The Chi-square statistic is 0.2841. The P value is 0.594032. This result is not significant at $p < 0.05$.

ABPI value	CASES	CONTROLS	Interpretation
Above 1.2	2	2	Abnormal Vessel hardening from PVD
1.0 - 1.2	27	29	Normal range
0.9 - 1.0	10	16	Acceptable
0.8 - 0.9	7	1	Some arterial disease
0.5 - 0.8	4	2	Moderate arterial disease
Under 0.5	0	0	Severe arterial disease

Table 3: Distribution study subjects with respect to Mean ABI and the related risk

DISCUSSION: In our study, in the cases group maximum patients with mean ABI < 0.9 were found in the age group between 41-50 years (63.6%) and proportion was less in higher age groups. In the control group only 3(20%) had PVD in the age group of 51-60years.

Other studies showed that prevalence of PVD increases with increase in age which are not in concordance with our results. This discordance may be due to small sample size of our study. Criqui MH et al while studying the prevalence of PAD reported that it is highly age-dependent and increases

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with age.¹⁷ Gregg EW et al studied the prevalence of peripheral arterial disease in patients with or without diabetes over the age of 40 years using ankle brachial index.¹⁸ They reported that prevalence of PAD, PN, and overall LED increases steeply with age. Lekshmi RM et al while studying the Peripheral arterial disease in community-based patients with diabetes in Singapore reported that, prevalence of PAD was positively associated with increasing age.¹⁹

In our study, the cases showed a total of 11(22%) patients with PVD only 7(14%) showed clinical symptoms of PVD. This data was statistically significant ($p=0$) whereas in the control group 3(6%) had PVD but were symptomless and of the patients with mean ABI in normal ranges 6(12%) showed clinical symptoms. The data was not statistically significant ($p=0.5$). This is in concordance with the study done by Eason SL et al,²⁰ Buitrón LV et al²¹ which showed that the presence of either signs or symptoms was more frequent in subjects with PAD.

This study shows in the cases group total of 13(26%) had raised levels of LDL but PVD was present in 5(45.5%) of these cases and in patients with normal levels of LDL 6(54.5%) had PVD. The data is statistically significant ($p=0.00097$). In the control group, in those with high LDL levels, 2(16.6%) had PVD and in the ones with normal LDL levels 1 had PVD. Data is not significant ($p=0.07$). This is in concordance with the study done by Cacoub P et al.²² They measured ABI in 5679 adults aged 55years or older and found that peripheral arterial disease was positively correlated with LDL cholesterol levels.

In the cases group, 15(30%) had triglyceride levels >150 of which only 6 had PVD and in those with normal levels 5 had PVD. The data is statistically significant ($p=0.002$). In the control group, 7(14%) had high levels of triglycerides but none had PVD and in those with normal levels, 3 had PVD. The data is not significant ($p=0.47$). This is in concordance with the study done by Lahoz et al which showed that subjects with triglyceride levels >150 mg/dl were significantly associated with a low ABI.²³ Buitrón-Granados LV et al studied prevalence of peripheral arterial disease and related risk factors in an urban Mexican population.²¹ They included 400 adult subjects and finally concluded that serum triglycerides ≥ 150 mg/dL was one of the risk factors related to PAD.

In our study it was found that maximum PVD cases were found in those having 61-70 grams/day alcohol (66%). this is statistically significant ($p=0.0004$). Xie X et al²⁴ observed that the ABI value of individual with daily alcohol level >60g/d was significantly lower than those never drink or than those with daily alcohol level <60g/d. Also it was observed in this study that more prevalence of PVD around 72% was found in those who consumed alcohol regularly for around 6-10years as compared to those who consumed for lesser period. This data is statistically significant ($p=0.007$).

Corrao G et al suggested that risk decreased from 0 to 20g/day; there was evidence of a protective effect up to 72g/day and increased risk above > 89g/day.⁸ In study by Goffin R et al, the odds of intermittent claudication for a one standard deviation increase in alcohol intake was 1.0, suggesting that alcohol had no influence on the disease.²⁵ However, in the Edinburgh Artery Study (Scotland) by Jepson R G,²⁶ a cross sectional analysis of alcohol intake and relationship with ankle brachial pressure index, a greater alcohol intake in males was related to a higher index, i.e. less severe peripheral arterial disease. In this study the protective effect was more related to wine consumption than to beer or spirits. Also in a large study by Camargo C A²⁷ on approximately. 22 000 US male physicians the results showed that alcohol consumption (Regardless of type of alcohol) decreased the risk of peripheral arterial disease in apparently healthy men.

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CONCLUSION: The present study was conducted to determine the prevalence of Peripheral Arterial Disease in chronic alcoholics using the ankle brachial pressure index. The results obtained were evaluated according to standard statistical analysis and following conclusions were denuded from the study.

The study sample of 50 cases and 50 controls maximum number of patients were in age group of 41-50yrs. 11(22%) cases and 3(6%) controls had peripheral vascular disease.

- Out of 11(22%) patients of peripheral vascular disease 4 patients were asymptomatic and in controls all the 3 were asymptomatic.
- High triglyceride levels (>150mg/dl) were found in patients having peripheral vascular disease. 6(54%) cases out of 11 had high triglyceride (>150mg/dl).
- Peripheral vascular disease has positive correlation with LDL cholesterol levels. 7(63%) patients having peripheral vascular disease had serum LDL cholesterol levels >190 mg/dl.
- The prevalence of higher rate of peripheral vascular disease were in cases consuming alcohol 71-80grams/day and for a duration of 6-10yrs.

REFERENCES:

1. Doobay AV, Anand SS. Sensitivity and specificity of the ankle brachial index to predict future cardiovascular outcomes: a systematic review. *Arterioscler Thromb Vasc Biol* 25: 1463–69.
2. Greenland P, Abrams J, Aurigemma GP, Bond MG, Clark LT. Prevention Conference V: beyond secondary prevention: identifying the high-risk patient for primary prevention: noninvasive tests of atherosclerotic burden: Writing Group III. *Circulation* 101: E16–E22.
3. Smith SC, Greenland P, Grundy SM. AHA Conference Proceedings. Prevention conference V: beyond secondary prevention: identifying the high-risk patient for primary prevention: executive summary. American Heart Association. *Circulation* 101: 111–16.
4. Newman AB, Tyrrell KS, Kuller LH. Mortality over four years in SHEP participants with a low ankle-arm index. *J Am Geriatr Soc* 45: 1472–78.
5. Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M. Ankle-arm index as a predictor of CVD and mortality in the Cardiovascular Health Study: the Cardiovascular Health Study Group. *Arterioscler Thromb Vasc Biol* 19: 538–45.
6. Migliacci R, Nasorri R, Ricciarini P, Gresele P. Ankle-brachial index measured by palpation for the diagnosis of peripheral arterial disease. *Family Practice* 25: 228–32.
7. Fagrell B, De Faire U, Bondy S, Criqui M, Gaziano M. The effects of light to moderate drinking on cardiovascular diseases. *J Intern Med* 246: 331–40.
8. Corrao G, Rubbiati L, Bagnardi V, Zambon A, Poikolainen K. Alcohol and coronary heart disease: a meta-analysis. *Addiction* 95: 1505–23.
9. O'Keefe JH, Bybee KA, Lavie CJ (2007) Alcohol and cardiovascular health: the razor-sharp double-edged sword. *J Am Coll Cardiol* 50: 1009–14.
10. Di Castelnuovo A, Costanzo S, Bagnardi V, Donati MB, Iacoviello L. Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. *Arch Intern Med* 166: 2437–45.
11. Vowden P, Vowden K. "Doppler assessment and ABPI: Interpretation in the management of leg ulceration". *Worldwide Wounds*. - describes ABPI procedure, interpretation of results, and notes the somewhat arbitrary selection of "ABPI of 0.8 has become the accepted endpoint for high

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- compression therapy, the trigger for referral for a vascular surgical opinion and the defining upper marker for an ulcer of mixed aetiology". *J Intern Med* 246: 353–60.
12. McDermott MM, Criqui MH, Liu K, Guralnik JM, Greenland P, Martin GJ, Pearce W. "Lower ankle/brachial index, as calculated by averaging the dorsalis pedis and posterior tibial arterial pressures, and association with leg functioning in peripheral arterial disease". *J Vasc Surg*. 32 (6): 1164–71.
 13. Allison MA, Hiatt WR, Hirsch AT, Coll JR, Criqui MH. "A high ankle-brachial index is associated with increased cardiovascular disease morbidity and lower quality of life". *J Am Coll Cardiol*. 51 (13): 1292–8.
 14. American Diabetes Association. (December 2003). "Peripheral Arterial Disease in People with Diabetes". *Diabetes Care* 26 (12): 3333–41.
 15. Aboyans V, Ho E, Denenberg JO, Ho LA, Natarajan L, Criqui MH. "The association between elevated ankle systolic pressures and peripheral occlusive arterial disease in diabetic and nondiabetic subjects". *J Vasc Surg*. 48 (5): 1197–203.
 16. Novo S. "Classification, epidemiology, risk factors, and natural history of peripheral arterial disease". *Diabetes Obes Metab*. 4: S1–6.
 17. Criqui MH, Fronek A, Barrett-Connor E. The prevalence of peripheral arterial disease in a defined population. *Circulation*. 1985 Mar; 71(3): 510-5.
 18. Gregg EW, Sorlie P, Paulose R. The 1999-2000 National Health and Nutrition Examination Survey: Prevalence of lower-extremity disease in the U.S. adult population ≥ 40 years of age with and without diabetes: 1999-2000 National Health and Nutrition Examination Survey. *Diabetes Care*. 2000; 27: 1591-7.
 19. Lekshmi Narayanan RM, Koh WP, Phang J. Peripheral arterial disease in community-based patients with diabetes in Singapore: Results from a Primary Healthcare Study. *Ann Acad Med Singapore*. 2010 Jul; 39(7): 525-7.
 20. Eason SL, Petersen NJ, Suarez-Almazor M. Diabetes mellitus, smoking, and the risk for asymptomatic peripheral arterial disease: whom should we screen? *J Am Board Fam Pract*. 2005 Sep-Oct; 18(5): 355-61
 21. Buitrón-Granados LV, Martínez-López C, Escobedo-de la Peña J. Prevalence of peripheral arterial disease and related risk factors in an urban Mexican population. *Angiology*. 2004 Jan-Feb; 55(1): 43-51.
 22. Cacoub P, Cambou J, Kownator S. Prevalence of peripheral arterial disease in high-risk patients using ankle-brachial index in general practice: a cross-sectional study *Int J Clin Pract*. 2009 January; 63(1): 63–70.
 23. Lahoz C, Vicente I, Laguna F. Metabolic syndrome and asymptomatic peripheral artery disease in subjects over 60 years of age. *Diabetes Care*. 2006 Jan; 29(1): 148-50.
 24. Xie X, Ma Y-T, Yang Y-N, Li X-M, Liu F. Alcohol Consumption and Ankle-to-Brachial Index: Results from the Cardiovascular Risk Survey. *PLoS ONE* 5(12): e15181. doi: 10.1371/journal.pone.0015181.
 25. Gofin R, Kark JD, Friedlander Y, et al. Peripheral vascular disease in a middle-aged population sample. The Jerusalem Lipid Research Clinic Prevalence Study. *Isr J Med Sci* 1987; 23: 157 67.

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26. Jepson, R., Fowkes, F., Donnan, P. and Housley, E. (1995). Alcohol intake as a risk factor for peripheral arterial disease in the general population in the Edinburgh Artery Study. *Eur J Epidemiol*, 11(1), pp.9-14.
27. Camargo, C., Stampfer, M., Glynn, R., Gaziano, J., Manson, J., Goldhaber, S. and Hennekens, C. (1997). Prospective Study of Moderate Alcohol Consumption and Risk of Peripheral Arterial Disease in US Male Physicians. *Circulation*, 95(3), pp.577-580.

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