The Role of Different Serum Lipid Profile Parameters In Secondary Prevention of Further Ischemic Attack In Patients With CHD

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Abstract

The study which conducted in Mosul during the period from February to May 2008 as a case-control study including 44 patients with single attack of coronary heart diseases and 37 healthy volunteers as a control group. Concentrations of fasting serum glucose and serum lipid profile parameters including serum total cholesterol, high density lipoprotein cholesterol, both calculated and direct low density lipoprotein cholesterol, triglycerides and total cholesterol/high density lipoprotein cholesterol ratio was determined in both groups.

Results in both groups showed significant positive correlation between calculated and direct low density lipoprotein cholesterol, no significant differences in the fasting serum glucose and in patients with coronary heart diseases significant elevation of all serum lipid profile parameters except significant reduction of high density lipoprotein cholesterol in addition to significant positive correlation between both calculated and direct low density lipoprotein cholesterol with total cholesterol and total cholesterol/high density lipoprotein cholesterol ratio.

It is recommended for secondary prevention of ischemic attack in patients with established coronary heart diseases is to use low density lipoprotein cholesterol and non-high density lipoprotein cholesterol at triglycerides >2.26 mmol/L.

Keywords: CHD, LDL-C, Non-HDL-C.

Introduction

Coronary heart disease[CHD] is the end result of atheromatous plaques accumulation within the walls of the arteries that supply the myocardium with oxygen and nutrients, it is the most common form of heart disease and the single most important cause of premature or sudden death in men and women all over the world[1-3]. Patients with established CHD are at very high risk for another attack especially in the presence of predisposing risk factors[4].

The association between total cholesterol[TC] and the risk of developing CHD has been well established by studies such as the Framingham Heart Study[5]. Although low density lipoprotein cholesterol[LDL-C] which constitute most of the cholesterol in the circulation has been conclusively shown by many prospective studies and randomized clinical trials to be primarily responsible for the association with CHD risk[5, 6], many people who develop CHD have LDL-C that are normal or mildly elevated but have other lipid profile abnormalities[7], in addition to that intervention studies performed in patients with [secondary prevention][8, 9] and without [primary prevention] clinically manifested CHD[10-13] clearly demonstrated the efficacy of lipid-lowering therapies even at relatively low LDL-C concentrations. Therefore, the aims of this study is to demonstrate the abnormalities of lipid profile parameters in patients with CHD in Mosul city and their role in secondary prevention of further ischemic attack.

Patients and Methods

The study was conducted during the period from February to May 2008, the subjects enrolled in this study were divided into two groups [group I and II], those with serum triglycerides[TGs] value >4.52 mmol/L are excluded.

Group I considered as a control group composed of 37 apparently healthy volunteers [22 males and 15 females] from my relative and the members of Nineveh College of Medicine, their ages ranged from [35-77] years with a mean ± standard deviation[SD] of 50.6±12.6 years.

Group II composed of 44 patients [25 males and 19 females] with past history of single attack of CHD in the form of myocardial infarction attending my private lab for investigations, their ages ranged from [39-78] years with a mean ± SD of 54.0 ±9.8 years.

A complete record of history was obtained, including name, age, sex, duration of illness, past-medical and drug history. All members of group I and II had no history of diabetes mellitus, hypertension and smoking.

Blood samples were obtained from both groups in the fasting state by anticubital venepuncture, then within one hour the blood samples were centrifuged at 3000 rpm for 15 minutes for the measurement of serum glucose and serum lipid profile parameters including TC, TGs, high density lipoprotein cholesterol[HDL-C], LDL-C and TC/HDL-C Ratio.

Measurement of serum glucose, TC and TGs were done by specific enzymatic colorimetric methods[14] using a kits supplied by biolabo and biomeriux companies respectively, HDL-C was measured by the precipitation/enzymatic method[15] using a kit supplied by biomeriux company, LDL-C was estimated by both calculation to have calculated LDL-C[C-LDL-C] using Friedwald formula[14] and by precipitation/enzymatic method[16] to have direct LDL-C[D-LDL-C] using a kit supplied by Syrbio company that LDL particles were precipitated with reasonable specificity by the addition of heparin at pH 5.12[16–23], after centrifugation LDL-C was estimated as the difference between TC in serum and supernatant [non-LDL-C].

The results were statistically evaluated by standard statistical methods including mean, SD, range [minimum-maximum], Linear regression analysis [Pearson correlation coefficient r], paired and unpaired student's t-test[24-26] with software programs including Microsoft excel 2003 and SPSS 11.5 to evaluate the relation between different parameters in group I and II. Differences between observations were considered not significant at $p>0.05$.

Results

There are no significant differences [P>0.05, Table 1] in the age and fasting serum glucose between the two groups.

Serum lipid profile parameters were differ significantly between two groups; TC, TGs, D-LDL-C, C-LDL-C and TC/HDL-C Ratio are significantly higher in group II than group I [P<0.001 except D-LDL-C; P<0.005, Table 1, Fig 1], HDL-C is significantly lower in group II than in group I [P<0.001, Table 1, Fig 1].

There is a significant positive correlation between C-LDL-C and D-LDL-C in both group I [Fig 2, r^2=0.699, P<0.001] and group II [Fig 3, r^2=0.665, P<0.001] with no significant difference between them within the group.

In group II both C-LDL-C and D-LDL-C have significant positive correlation with TC [Fig 4 and 5, r^2=0.839 and 0.691 respectively, P<0.001] and with TC/HDL-C Ratio [Fig 6 and 7, r^2=0.445 and 0.402 respectively, P<0.001].

Table 1: Comparison between parameters of both groups.

Values are presented as mean ± SD NS = Not Significant

Parameter	Croup I [Control] n = 37	Group II [CHD Patients] n = 44	P-Value
Age [years]	50.6 ± 12.6	54.0 ± 9.8	NS
Glucose [mmol/L]	4.44 ± 0.42	4.42 ± 0.59	NS
Total Cholesterol (TC) [mmol/L]	4.26 ± 0.63	5.10 ± 1.06	P < 0.001
Triglycerides (TGs) [mmol/L]	1.02 ± 0.35	1.92 ± 0.82	P < 0.001
Direct Low Density Lipoprotein Cholesterol (D-LDL-C) [mmol/L]	2.47 ± 0.73	3.20 ± 1.13	P < 0. 005
Calculated Low Density Lipoprotein Cholesterol (C-LDL-C) [mmol/L]	2.35 ± 0.66	3.17 ± 1.11	P < 0.001
Total Cholestero/High Density Lipoprotein Cholesterol (TC/HDL-C) Ratio	3.12 ± 0.97	5.29 ± 1.97	P < 0.001
High Density Lipoprotein Cholesterol (HDL-C) [mmol/L]	1.45 ± 0.38	1.05 ± 0.32	P < 0.001

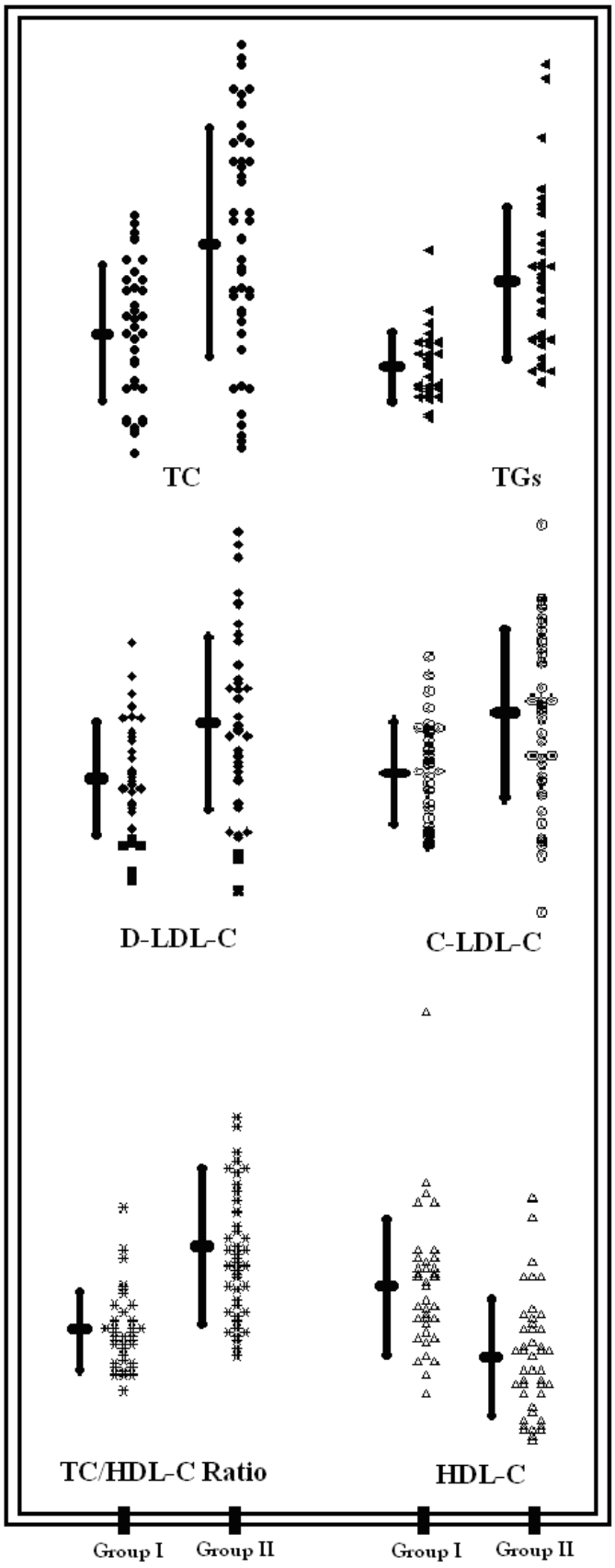

Fig 1: Comparison between lipid profile parameters of both groups.

presented as mean $\pm$ SD

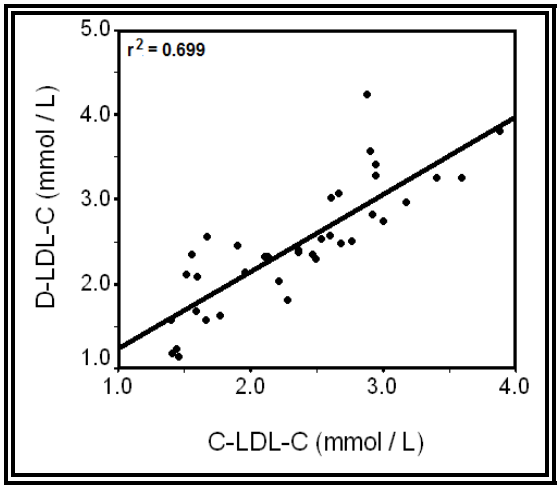

Fig 2: Correlation between C-LDL-C and D-LDL-C in group I.

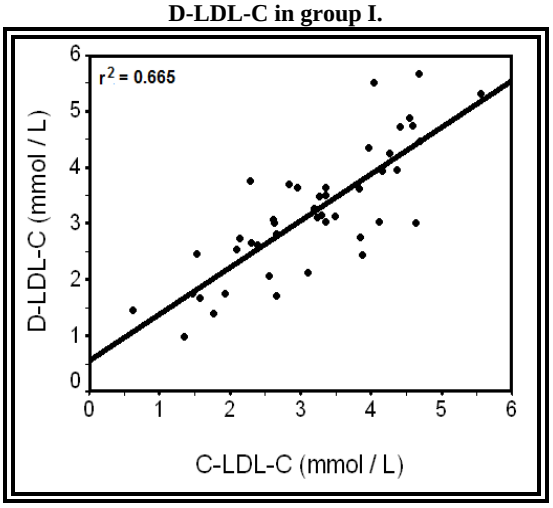

Fig 3: Correlation between C-LDL-C and D-LDL-C in group II.

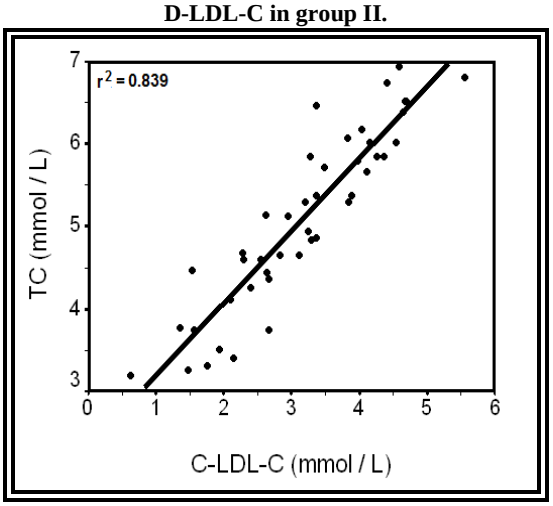

Fig 4: Correlation between C-LDL-C and TC in group II.

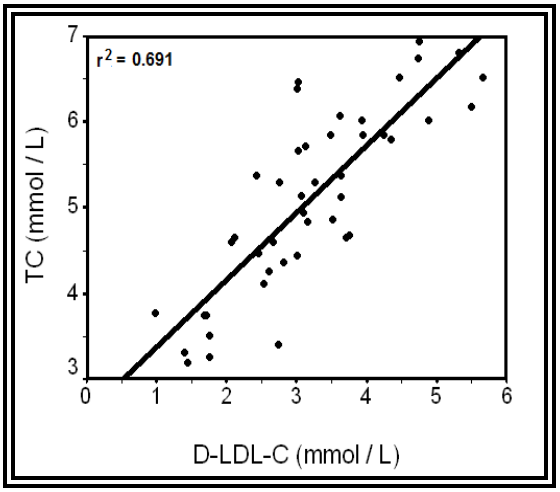

Fig 5: Correlation between D-LDL-C and TC in group II.

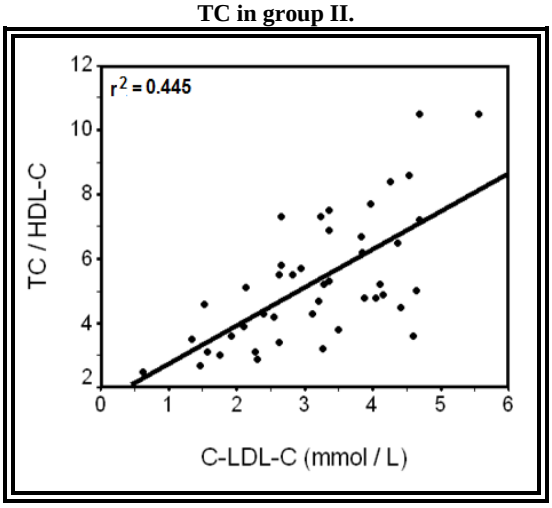

Fig 6: Correlation between C-LDL-C and TC/HDL-C Ratio in group II.

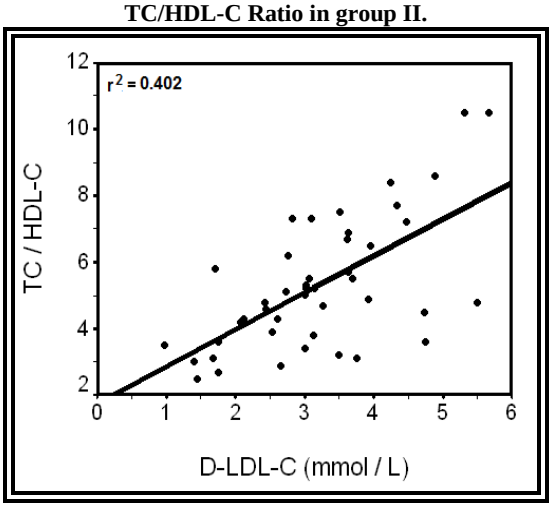

Fig 7: Correlation between D-LDL-C and TC/HDL-C Ratio in group II.

Discussion

Since hyperlipidemia considered as an important risk factor for CHD development[5, 6] and its treatment especially LDL-C has an important role in secondary prevention of another attack[8, 9, 27-30], therefore, many studies concerned with lipid profile in CHD.

In this study serum lipid profile parameters including TC, TGs, LDL-C [D-LDL-C and C-LDL-C], TC/HDL-C Ratio was significantly higher in CHD patients than control group while HDL-C was significantly lower. After exclusion of other risk factors mainly diabetes mellitus, hypertension and smoking, these findings suggesting that these abnormalities may be an important risk factor led to CHD development in group II patients and may lead

to second heart attack in future, these finding is in agreement with other studies that proved abnormal lipid profile parameters is an important cause for atherosclerosis and subsequently to CHD development[5, 6].

Epidemiological surveys have shown that serum TC levels are continuously correlated with CHD risk over a broad range of cholesterol values[31-33]. In this study as serum LDL-C levels [D-LDL-C and C-LDL-C] in group II have a high positive significant correlation with TC and as both TC and LDL-C are significantly elevated, therefore, the same relation must be exist between LDL-C and CHD risk, this relation as proved by other studies not linear but rises more steeply with increasing LDL-C value[34], other studies proved that for every 1% reduction in LDL-C levels, relative risk for major CHD events is reduced by approximately1%[8, 27–29, 35], therefore, LDL-C is superior than TC and considered by many studies as the primary target of treatment in clinical lipid management[4, 7-9, 27–30]. For this reason in this study LDL-C was determined by both calculation to estimate C-LDL-C depending on Friedwald formula[14] and by the early direct method depending on precipitation/enzymatic principle[16] to estimate D-LDL-C, however, in this study there is no significant differences between these two values in both groups. This finding is in agreement with other studies which demonstrated that this early precipitation method for D-LDL-C estimation did not replace the more convenient Friedwald calculation as has no appreciable advantages in precision, accuracy, or specificity[36] even at serum TGs higher than 4.52 mmol/L which is known to compromise the Friedwald calculation[36]. As the most common approach to determining LDL-C in the clinical laboratory at TG <4.52 mmol/L is the Friedwald calculation[37] which is even employed by NCEP to classify subjects into their cut-points[34] and as it proved by other study that D-LDL-C have no advantage over C-LDL-C value at TGs concentration up to 4.52 mmol/L[38] even by other study proved that C-LDL-C have slightly better than homogeneous D-LDL-C assay at TGs up to 4.52 mmol/L[39], therefore, in this study C-LDL-C value was used to define those patients in group II their LDL-C ≥2.58 mmol/L who have the goal for LDL-C lowering according to the program of Adult Treatment Panel III[ATP III] recommended by NCEP as the primary target of therapy[34], accordingly 70.5% [31 from 44] of patients in group II have the goal for LDL-C lowering according to ATP III[34] in which 35.5% of them whose LDL-C between 2.58-3.36 mmol/L require diet therapy alone while the remaining 64.5% whose LDL-C ≥3.36 mmol/L require LDL-lowering drug simultaneously with dietary therapy.

ATP III introduced a new secondary target of therapy, namely Non-HDL-C calculated as TC minus HDL-C in patients with TGs >2.26 mmol/L[7, 34]. Non-HDL-C goal is 0.78 mmol/L higher than the LDL-C goal[34], therefore, in this study Non-HDL-C value was used to define those patients in group II their Non HDL-C ≥3.36 mmol/L. The measurement of Non-HDL-C has the advantage is that it provides a single index of all the atherogenic apolipoprotein[apo] B containing lipoproteins including LDL, very low-density lipoprotein [VLDL], intermediate-density lipoprotein[IDL] and lipoprotein-a[7, 40]. In spite of VLDL and IDL are triglyceride-rich lipoproteins [TGRLPs] they also carry cholesterol[14] and has been shown to correlate with coronary artery disease severity and progression as well as predict cardiovascular morbidity and mortality[7, 34, 41, 42]. Although apo B can be assessed directly, measurement of Non-HDL-C is more practical reliable inexpensive and is accepted as a surrogate marker for apo B in routine clinical practice[42-44] and unlike LDL-C which can be incorrectly calculated in the presence of postprandial hypertriglyceridemia, Non-HDL-C is reliable even when measured in nonfasting state[5 ,42 , 44]. Accordingly in this study 1 from 13 group II patients [7.7%] whose their LDL-C <2.58 mmol/L has TG >2.26 mmol/L and Non-HDL-C ≥3.36 mmol/L, therefore , require LDL-C lowering therapy in spite of low LDL-C, this finding is in the agreement with ATP III recommendation and with other studies that proved Non-HDL-C serve as an additional tool to assess cardiovascular risk in people whose risk is not accurately identified by LDL-C alone[42, 45, 46], this explained that in the presence of hypertriglyceridemia, TGRLPs may be partly depleted of their TGs content and become enriched with cholesterol from LDL result in the generation of modified remnant lipoproteins that are believed to be highly atherogenic because of their small size, high cholesterol content and increased residence time in plasma[43, 45, 47] even they are able to deliver more cholesterol to macrophages than LDL particles[48] because they can penetrate the arterial wall with ease, be taken up directly by macrophages and participate in foam cell formation[49, 50] thus initiating the lipid-laden plaque. At the same time, LDL exchanges core lipids with VLDL to become triglyceride rich and undergoes lipolysis, resulting in a smaller and denser LDL particle[47] which are more atherogenic because they are more easily oxidized and readily penetrate the arterial wall. However, even though LDL-C levels appear “normal” rather than “high” on standard measurements because small, dense particles are lipid poor[47].

Although LDL-C was recognized by NCEP as the primary target of therapy for dyslipidemia as it represent risk-prediction instrument[51, 52] and guidelines for CHD prevention[5, 53], however, the lipid goal according to ATPIII in patients with CHD [high risk] need to meet all the goals for lipid profile including HDL-C >1.03 mmol/L and optimal ≥1.55 mmol/L, TGs <1.7 mmol/L and TC <5.17 mmol/L in addition to LDL-C[4], furthermore, other studies

recommend TC/HDL-C Ratio <5[54] assumed that value >5 performed better than individual lipids including LDL-C in terms of risk prediction of future CHD[54, 55] with a hazard ratio 1.21[56], this ratio contains information about VLDL-C, thereby rendering it more comparable with the apo B:apo A-I ratio[56]. In this study all patients in group II with LDL-C ≥2.58 mmol/L have additional one or more abnormalities of other lipid parameters mentioned before [Table 2], this finding is in agreement with NCEP recommendation that LDL-C is the primary target of therapy for dyslipidemia as it represent 'bad cholesterol' causing atherosclerosis mainly by scavenger pathway when it present in excess concentration in the blood[4].

Although there is a significant positive correlation between LDL-C [calculated and measured] with both TC and TC/HDL-C Ratio [Fig 2-7], the sensitivity [calculated by dividing the number of patients with abnormal TC and TC/HDL-C Ratio having LDL-C ≥ 2.58 mmol/L to the whole number of patients having LDL-C ≥ 2.58 mmol/L], specificity [calculated by dividing the number of patients with normal TC and TC/HDL-C Ratio having LDL-C < 2.58 mmol/L to the whole number of patients having LDL-C < 2.58 mmol/L], predictive value and efficiency of both TC and TC/HDL-C Ratio for detecting patient with LDL-C ≥2.58 mmol/L remain inferior [Table 3], this finding is further distinguish LDL-C as the primary target of therapy for dyslipidemia as recognized by NCEP[4].

In this study 25 patients in group II have TGs level ≥1.7 mmol/L, however, in all of them have one or more additional lipid parameter abnormalities especially all have HDL-C below the optimal level as described by NCEP [Table 4], this finding is in agreement with study which attribute that the role of TGs as a risk factor is controversial and much of its risk may be attributed to the associated low HDL-C level, along with contributions from all of the other related variables that although TGs do appear to be an independent risk factor, they likely act only as a marker for these associated features[57].

Table 2: Additional lipid abnormalities in group II patient with LDL-C ≥ 2.58 mmol/L.

Patients	%	TG ≥1.7mmol/L	TC ≥ 5.17mmol/L	HDL-C <1.03 mmol/L	HDL-C 1.03-1.55 mmol/L	TC/HDL Ratio >5
7	22.58	+	+	+	-	+
1	3.23	+	+	-	+	+
3	9.68	+	+	-	+	-
6	19.35	+	-	+	-	+
3	9.68	-	+	+	-	+
2	6.45	-	+	-	+	+
3	9.68	-	+	-	+	-
2	6.45	-	+	-	-	-
2	6.45	-	-	+	-	+
2	6.45	-	-	-	+	-

Table 3: Significance of TC and TC/HDL-C Ratio to detect patients in group II with LDL-C ≥ 2.58 mmol/L

Test	Sensitivity	Specificity	Predictive value of positive result	Predictive value of negative result	Efficiency
TC ≥ 5.17mmol/L	67.7%	100.0%	100.0%	56.5%	77.3%
TC / HDL-C Ratio > 5	67.7%	92.3%	95.5	54.5%	75.0%

Table 4: Additional lipid abnormalities in group II patient with TG ≥1.7 mmol/L

Patients	%	TC ≥5.17 mmol/L	LDL-C ≥2.58 mmol/L	TC/HDL-C Ratio >5	Non-HDL-C ≥3.36 mmol/L at TG >2.26 mmol/L	HDL-C below optimum level
7	28.0	-	-	-	-	+
5	20.0	+	+	+	+	+
3	12.0	-	+	+	+	+
3	12.0	+	+	+	-	+
3	12.0	+	+	-	-	+
3	12.0	-	+	+	-	+
1	4.0	-	-	-	+	+

In conclusions: In patients with CHD; hyperlipidemia may be an important risk factor led to the heart attack development and may lead to second heart attack in the future; therefore, doing serum lipid profile in those patients is mandatory. Although serum lipid profile include many tests, C-LDL-C at level ≥2.58 mmol/L remain superior over others regarding sensitivity, specificity, predictive values and efficiency to detect patients with CHD at risk of second attack and so require treatment by LDL-C lowering program in addition Non-HDL-C at level ≥3.36 mmol/L when TGs>2.26 mmol/L remain

mandatory as second target for detection of patients with CHD at risk of second attack that cannot be recognized by LDL-C. The role of TGs as risk factor is controversial as much of its risk may be attributed to the associated low HDL-C level. It is recommended for the secondary prevention of ischemic attack in patients with established CHD is the estimation of LDL-C and Non-HDL-C as they are relatively cheap, available and even dependable as apoproteins estimation which are not widely available, further studies are required in future to study the effect of Selenium , Glutathione-Peroxidase, Zinc and Copper levels and the findings of complete blood pictures and electrocardiograph on the secondary prevention.

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الملخص

الدراسة التي أجريتْ في الموصل أثناء الفترةِ مِنْ شباط ولغاية أيار من عام ٢٠٠٨ بطريقة مقارنة الحالات ألمرضيه مع ألمجموعه الضابطة شملت ٤٤ مِنْ المرضى المصابين بأمراض القلب التاجية بنوبة واحده و ٣٧ من المتبرعين الأصحاء كمجموعه ضابطه. تم قياس مستوى الجلوكوز الصائم لمصل الدم وواجهة شحوم مصل الدم والتي تشمل الكوليستيرول الكلي، البروتين ألشحمي رفيع الكثافة، البروتين ألشحمي خفيف الكثافة المحسوب و المباشر، الشحوم الثلاثية و نسبه الكوليستيرول الكلي/البروتين ألشحمي رفيع الكثافة لكلتا المجموعتين.

النَتائِج في كلتا المجموعتين دلت على وجود ارتباط إيجابي معنوي بين البروتين ألشحمي خفيف الكثافة المحسوب و المباشر، عدم وجود اختلافا معنويا في مستوى الجلوكوز الصائم لمصل الدم وفي المرضى المصابين بأمراض القلب التاجية هناك ارتفاعا معنويا في جميع قيم واجهة شحوم مصل الدم باستثناء الانخفاض المعنوي للبروتين ألشحمي رفيع الكثافة أضافه لوجود ارتباطات ايجابيه معنوية بين كل من البروتين ألشحمي خفيف الكثافة المحسوب و المباشر وبين الكوليستيرول الكلي و نسبه الكوليستيرول الكلي/البروتين ألشحمي رفيع الكثافة.

ما يوصّى بيه للمنعِ الثانوي لحدوث ذوي القلبية في المرضى المصابين بأمراض القلب التاجية هو إجراء كشفي البروتين ألشحمي خفيف الكثافة و الكوليستيرول غير رفيع الكثافة عندما يكون مستوى الشحوم ألثلاثيه <٢،٢٦ ممول/لتر.