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Serum Total Homocysteine Levels and its Association with Lipid Profile in Early-Onset Coronary Artery Disease

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ABSTRACT

Background: Coronary artery disease (CAD) remains the leading cause of mortality worldwide, affecting both developed and developing nations. Notably, Pakistani populations exhibit a higher predisposition to early-onset CAD. While traditional risk factors account for many cases, a significant subset of CAD patients presents without conventional risk factors, suggesting the involvement of alternative mechanisms. Elevated homocysteine levels (hyperhomocysteinemia) have emerged as a 'modifiable risk factor for CAD'. 'This study aimed to investigate the association between hyperhomocysteinemia and CAD, as well as its relationship with lipid profile in young Pakistani adults'

Keywords: Homocysteine; Hyperhomocysteinemia; Coronary Artery Disease; Lipid Profile.

Methods: This cross-sectional study comparison was 'conducted at the Punjab Institute of Cardiology in Lahore from October 2009 to June 2010'. The research 'included 30 patients' with CAD '(20-45 years)' and 30 controls of the same age who did not have CAD. All subjects had their fasting serum total homocysteine, total cholesterol, triglycerides, HDL, and LDL levels assessed. Statistical analysis was conducted using SPSS version 16.
Results: Patients with CAD revealed a statistically significant elevation in their mean homocysteine levels (18.1 ± 5.3 µmol/L) compared to the controls (14.7 ± 4.93 µmol/L, p = 0.013).Hyperhomocysteinemia (>15µmol/L) was present in 21 CAD patients (70%) versus 12 controls (40%), yielding an odds ratio of 3.5. 'However, no significant correlation was found between homocysteine levels and lipid profile parameters'.
Conclusion: The study reveals a strong correlation between elevated homocysteine and CAD, while no significant relationship was found between homocysteine and lipid levels in young Pakistani adults, supporting its role as an independent cardiovascular risk factor. In this particular high-risk group, it would be appropriate to investigate further the effects of lowering homocysteine concentrations.

INTRODUCTION

Coronary Artery Disease (CAD) continues to be the most prevalent condition causing mortality and Disability Adjusted Life Years (DALYs) globally. This burden is largely shouldered by 'low- and middle-income countries, contributing nearly seven million deaths alongside 129 million DALYs annually'[1].

Coronary artery disease (CAD) rates are notably high among South Asians, with this population facing one of the highest prevalence rates globally. Of particular concern is the fact that individuals in this region tend to 'experience acute myocardial infarction (AMI) at younger ages than other populations, although the precise causes of this trend remain uncertain' [2]. In Pakistan, the impact of CAD is especially pronounced, affecting one in four middle-aged adults [3].

While traditional risk factors like smoking, dyslipidemia, a family history of coronary artery disease (CAD), diabetes mellitus, and aging are well-known contributors to CAD, they do not fully account for the disease's widespread prevalence. Around 20% of individuals with CAD do not show these typical risk factors, prompting researchers to explore other potential biomarkers. 'One such marker, homocysteine (Hcy), has gained attention because it may play a role in the development of CAD' [4].

'Homocysteine is a sulfur-containing, nonessential amino acid derived from methionine, an essential amino acid'. It is not typically obtained through diet but is produced during methionine metabolism. 'Elevated levels of homocysteine, known as hyperhomocysteinemia (HHcy), are classified as mild (16–30 µmol/L), moderate (31–100 µmol/L), or severe (>100 µmol/L)' [5].

The relationship between coronary artery disease (CAD) and hyperhomocysteinemia (HHcy) has been investigated in various studies. Some research 'indicates a significant association between elevated homocysteine levels and an increased risk of CAD, whereas other studies have found no consistent link between the two' [6, 7].

Dyslipidemia, which includes hypercholesterolemia (elevated total cholesterol), hypertriglyceridemia (elevated triglycerides), 'low levels of high-density lipoprotein cholesterol (HDL-C), and high levels of low-density lipoprotein cholesterol (LDL-C), is widely recognized as a major risk factor for the development of CAD' [8].

There are conflicting studies regarding the relationship between serum total homocysteine (tHcy) levels and lipid profile in the development of coronary artery disease (CAD). Some studies suggest a correlation between serum total homocysteine levels and lipid profile, while others find no such relationship [9, 10].

Since tHcy concentration is affected by lifestyle, 'genetic, and nutritional factors [11, 12], studies on tHcy levels in different ethnic groups are important'. There is a lack of sufficient research in the 'Pakistani population to establish a clear connection between tHcy and coronary artery disease (CAD), as well as its relationship with lipid profile in younger CAD patients'. Due to the contradictory evidence, our aim was to compare tHcy levels between CAD patients and healthy controls, and 'to assess the association of tHcy levels with lipid profile in CAD patients'.

MATERIAL AND METHODS

This 'cross-sectional comparative study was carried out in the Punjab Institute of Cardiology (PIC), Lahore, from October 2009 to June 2010'. The study received ethical approval from the Advanced Studies and Research Board, University of Health Sciences, Lahore and from the 'Ethical Committee of Postgraduate Medical Institute, Lahore'. All participants provided 'written informed consent prior to enrolling in the study'.

The study population was separated into two groups Group A: Included '30 patients (both genders, 20 to 45 years) with hospitalization due to the first acute ST elevating myocardial infarction (STEMI) or Non-STEMI or unstable angina'. 'Patients were identified to have the disease on the basis of clinical history which in our case is typical chest pain, computerized ECG and raised cardiac markers like creatine kinase (CK) along with its isoenzyme CK-MB, Troponin T and Troponin I'.

'Group B: Included 30 healthy controls (aged 20-45 years, both genders) recruited from the Exercise Tolerance Test (ETT) department of PIC'. These individuals had no evidence of coronary artery disease (negative ETT) and normal lipid profiles. Exclusion criteria for both groups comprised a history of CAD, premature CAD in the family, diabetes mellitus, hypertension, smoking, renal dysfunction, non-cardiac chest pain, or use of supplements/medications such as vitamin B6, B12, folic acid, antiepileptics, or methotrexate which affect the serum tHCy levels.

Each participant's 'blood samples were taken after a 12-14-hour overnight fast, using a sterile disposable syringe to draw 5mL of blood'. A clot was formed within '30-60 minutes and was then centrifuged at 3000rpm for 10 minutes'. Separated 'serum was kept in labeled vials at 2-8 degrees Celsius until further analysis was conducted'. Fasting serum homocysteine levels were analyzed on an ARCHITECT analyzer using Chemiluminescent Microparticle Immunoassay (CMIA) while other parameters of the triglyceride lipid profile were measured using colorimetric methods, with the exception of LDL cholesterol which was computed using the Friedewald equation.

Data analysis was performed using SPSS version 16.0. Student's *t*-test assessed differences in means between groups, while odds ratios (OR) were calculated via a 2×2 contingency table to evaluate the association between hyperhomocysteinemia and CAD (OR = [a×d]/[b×c]). Pearson's coefficient of correlation (Pearson's r) was calculated to determine correlation between tHCY and lipid profile parameters. A p-value < 0.05 denoted statistical significance.

RESULTS

Total cholesterol was higher in CAD patients (185.1 ± 39.1 mg/dL) compared to controls (176.5 ± 14.4 mg/dL), though the difference was not statistically significant (p = 0.263). Triglyceride levels were significantly elevated in CAD patients (155.9 ± 70.2 mg/dL) versus controls (113.9 ± 39.7

mg/dL) (p = 0.006). HDL-C was notably lower in CAD patients (37.00 ± 7.45 mg/dL) compared to controls (43.1 ± 5.4 mg/dL) (p = 0.001). LDL-C levels were slightly higher in CAD patients (116.4 ± 30.5 mg/dL) than in controls (109.7 ± 10.4 mg/dL), but this difference was not significant (p = 0.224). 'Serum tHcy was significantly higher in CAD patients (18.1 ± 5.32 µmol/L) than in controls (14.7 ± 4.93 µmol/L) (p = 0.013)'. These comparisons are summarized in Table 1**.** The study found no significant correlations between tHcy and lipid profile parameters in CAD patients: 'TC (r = - 0.122, p = 0.521), triglycerides (r = 0.219, p = 0.245), HDL-C (r = - 0.138, p = 0.468), or LDL-C (r = - 0.212, p = 0.260)'. These results are shown in Table 2.

The research data indicates that out of the 30 participants diagnosed with CAD, 9 had normal tHcy levels, 20 presented with moderate hyperhomocysteinemia, and only one participant had intermediate hyperhomocysteinemia. Furthermore, from the set of 30 control participants, '18 had normal tHcy levels, 11 had moderate hyperhomocysteinemia, and one participant showed intermediate hyperhomocysteinemia'. 'An odds ratio of 3.5 (95% CI : 1.20 - 10.19) p-value 0.02 was obtained, which was statistically significant'. These findings are presented in Table 3.

Table: 1Comparison between cases and controls

	Groups		
Variables	**Cases (Mean ±SD)**	**Controls (Mean ±SD)**	**p-value**
TC (mg/dl)	185.1 ± 39.1	176.5±14.5	0.263
TGs (mg/dl)	155.9 ± 70.2	113.9±39.7	0.006*
HDL-C(mg/dl)	37±7.5	43.1±5.4	0.001*
LDL-C (mg/dl)	116.4±30.5	109.2±10.4	0.224
tHcy (µmol/L)	18.1±5.3	14.7±4.9	0.013*

* Significant

Table: 2: Correlation Between tHcy and Lipid Profile Parameters in CAD Patients (number = 30)

Lipid Parameter	**Mean ± SD**	**tHcy (µmol/L) ± SD**	**r-value**	**p-value**
TC (mg/dL)	185.1 ± 39.1	18.1 ± 5.32	-0.122	0.521
TGs (mg/dL)	155.9 ± 70.2	18.1 ± 5.32	0.219	0.245
HDL-C (mg/dL)	37.0 ± 7.45	18.1 ± 5.32	-0.138	0.468
LDL-C (mg/dL)	116.4 ± 30.5	18.1 ± 5.32	-0.212	0.260

Table: 3 'Contingency table for calculation of Odds Ratio'

	'Total Homocysteine (mmol/L)' I am running a few minutes late; my previous meeting is running over.	**'CAD patients (Number)'**	**'Controls (Number)'**	**'Odds Ratio (OR)'**	**'95% Confi-dence Interval'**	**'p-value'**
'Total subjects' = 60						

	> 15 mmol/L	a) 21	c) 12			
	≤ 15 mmol/L	b) 9	d) 18	3.5	1.20 to 10.19	0.02*

*Significant

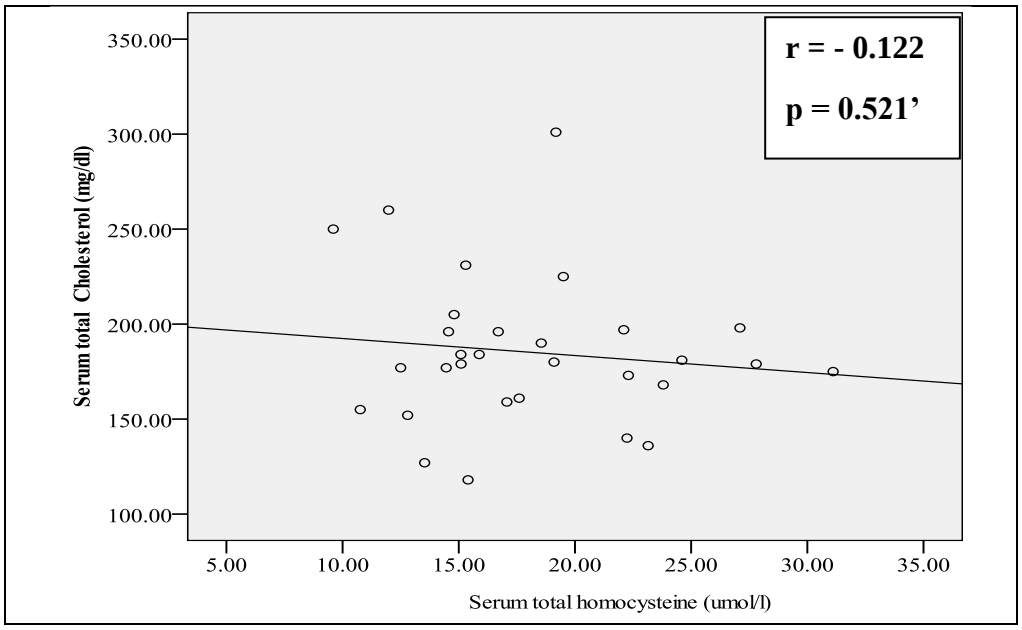

Figure 1: 'Correlation between serum total homocysteine and serum total cholesterol in coronary artery disease patients'

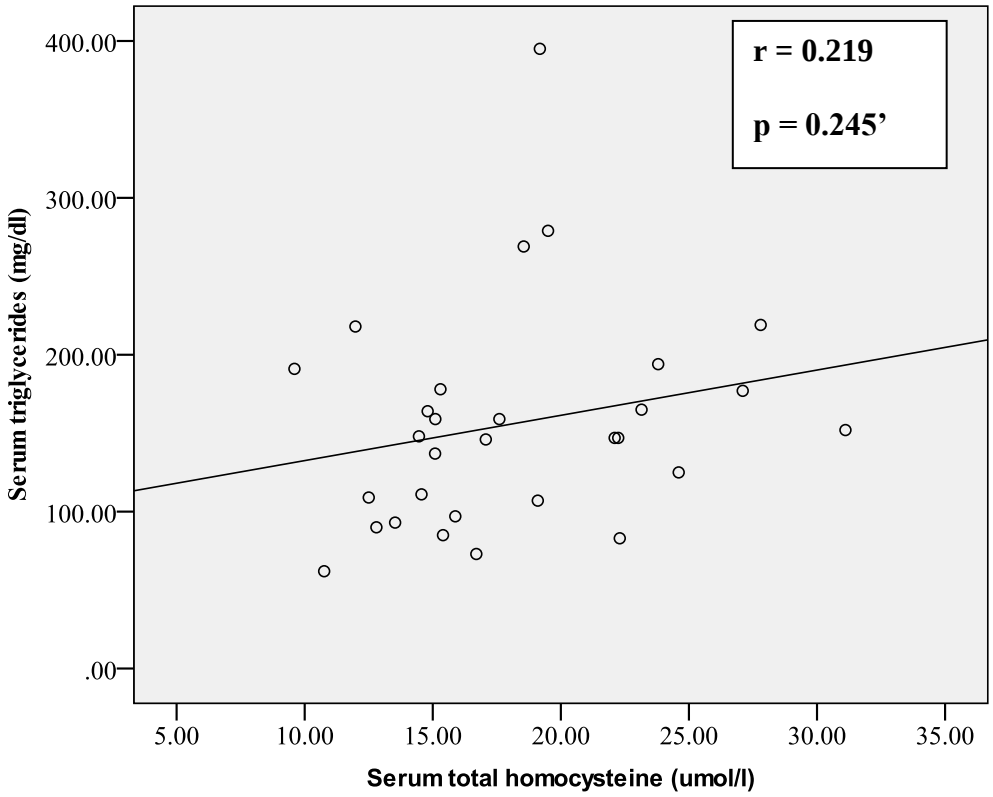

Figure 2: Correlation between 'serum total homocysteine and serum triglycerides in coronary artery disease patients'

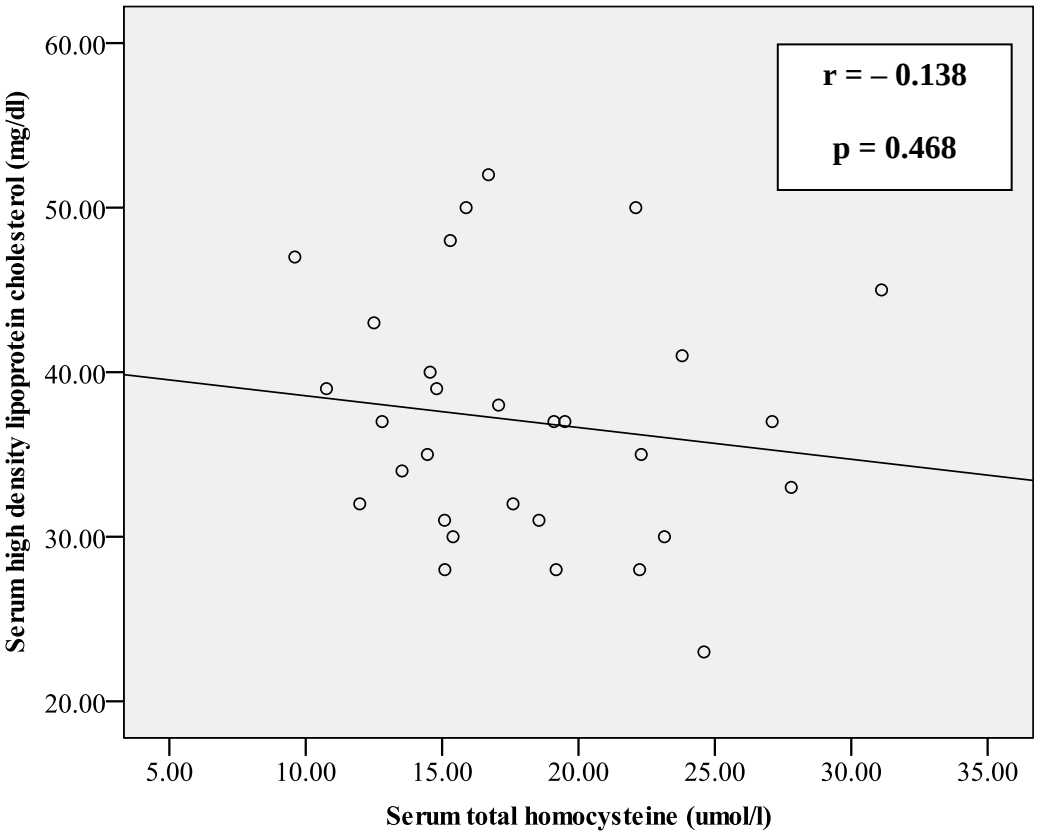

Figure 3: Correlation between serum total homocysteine and serum high density lipoprotein cholesterol in coronary artery disease patients.

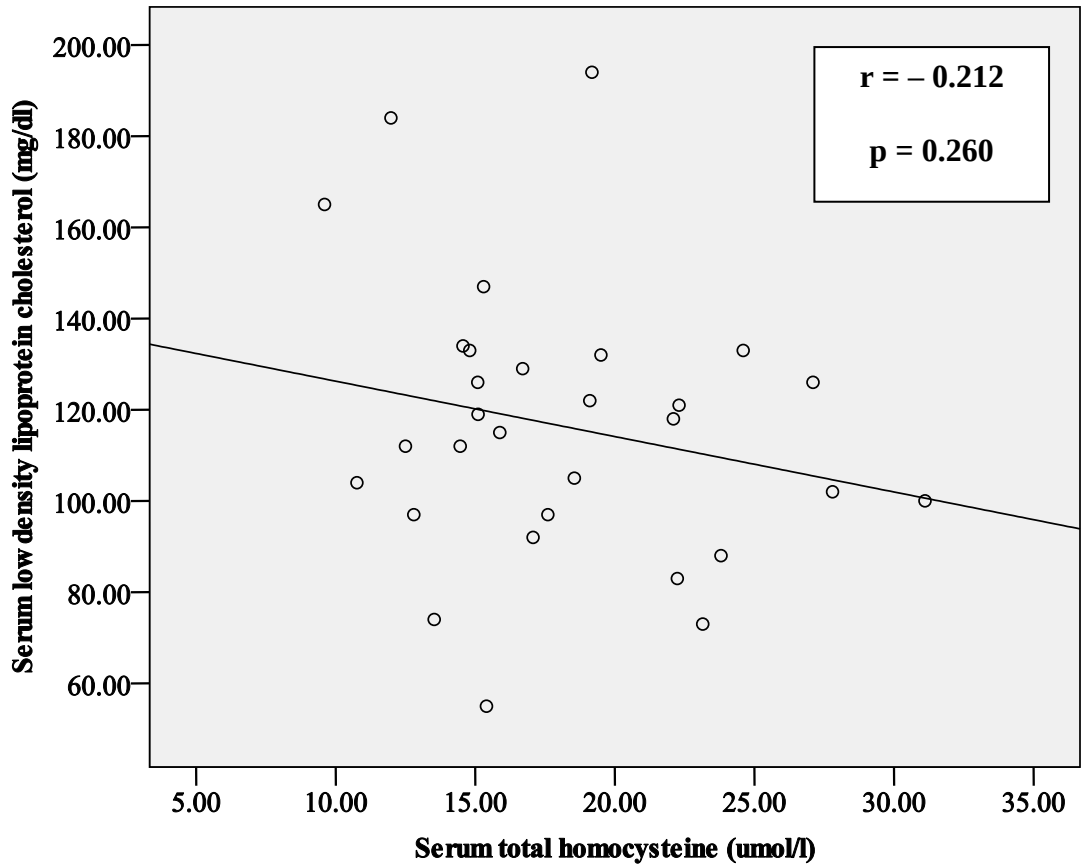

Figure 4: Correlation between serum total homocysteine and serum low density lipoprotein cholesterol in coronary artery disease patients.

DISCUSSION

Most people with coronary artery disease (CAD) have traditional risk factors, but some do not. This has led researchers to explore additional risk factors to better understand CAD and improve prevention and treatment[4].

An increase in 'serum tHcy levels is considered a novel risk factor for CAD'. However, 'studies associating tHcy levels with CAD across different populations have produced conflicting results; some studies have found evidence, while others have not' [6,7.] Pakistan has limited evidence on these studies, and they also lack coherence.

The research carried out by 'Hammad et al in Pakistan demonstrated markedly elevated levels of tHcy in CAD patients in comparison to the healthy participants'. Conversely, 'Iqbal's study noted no substantial increase in tHcy levels among CAD patients relative to the normal control group'. [13, 14].

The relationship between homocysteine (tHcy) levels and lipid profile in CAD patients remains unclear, with studies reporting conflicting results. Some have found a positive correlation, while others have observed no significant association [7,9].

'In our study, the mean serum tHcy levels were significantly higher in patients (18.1 ± 5.3 μmol/L) compared to controls (14.7 ± 4.9 μmol/L) (p = 0.03)'. These findings align with those of 'Khadija et al. and Rao et al. Khadija stated 25.0 ± 0.1 μmol/L vs. 5.71 ± 0.2 μmol/L and Rao noted 27.8 ± 5.4 μmol/L vs 14.1 ± 2.0 μmol/L' [15, 16]

In these studies, tHcy levels were much higher in CAD patients compared to our study. We omitted CAD patients with diabetes, hypertensive conditions, history of smoking, age over 45, and family history of early-onset CAD. These criteria were not excluded in the two studies previously mentioned. This may account for the higher tHcy levels in their CAD patients since these risk factors tend to increase tHcy levels [17, 18,19,20, 21].

In our study, 'the association between hyperhomocysteinemia and coronary artery disease (CAD) was assessed using Contingency table'. The calculated 'odds ratio (OR) was 3.5 (95% CI: 1.20–10.19, $p = 0.02$), indicating that individuals with hyperhomocysteinemia had 3.5 times more risk of developing CAD compared to those with normal homocysteine levels'.

'Our findings are consistent with previous studies that have demonstrated a strong link between elevated homocysteine levels and CAD: Muzaffar et al. reported an even higher risk association, with an OR of 7.45 (95% CI: 3.12–12.83, $p = 0.000$), suggesting a more pronounced effect in their study population'. Sun et al. also found a significant association, with an OR of 4.56 (95% CI: 3.29–6.33, $p = 0.001$), reinforcing the strength of this relationship across different groups.

Despite these differences, the consistently significant associations across multiple studies strengthen the evidence that 'hyperhomocysteinemia is an important modifiable risk factor for CAD'. [22, 23]

'This study found no significant association between serum tHcy levels and lipid profile components such as total cholesterol, triglycerides, HDL, or LDL'. 'Similar findings have been reported in previous Indian studies, including those by Sule et al. (2019) and Ranjith and Devika (2017)' both of which observed no correlation between tHcy and lipid parameters in CAD patients [9, 24]

In our study about 309 young patients of CAD were interviewed. Out of these only 30 patients were selected who fulfilled the inclusion criteria while rest of the patients were excluded due to the presence of one or more conventional risk factors. This shows that only about 10% patients with 'CAD in our study had no conventional risk factors other than dyslipidemia'. 'This aligns with findings by Figtree et al. (2022), who reported that 10% of CAD patients presented without any traditional risk factors' [25]

CONCLUSION

Our findings reveal that serum tHcy levels are markedly elevated in CAD patients compared to controls, though they show no significant correlation with lipid profile components such as 'total cholesterol, LDL-C, HDL-C, and triglycerides'. Thus, elevated tHcy is an independent CAD risk factor in the younger Pakistani population. Dietary interventions such as increasing vitamin rich foods (fruits, leafy greens) and replacing animal proteins (high in methionine) with plant proteins may lower homocysteine and reduce CAD risk. Additionally, serum tHcy measurement is recommended, particularly for young CAD patients without major risk factors.

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