ASSESSMENT OF LIPID DYSFUNCTION IN PATIENTS ON MAINTENANCE HAEMODIALYSIS

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Background: Dyslipidaemia is a major risk factor of cardiovascular disease in patients on maintenance haemodialysis. Both increased and decreased levels of cholesterol are associated with increased cardiovascular mortality in haemodialysis patients. **Objective**: To assess the lipid dysfunction among patients on maintenance haemodialysis in a nephrology unit at Rawalpindi as compared with healthy individuals. **Methodology**: A descriptive comparative study was carried out in a nephrology unit at Rawalpindi, Pakistan. A total of 140 subjects were included consisting of 70 patients on maintenance haemodialysis (MHD) and 70 healthy controls. Body mass index (BMI) was measured according to WHO guidelines. Serum total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) were assayed on chemistry analyser. Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedwald equation. **Result**: MHD patients had significantly lower BMI, mean (SD) 20.07(3.66) as compared with the controls 22.88(3.97) kg/m^2 (p<0.001). The lipid profile among MHD patients and controls are given as mean (SD): (a) Total Cholesterol 3.84(1.06) vs 4.65(0.97) (p<0.001), (b) LDL-C 2.21(0.77) vs 2.93(0.71) (p<0.001), (c) HDL-C 0.95(0.166) vs 0.97(0.138) (p=NS), (d) Non HDL 2.88(0.95) vs 3.67(0.88) (p<0.0001), (e) Triglycerides 1.68(1.09) vs 1.69(0.86) (p=NS). The most common abnormality observed in haemodialysis patients was low HDL-C (81%) followed by increased Non-HDL-C (23%) and increased serum triglycerides (19%). **Conclusion:** It is concluded that our patients on maintenance haemodialysis have significantly low BMI, total Cholesterol, LDL-C and Non-HDL-C depicting malnutrition leading to inflammation, accelerated atherosclerosis process and cardiovascular complications.

Key words: total Cholesterol, lipoproteins, BMI, haemodialysis, cardiovascular disease

INTRODUCTION

Dyslipidaemia is highly prevalent in patients on maintenance haemodialysis (MHD), with predominance of the atherogenic triad, i.e., hypertriglyceridemia, elevated VLDL and reduced HDL.[1] This mimics the lipid abnormalities of metabolic syndrome, which accelerate the progression of atherosclerosis and increase the risk for cardiovascular mortality.[2] Patients with CKD are in the highest risk category, i.e., a coronary heart disease (CHD) risk equivalent, for risk factor management of CVD.[3] The incidence of cardio vascular disease (CVD) is high in patients on haemodialysis.[4]

CHD risk factors in the general population remain predictive of CVD among patients with CKD.[5] Cardiovascular disease is the leading cause of death in haemodialysis patients accounting for almost 50 percent of deaths.[6] Many atherosclerotic cardio vascular disease (ASCVD) risk factors are more prevalent in end stage renal disease (ESRD) than in the general population. Of the traditional risk factors for ASCVD in patients with ESRD, dyslipidaemia may play a major role. Control of these risk factors may have a substantial impact in reducing the excess burden of CHD.[7] Kidney Dialysis Outcome Quality Initiative (K/DOQI) states that patients on MHD with 1) Fasting triglycerides >5.65 mmol/L; 2) LDL >2.59 mmol/L and 3) Triglycerides ≥2.26 mmol/L, LDL-C <2.59 mmol/l, and non-HDL cholesterol >3.36 mmol/L, should be considered for treatment to reduce the cardiovascular complications in these patients.[8]

Cholesterol levels may be lower in MHD patients. In this setting, there is an inverse relationship between mortality and the cholesterol concentration.[9] This pattern of reverse epidemiology, i.e., hypercholesterolemia associated with decreased mortality and low cholesterol concentration in MHD patients associated with increased CVD mortality has been associated with malnutrition inflammation atherosclerosis complex.[10,11]

Keeping in view, the mortality associated with CVD in haemodialysis patients and the association of cholesterol levels with CVD in MHD patients, we planned to study the lipid profile of patients on maintenance haemodialysis in our centre compared to healthy controls. This study was done to know the burden and the type of lipid dysfunction in our MHD patients to adopt appropriate measures to decrease CVD mortality in this population.

MATERIAL AND METHODS

This study was carried out in Nephrology Department Military Hospital Rawalpindi. Seventy patients (44

males and 26 females) on maintenance haemodialysis and 70 age and sex matched healthy volunteers were included. Individuals having hypertension, diabetes mellitus, ischaemic heart disease, nephrotic syndrome, hypothyroidism, chronic liver disease and patients taking lipid-lowering medications were excluded.

Clinical history and physical examination of each subject was carried out. The height and weight of all individuals were measured by measuring scale and weighing machine. Body mass index (BMI) was calculated in kg/m^2. Five ml. of venous blood after overnight fast was collected for analysis of lipid parameters.

Serum total cholesterol (TC) was estimated by enzymatic cholesterol oxidase method CHOD-PAP[12] and Serum triglycerides by lipase/GPO-PAP colorimetric method.[13] Serum high-density lipoprotein cholesterol (HDL-C) by enzymatic colorimetric method. Low-density lipoproteins cholesterol (LDL-C) was calculated by Friedwald equation LDL-C=TC–(HDL-C+TG/2.2.[14] Non-HDL-C was calculated by subtracting HDL- C from TC. All of them were done on chemistry analyser Selectra using reagent kits from Merck Co.

Data was analysed by using SPSS 15. Mean, SD and percent were calculated. Chi-square test was applied to determine the difference between MHD patients and controls with different grades of BMI. Independent student's t-test was applied to know difference in lipid parameters among MHD patients and control groups and *p* value ≤0.05 was taken as significant.

RESULTS

One hundred-forty subjects, 70 in each of control and MHD patients groups completed the study. Forty-four individuals were male and 26 were females in each group (Figure-1). The age range of control and test subjects were 17–75 yrs with a mean (SD) of 46.99(15.2) vs 46.46(14.8) for MHD patients and control groups (Figure-2).

The MHD patients had lower BMI as compared to controls mean (SD) 20.07(3.66) vs 22.88(3.97) (Table-I). TC, LDL-C and Non-HDL-C of MHD patients were significantly lower compared with control groups as shown in Table-2. TC, LDL-C, and Non-HDL-C of male MHD patients were significantly lower compared with control group (Table-3). The same variables were higher in females of control group compared to MHD patients but the difference was not statistically different as shown in Table-4.

Fifty-four (77%) MHD patients had low serum TC levels, i.e., <4.5 mmol/l compared to 31 (40%) controls. The most common abnormality observed in haemodialysis patients was low HDL Cholesterol (81%) followed by increased Non-HDL-C (23%) and increased serum Triglycerides (19%).

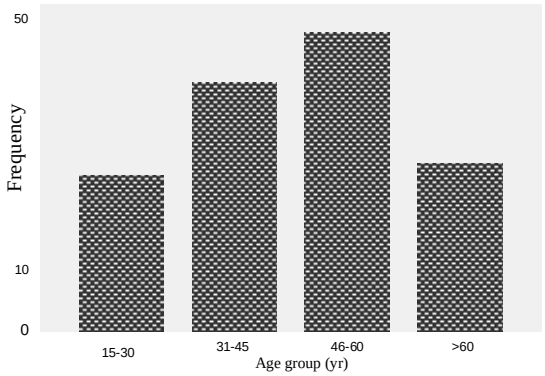

Figure-1: Age distribution among study population

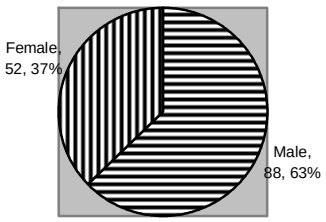

Figure-2: Sex distribution of study subjects

Table-1: Distribution of BMI among MHD patients (n=70) and controls (n=70).

BMI (kg/m^2)	MHD patients (%)	Controls (%)	*p* value
<18.5	26 (37%)	5 (7.1%)	0.0001
18.5-24.9	34 (48.5%)	43 (61.4%)	0.0001
24.9-29.9	9 (12.8%)	19 (27.1%)	0.0001
>30	1 (1.42%)	3 (4.28%)	0.0001

Table-2: Lipid Profile of 140 Study Individuals.

Serum Cholesterol/ Triglycerides (mmol/l)	MHD patients (n=70) Mean (SD)	Controls (n=70) Mean (SD)	*p* value
Total cholesterol	3.84 (1.06)	4.65 (0.97)	0.0001
LDL cholesterol	2.21 (0.77)	2.93 (0.71)	0.0001
HDL cholesterol	0.95 (0.166)	0.97 (0.138)	0.455
Non-HDL cholesterol	2.88 (0.95)	3.67 (0.88)	0.0001
Triglycerides	1.68 (1.09)	1.69 (0.86)	0.960

Table-3: Comparison of lipid profile of male haemodialysed patients and controls. (n=88)

Serum Cholesterol/ Triglycerides (mmol/l)	MHD patients (males) Mean(SD)	Controls (males) Mean(SD)	*p* value
Total Cholesterol	3.59(0.75)	4.69(0.79)	0.0001
LDL Cholesterol	2.09(0.65)	2.95(0.60)	0.0001
HDL Cholesterol	0.91(0.10)	0.95(0.11)	0.065
Non-HDL Cholesterol	2.65(0.72)	3.74(0.73)	0.0001
Triglycerides	1.60(1.10)	1.82(0.88)	0.305

Table-4: Comparison of lipid profile of female haemodialysed patients and controls.

Serum Cholesterol/ Triglycerides (mmol/l)	MHD patients Mean(SD)	Control group Mean(SD)	*p* value
Total Cholesterol	4.27(1.36)	4.57(1.22)	0.409
LDL Cholesterol	2.41(0.93)	2.90(0.89)	0.06
HDL Cholesterol	1.03(0.21)	1.00(0.16)	0.671
Non-HDL Cholesterol	3.28(1.13)	3.56(1.11)	0.370
Triglycerides	1.81(1.06)	1.46(0.80)	0.188

Twenty-six (37%) of the haemodialysis patients would have required treatment for dyslipidaemia as per K/DOQI guidelines, 2 patients for hypertriglyceridemia, 21 for increased LDL levels and 3 for increased Non HDL levels.

DISCUSSION

We determined the lipid profile along with BMI of patients undergoing maintenance haemodialysis at our centre for cardiovascular risk assessment and to adopt appropriate measures to improve mortality in MHD patients.

Our haemodialysis patients had significantly lower BMI (p=0.001). Several other studies have shown similarly lower BMI in MHD patients as compared to controls.[15,16] We found 49% normal weight, 13% overweight and 1% obese patients undergoing haemodialysis in comparison to 59% normal weight, 24% overweight and 17% obese individuals under going haemodialysis as reported by Torun and associates.[17] Thirty-seven percent of MHD patients had BMI less than 18.5kg/m^2. This indicates increased prevalence of malnutrition in our MHD patients according to WHO guidelines for adults.[18] Survival among haemodialysis patients is enhanced in over weight individuals.[19] Every one-unit increase in the BMI is associated with a reduction of 30 percent in the relative risk of dying.[20]

TC and LDL-C was significantly lower in MHD patients as compared to healthy controls (p=0.0001). Among male haemodialysed patients similar observation was recorded. Kalantar-Zadeh *et al* also observed low total cholesterol, LDL-C and HDL-Cl in MHD patients compared to healthy controls similar to our study.[21]

Other common lipid abnormality observed in our haemodialysis patients was low HDL-C levels. However serum HDL-C was non-significantly lower in MHD patients as compared to controls. HDL-C <40 mg/dl (1.03 mmol/l) was found in 81% of MHD patients in contrast to 51% incidence found by Pennell P *et al*[1] and 33% in CHOICE study.[22]

Non-HDL-C >3.36 mmol/l were found only in 23% of our MHD patients. Pennell and Co workers (2006) found 54% patients having Non-HDL alone at the level of ≥ 3.36 mmol/l.[1] Non-HDL Cholesterol is reported to be uninfluenced by non-fasting state and thus has the advantage in haemodialysis patients in whom fasting samples are difficult to obtain for lipid analysis.[23]

Only 19% of our haemodialysis patients had serum TG levels more than 2.26 mmol/l. In CHOICE study 36% of haemodialysed patients had hypertriglyceridemia where as Pennell and coworkers found the incidence to be 52%.[1,22] Non-fasting sample collection by Pennell may be the cause of this difference as triglyceride levels increase after meals.

MHD female patients in our study had lower TC, LDL-C, HDL-C and Non-HDL-C compared to healthy control females but the difference was not statistically significant. Small sample size may be one reason for this observation. The other reason may be that mean age of our female patients on MHD was 51 years and almost 80% of these were postmenopausal. After menopause serum total cholesterol and LDL cholesterol increase and HDL cholesterol decreases.[24,25] This is secondary to decreased levels of oestrogen. Females are likely to have early menopause in ESRD and have unfavourable lipid profile for CVD in ESRD.[26]

In our study 37% of the haemodialysis patients would have required treatment as per K/DOQI guidelines versus 57% in Pennell P study.[1] This high percentage of MHD patients having low cholesterol and lower percentage qualifying treatment for hyperlipidaemia again indicates malnutrition. Our general population also has lower incidence of hyperlipidaemia.[27]

Total and LDL hypercholesterolemia as well as hypertriglyceridemia have a paradoxical association with better survival.[28] Low serum cholesterol in MHD patients is associated with increased CVD mortality. This pattern of reverse epidemiology for CVD risk factors has been associated with malnutrition-inflammation-complex syndrome / malnutrition inflammation-atherosclerosis complex (MICS/MIA).[29] Both malnutrition and inflammation are common in CKD patients, are associated with high short-term mortality in haemodialysis patients and appear to be the main cause of worsening ASCVD in CKD patients.[30,31]

Malnutrition may lead to inflammation and vice versa. Malnourished dialysis patients are hypocholesterolemic, deficient of antioxidants and are predisposed to infection that may decrease the ability to remove circulating endotoxins.[32] Based upon the lipoprotein-endotoxin hypothesis, there is an optimum serum lipoprotein concentration below which lipid reduction is detrimental as it leads to decreased ability of lipoproteins to bind lipopolysaccharide; this, in turn, may prevent lipoproteins from neutralizing the detrimental effects of endotoxin.[33] Uraemia and renal replacement therapies result in markedly enhanced oxidative

stress, the production of complement fragments and cytokines, increased adhesion molecules in endothelial cells, and other pro-inflammatory factors.[34] These factors may provide the proper milieu for the development of accelerated atherosclerosis.[35]

Successful management of MICS may ameliorate the cardiovascular mortality and poor outcome in dialysis patients. Because MICS is multifactorial, its correction will require an integral approach rather than a single intervention.[29] The early stage of chronic renal failure may be the ideal time to start therapeutic interventions.[36]

Routine counselling and encouragement for physical activity in MHD patients has the potential to improve physical functioning, and optimise quality of life.[37] For MHD patients, incorporation of exercise into the dialysis session may increase patient participation and tolerance of exercise. A study in normal adults concludes that a regular exercise program can improve plasma lipid and lipoprotein patterns, results, which should be applicable to haemodialysis patients as well.[38] MHD patients can adhere to long-term physical training programs on the non-dialysis days, as well as during haemodialysis with considerable improvements in physical fitness and health.[39]

Further studies are needed in different haemodialysis centres in large number of patients especially in female patients in our country to know the impact of different strategies adopted to ameliorate malnutrition, inflammation and cardiovascular disease in haemodialysis patients in our set-up.

In conclusion, hypocholesterolaemia and decreased HDL-C along with low BMI are prevalent in our MHD patients. This may increase mortality in these patients through malnutrition inflammation atherosclerosis process leading to CVD complications. Dietary education of MHD patients, improvement in dialysis practices and inclusion of exercise programmes in dialysis centres is likely to improve CVD mortality in MHD patients.

REFERENCES

1. Pennell P, Leclercq B, Delahunty MI, Walters BA.. The utility of non-HDL in managing dyslipidemia of stage 5 chronic kidney diseases. Clin Nephrol 2006 Nov; 66(5):336-47.
2. Abrass CK. Lipid metabolism and renal disease. Contrib Nephrol. 2006;151:106-21.
3. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis. 2002;39:S1-266.
4. Gowdak LH, Arantes RL, de Paula FJ, Krieger EM, De Lima JJ. Under use of American College of Cardiology/American Heart Association Guidelines in hemodialysis patients. Ren Fail. 2007;29(5):559-65.
5. Soubassi LP, Papadakis ED, Theodoropoulos IK, Poulos GD, Chaniotis D, Tsapakidis IP *et al*. Incidence and risk factors of coronary artery disease in patients on chronic hemodialysis., Int Artif Organs 2007 Mar;30(3):253-7.
6. Al Wakeel JS, Mitwalli AH, Al Mohaya S, Abu-Aisha H, Tarif N, Malik GH, *et al*. Morbidity and mortality in ESRD patients on dialysis. Saudi J Kidney Dis Transpl. 2002 October-December;13(4):473-7.
7. Muntner P, He J, Astor BC, Folsom AR, Coresh J. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. J Am Soc Nephrol. 2005 Feb;16(2):529-38.
8. National Kidney Foundation. K/DOQI clinical practice guidelines for managing dyslipidemias in chronic kidney disease. Am J Kidney Dis. 2003;41(suppl 3):S1-S92.
9. Iseki K, Yamazato M, Tozawa M, Takishita S. Hypocholesterolemia is a significant predictor of death in a cohort of chronic hemodialysis patients. Kidney Int 2002;61:1887-93.
10. Liu Y, Coresh J, Eustace JA, Longenecker JC, Jaar B, Fink NE, *et al*. Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. JAMA 2004;291:451-9.
11. Kalantar-Zadeh K**,** Block G**,** Humphreys MH**,** Kopple JD**.** Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. Kidney 2003 Mar;63(3):793-808
12. Allain CC, Poon LS, C.S.G, Richmond, W and Fu. Enzymatic determination of serum cholesterol. P.D. Clin.Chem 1974;20:470.
13. Fossati R, Prencipe L. Serum triglycerides determined colorimetrically with an enzyme that produces hydrogen peroxide. Clin Chem 1982;28:2077.
14. Friedwald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of preparative ultracentrifuge. Clin Chem 1972;18:499-502.
15. Bednarek-Skublewska A, Baranowicz-Gaszczyk I, Jóźwiak L, Dzik M, Majdan M, Ksiazek A. Comparison of some nutritional parameters in hemodialysis patients over and below 65 years of age. Pol Arch Med Wewn. 2005 May; 113(5):417-23.
16. Basaleem HO, Alwan SM, Ahmed AA, Al-Sakkaf KA. Assessment of the nutritional status of end-stage renal disease patients on maintenance hemodialysis. Saudi J Kidney Dis Transpl. 2004 October-ecember;15(4):455-6.
17. Torun D, Micozkadioglu H, Torun N, Ozelsancak R, Sezer S, Adam FU *et al*. Increased body mass index is not a reliable marker of good nutrition in hemodialysis patients. Ren Fail. 2007;29(4):487-93.
18. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. Geneva, World health Organization, 1995 (WHO Technical Report Series, No.854).
19. Johansen KL, Young B, Kaysen GA, Chertow GM. Association of body size with outcomes among patients beginning dialysis. Am J Clin Nutr 2004;80:324-32.
20. Leavey SF, McCullough K, Hecking E, Goodkin D, Port FK, Young EW. Body mass index and mortality in 'healthier' as compared with 'sicker' haemodialysis patients: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant 2001;16:2386-94.
21. Kalantar-Zadeh K, Kilpatrick RD, Kopple JD, Stringer WW. A matched comparison of serum lipids between hemodialysis patients and nondialysis morbid controls. Hemodial Int. 2005 Jul;9(3):314-24.
22. Longenecker JC; Coresh J; Powe NR; Levey AS; Fink NE; Martin A *et al*. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. J Am Soc Nephrol 2002 Jul;13(7):1918-27.
23. Desmeules S, Arcand-Bossé JF, Bergeron J, Douville P, Agharazii M. Nonfasting non-high-density lipoprotein

cholesterol is adequate for lipid management in hemodialysis patients. Am J Kidney Dis. 2005 Jun;45(6):1067-72.
24. Caparević Z, Kostić N. The influence of age and the beginning of menopause on the lipid status, LDL oxidation, and CRP in healthy women. Srp Arh Celok Lek. 2007 May-Jun;135(5-6):280-5.
25. Trémollières FA, Pouilles JM, Cauneille C, Ribot C. Coronary heart disease risk factors and menopause: a study in 1684 French women. Atherosclerosis. 1999 Feb;142(2):415-23.
26. Jang C, Bell RJ, White VS, Lee PS, Dwyer KM, Kerr PG *et al.* Women's health issues in haemodialysis patients. Med J Aust. 2001 Sep 17;175(6):298-301.
27. Shamim Alam, Ihteshamul Haq. Association of ABO, Rh blood groups systems with lipids and other anthropometric co variables as predictors of cardiovascular risk in NWFP, Pakistan. Ann King Edward Med Coll Jun 2004;10(2):166-9.
28. Kilpatrick RD, McAllister CJ, Kovesdy CP, Derose SF, Kopple JD, Kalantar-Zadeh K. Association between serum lipids and survival in hemodialysis patients and impact of race. J Am Soc Nephrol. 2007 Jan;18(1):293-303.
29. Kalantar-Zadeh K. Recent advances in understanding the malnutrition-inflammation-cachexia syndrome in chronic kidney disease patients: What is next? Semin Dial. 2005 Sep-Oct;18(5):365-9.
30. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. Am J Kidney Dis. 2003 Nov;42(5):864-81.
31. Qureshi AR, Alvestrand A, Divino-Filho JC, Gutierrez A, Heimbürger O, Lindholm B *et al.* Inflammation, malnutrition, and cardiac disease as predictors of mortality in hemodialysis patients.J Am Soc Nephrol. 2002 Jan;13 Suppl 1:S28-36.
32. Deicher R, Ziai F, Bieglmayer C, Schillinger M, Horl WH. Low total vitamin C plasma level is a risk factor for cardiovascular morbidity and mortality in hemodialysis patients. J Am Soc Nephrol 2005 Jun;16(6):1811-8.
33. Rauchhaus M, Coats AJ, Anker SD. The endotoxin-lipoprotein hypothesis. Lancet 2000 Sep 9;356(9233):930-3.
34. Horl WH, Cohen JJ, Harrington JT, Madias NE, Zusman CJ. Atherosclerosis and uremic retention solutes. Kidney Int 2004 Oct;66(4):1719-31.
35. Bro S, Bentzon JF, Falk E, Andersen CB, Olgaard K, Nielsen LB. Chronic renal failure accelerates atherogenesis in apolipoprotein E-deficient mice. J Am Soc Nephrol 2003 Oct;14(10):2466-74.
36. Pawlaczyk K, Oko A, Lindholm B, Czekalski S. Malnutrition-inflammation-atherosclerosis (MIA syndrome) in patients with renal failure. Pol Merkur Lekarski. 2003 Oct;15(88):334-43.
37. Painter P. Physical functioning in end-stage renal disease patients: update 2005. Hemodial Int. 2005 Jul;9(3):218-35.
38. Iffat Ara, Riffat Khurshid, Imran Ahmad Qureshi, Munir Ahmad Khan. The Effect of Physical fitness on Plasma Lipids in Young Pakistani Male Medical Students. J Rawal Med Coll Dec 2000;4 (1-2):34-8.
39. Kouidi E, Grekas D, Deligiannis A, Tourkantonis A. Outcomes of long-term exercise training in dialysis patients: comparison of two training programs. Clin Nephrol. 2004;61 (Suppl 1):S31-8.

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