Original Research Article

A Study on Insulin Resistance and the Relationship of TG/HDL Cholesterol Index and HSCRP with Coronary Heart Disease

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Abstract

Background: Coronary heart disease is a multifactorial disease. It has been appreciated for a long time that a number a cardiovascular risk factors tend to cluster in the same individuals. The risk factors are insulin resistance, hyperinsulinemia, hyperglycemia, dyslipidemia (high triglycerides and low HDL cholesterol), hypertension, smoking and T2DM. Insulin resistance is the main underlying metabolic deterioration in CHD. A significant body of evidence now supports an association between insulin resistance and endothelial dysfunction, an important early event in the development of atherosclerosis.**Aim & Objectives:** The present study was designed to assess the relationship between Insulin resistance measured by HOMA-IR, Dyslipidemia consisting of high triglycerides and low HDL cholesterol and HSCRP an emerging inflammatory bio marker in Coronary heart disease.**Methodology:** A case control study was conducted in the Department of Biochemistry, Osmania General Hospital, Hyderabad during December 2013 to May 2015.**Results:** In this study significant increase in Mean ± S.D of IR was seen in high risk individuals without CHD and in CHD cases when compared to controls. There was no significant decrease in high risk individuals and CHD cases implicating its strength as a predictor of CHD. Mean ± S.D of TG/HDL index levels were significantly increased in high risk individuals without CHD cases and in CHD cases. There is strong evidence that both high TG and a low HDL-C are a frequent consequence of IR and TG/HDL index can be used as a marker for insulin resistance. In the present study Increased HOMA-IR, TG/HDLc and HS CRP are positively associated with coronary heart disease. There is positive correlation with statistical significance among all the three parameters in CHD cases. Our present study provides clear evidence that for the end points of MI and CHD death, the risk associated with lower and higher levels of HDL-C and triglycerides can be more precisely defined in conjunction with a measure of IR. **Conclusion:** The combination of these evaluated markers has the potential to serve as a screening tool for cardiovascular risk assessment and clinical management. We believe that this simple and non-invasive set of tests may be a useful in optimizing the selection of patients to proceed to a more invasive investigation.

Keywords: Insulin resistance, HDL-C, Triglycerides, Coronary Heart Disease, HSCRP , HOMA-IR

Introduction

Coronary heart disease (CHD) is the leading cause of death in India and the leading cause of death worldwide. Previously thought to affect primarily high-income countries, CHD now leads to more death and disability in low- and middle-income countries, such as India[1].The rapid rise in CHD burden is due to socio-economic changes, increase in life span and acquisition of lifestyle related risk factors[2].The identification of measurable correlates of CHD constitutes one of the foremost advances in cardiovascular medicine. These measurable correlates are called risk factors. Coronary risk factors are important both for assessment of risk and as targets for intervention[3].Over the past decade, the availability of new investigative tools has resulted in a clearer understanding of the molecular mechanisms thatconnect altered cholesterol metabolism and other risk factors to the development of atherosclerotic plaque[4].Among the many cardiovascular risk factors, elevated plasma cholesterol level is unique in being sufficient to drive the development of atherosclerosis. The other risk factors, such as hypertension, diabetes, smoking, and inflammatory markers (e.g., C reactive protein, cytokines etc.), appear to accelerate the disease, driven by atherogenic lipoproteins[5].Dyslipidemia consisting of high triglycerides and low high-density lipoprotein cholesterol (HDL-C) is a widely recognized lipid pattern that is frequently associated with the development of coronary heart disease (CHD)[6].Both high triglycerides and low HDL-C are known to be associated with obesity and other features that define the metabolic syndrome (MetS). It is possible that much of the cardiovascular (CV) disease that is associated with the MetS may be explained by the presence of insulin resistance (IR)[7].There is compelling and long-standing evidence that both high triglycerides and a low plasma HDL-C are a frequent consequence of IR[8].Homeostatic model assessment of insulin resistance (HOMA-IR) has emerged as a practical and simple method for estimating insulin resistance. Insulin resistance (IR) could be potentially used as a cardiovascular risk marker since hyperglycemia and hyperinsulinemia are both related to cardiovascular disease. Also since triglycerides and HDL are independent predictors of cardiovascular risk, their ratio could be used as a simple cardiovascular risk marker[6].Laboratory and experimental evidence indicate that atherosclerosis, in addition to

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being a disease of lipid accumulation, also represents a chronic inflammatory process.Vascular inflammation plays a crucial role in the pathogenesis of atherosclerosis and mediates various stages of atherosclerotic plaque development, from lipid streak formation to the plaque rupture and destabilization that precedes the clinical syndromes of cardiovascular disease. Inflammatory biomarkers constitute valuable tools to study this process, enabling the effects of different therapeutic interventions to be assessed. Currently, C-reactive protein (CRP) determined by high-sensitivity methods (HSCRP) is the most extensively studied biomarker[9].

Several large-scale prospective studies demonstrate that HSCRP is a strong independent predictor of future myocardial infarction and stroke among apparently healthy men and women and that the addition of HSCRP to standard lipid screening may play an important role as an adjunct for global risk assessment and in the primary prevention of cardiovascular disease[10].Hence the present study was designed to assess the relationship between Insulin resistance measured by HOMA-IR, Dyslipidemia consisting of high triglycerides and low HDL cholesterol and HSCRP an emerging inflammatory bio marker in Coronary heart disease.

Aim of the Study

The aim of the present study is to

1. Study the association between homeostatic model assessment (HOMA-IR), Triglyceride/HDLc index (TG/HDLc) and HS CRP with the presence of coronary heart disease.
2. Understand the relationship between insulin resistance measured by HOMA-IR and TG/HDL-C index in coronary heart disease.
3. Determine the role of high sensitivity CRP (HSCRP) as an inflammatory bio- marker in CHD.
4. Understand the relationship between insulin resistance and HS CRP in coronary heart disease.

Hence an attempt has been made to assess whether IR can be used as a biomarker for coronary heart disease in clinical practice, to evaluate its role in development of CHD in conjunction with dyslipidemia and to assess whether HSCRP, an emerging sensitive inflammatory marker be used as a screening tool for cardiovascular risk assessment.

Material and Methods

Setting: A case control study was conducted in the Department of Biochemistry, Osmania General Hospital, Hyderabad during December 2013 to May 2015.

Source of samples and data: The cases and samples were collected from Department of Cardiology, Osmania General Hospital; Investigations were performed at the Department of Biochemistry, Osmania Medical College/Osmania General Hospital, Hyderabad.

In the present study the individuals included in the study were divided into 3 groups.

Table 1:Groups and subjects consideration

Group 1	Healthy subjects	30 subjects
Group 2	High risk individuals without CHD	30 subjects
Group 3	Individuals with CHD	30 subjects

- All the subjects were above 35 years of age and of either sex.
- Informed oral consent was taken from all individuals who took part in the study.
- Study subjects undergo complete anthropometric and clinical examination.
- Fasting blood samples are collected from patients referred for coronary angiography.

Group 1 included healthy controls who were matched for age and sex.

Group 2 included high risk individuals i.e. subjects with history of smoking, diabetes, hypertension, obesity, metabolic syndrome etc.

Group 3 included CHD cases.

Inclusion criteria:

- Patients with documented ischemia or clinical referral for coronary angiography

Exclusion criteria:

- Previous MI in the last 60 days
- Heart transplantation or revascularization procedure
- Known malignant neoplasia
- Hemodialysis
- Chronic inflammatory disease

Specimen collection: Fasting venous blood samples were collected from all groups. 3ml of blood was collected into serum tubes (red cap) and 2ml into sodium fluoride tubes (grey cap). Fasting plasma glucose was estimated in plasma daily from the grey tube while all other parameters were estimated in serum. Lipid profile was estimated in fresh sera on a daily basis. The remaining serum was stored at -20^{0}C in an aliquot for serum insulin and serum HSCRP estimation.

Parameters Estimated:

Plasma: 1) Fasting plasma glucose (FPG)

Serum: 1) Serum total cholesterol (TC)

1. Serum triglycerides (TG)
2. Serum high density lipoprotein (HDL)
3. Serum very low density lipoprotein (VLDL)
4. Serum low density lipoprotein (LDL)
5. TG/HDL index
6. Serum insulin
7. Serum insulin resistance by HOMA-IR
8. Serum HSCRP

Observations and Results

The present study was undertaken in the Department of Biochemistry, Osmania Medical College and Osmania General Hospital, Hyderabad.A total of 90 patients were recruited for the study which included 30 CHD cases, 30 high risk individuals without CHD and 30 healthy individuals as controls.The data was analyzed using GraphPad Prism software version 6.05. Descriptive results are expressed as mean and SD of various parameters in different groups. Multiple comparisons ANOVA was used to assess the significance of difference of mean values of different parameters in between the groups. The significance of difference of mean values of different groups and within the groups is represented by p values and p value < 0.05 is considered as significant.The results were expressed in milligrams /dL for Fasting plasma glucose, Serum Total Cholesterol, Serum HDL Cholesterol, Serum Triacylglycerol, Serum VLDL Cholesterol, Serum LDL Cholesterol , in μIU/mL for insulin and milligrams /L for HSCRP.

Table 1: The Mean ± SD of all the parameters in controls, high risk individuals without CHD and in CHD cases

Parameter	Controls		High Risk Individuals without CHD		CHD Cases	
	Mean	+sd	mean	+sd	Mean	+sd
1.Fasting plasma glucose	84	+13	135	+21	134	+17
2.serum insulin	3.3	+1.7	20	+11	19	+11

3.HOMA-IR	0.7	±0.3	6.8	±4.1	6.3	±3.5
4.HS-CRP	1.7	±0.5	5.3	±2	11	±2
5.Total cholesterol	123	±19	199	±60	215	±72
6.Triglycerides	80	±17	151	±80	229	±105
7.HDL	46	±5	39	±7	29	±4
8.VLDL	16	±3	30	±16	45	±21
9.LDL	61	±18	130	±58	140	±66
10.TG/HDL index	1.8	±0.4	4.1	±3.2	8.0	±4

The Mean ± S.D of FPG were higher and statistically significant in high risk individuals without CHD and in CHD cases when compared with controls.

The Mean ± S.D of serum insulin and IR measured by HOMA-IR was elevated in high risk individuals without CHD and in CHD cases when compared with controls

The Mean ± S.D of HS CRP was higher and statistically significant in CHD cases. They are moderately elevated in high risk individuals without CHD when compared with controls.

The Mean ± S.D of total cholesterol was higher and statistically significant in high risk individuals without CHD and in CHD cases when compared with controls.

The Mean ± S.D of triglycerides was higher and statistically significant in high risk individuals without CHD and in CHD cases when compared with controls.

The Mean ± S.D of HDL was variable and not significant in high risk individuals without CHD and in CHD cases when compared with controls

The Mean ± S.D of VLDL was higher and statistically significant in high risk individuals without CHD and in CHD cases when compared with controls.

The Mean ± S.D of LDL was higher and statistically significant in high risk individuals without CHD and in CHD cases when compared with controls

The Mean ± S.D of TG/HDL index was higher and statistically significant in high risk individuals without CHD and in CHD cases when compared with controls.

Table 2: Anova F value, P value and R^2 between CHD cases, high risk individuals without CHD and controls

Parameter	F value	P value	R2
1.Fasting plasma glucose	86.46	<0.0001(****)	0.6653
2.serum insulin	34.82	<0.0001(****)	0.4446
3.HOMA-IR	36.06	<0.0001(****)	0.4533
4.HS-CRP	226.5	<0.0001(****)	0.8389
5.Total cholesterol	23.65	<0.0001(****)	0.3522
6.Triglycerides	28.15	<0.0001(****)	0.3929
7.HDL	62.70	0.0001(****)	0.5905
8.VLDL	27.89	<0.0001(****)	0.3900
9.LDL	20.66	<0.0001(****)	0.3220
10.TG/HDL index	34.79	<0.0001(****)	0.4444

(*,**, **** : significant; n.s : not significant)

In order to assess the significance of the differences observed in the mean values of different parameters observed in different groups studied, the data is subjected to ANOVA test. The significance of difference of mean values of different groups and within the groups is represented by p values and p value <0.05 is considered as significant.

Table 3: Anova summary of different parameters in three groups

		Sum of Squares	DF	Mean Square	F	P value
FPG	Between groups	51690	2	25845	86.46	P < 0.0001
	Within groups	26007	87	298.9		
	Total	77697	89			
SERUM INSULIN	Between groups	5518	2	2759	34.82	P < 0.0001
	Within groups	6893	87	79.23		
	Total	12411	89			
IR	Between groups	706.3	2	353.2	36.06	P < 0.0001
	Within groups	851.9	87	9.792		
	Total	1558	89			
HS CRP	Between groups	1335	2	667.7	226.5	P < 0.0001
	Within groups	256.4	87	2.947		
	Total	1592	89			
TC	Between groups	145197	2	72599	23.65	P < 0.0001
	Within groups	267037	87	3069		
	Total	412234	89			
TG	Between groups	334629	2	167314	28.15	P < 0.0001
	Within groups	517164	87	5944		
	Total	851792	89			
HDL-C	Between groups	4216	2	2108	62.73	P < 0.0001

	Within groups	2924	87	33.61		
	Total	7140	89			
VLDL-C	Between groups	13275	2	6637	27.81	P < 0.0001
	Within groups	20764	87	238.7		
	Total	34038	89			

IR is positively associated with FPG,HSCRP, all lipid parameters like TC,TG,VLDL,LDL and TG/HDL index in high risk individuals without CHD.HSCRP is positively associated with IR in high risk individuals without CHD TG/HDL index is associated with IR,HSCRP in high risk individuals without CHD

IR is positively associated with FPG, HSCRP, lipid parameters like TC,TG,VLDL,LDL and TG/HDL index in CHD cases.

HSCRP is positively associated with IR in CHD cases. TG/HDL index is associated with IR,HSCRP in CHD cases.

ROC Curve Analysis: In order to assess the maximum sensitivity, specificity and diagnostic efficiency of various parameters in identifying abnormality, the best cut off values are calculated using ROC analysis. Best cut off values are established by selecting a point closer to the left hand curve that provides greatest sum of sensitivity and specificity.

Diagnostic efficiency is defined as the portion of all currently classified as having or not having disease.

$$\text{Diagnostic Efficiency} = \frac{\text{True positive} + \text{True Negatives} \times 100}{\text{Total no of patients evaluated}}$$

Area under curve provides unbiased estimates of sensitivity and specificity. It is a comprehensive representation of pure accuracy discriminating ability over the entire range of the test.

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Table 4 :Sensitivity (Sens), Specificity (Spf), and best cut off value (bcv) in discriminating CHD cases , high risk individuals without CHD and controls

	Insulin resistance			HS CRP			TG/HDL index		
	Sens%	Spf%	Bcv	Sens%	Spf%	Bcv	Sens%	Spf%	Bcv
highrisk individuals without CHD	96.67	100	>1.65	93.33	100	>2.9	80	86.67	>2.1
CHD cases	96.67	100	>1.70	100	100	>5.55	96.67	100	>3.3

1. ROC analysis showed 100% sensitivity of HSCRP when compared with IR and TG/HDL index in CHD cases.
2. ROC analysis showed specificity of IR is equivalent to that of HSCRP and TG/HDL index in CHD cases

Table 5:Area under curve (AUC), Diagnostic efficiency (DE) and Significance in discriminating analyzed parameters in CHD cases , high risk individuals without CHD and controls

	IR			HS CRP			TG/HDL index		
	AUC	DE	P value	AUC	DE	P value	AUC	DE	P value
highrisk individuals without CHD	0.9983	98.33	<0.0001	0.9889	96.66	<0.0001	0.8989	83.33	<0.0001
CHDcases	0.9844	98.33	<0.0001	1.000	100	<0.0001	0.9972	98.33	<0.0001

1. HS CRP shows a better diagnostic efficiency than others parameters in discriminating between CHD cases and controls
2. IR shows better diagnostic efficiency compared to TG/HDL index in discriminating between CHD cases and controls.

Discussion

CHD is responsible for a substantial amount of early deaths, reduced quality of life and significant costs to the health. The majority of cardiovascular disease (CVD) is caused by risk factors that can be controlled, treated or modified, such as high blood pressure, cholesterol, overweight/obesity, tobacco use, lack of physical activity and diabetes[11].Insulin resistance is associated with cardiovascular disease[12]. Possible mechanisms include induction of pro-inflammatory and pro-coagulant states which are detrimental to endothelial function and may play an important role in mediating atherogenesis[13].Hyperinsulinemia may be directly atherogenic but is more probable that it reflects insulin resistance which may be a factor enhancing atherogenesis by causing adverse changes in many CHD risk factors[14].We currently understand atherogenesis as a complex interaction of risk factors including cells of the artery wall and the blood and molecular messages that they exchange. Inflammation plays a major role in all stages of atherogenesis. Inflammation participates in the local, myocardial, and systemic complications of atherosclerosis[13]. nsulin resistance is associated with induction of pro inflammatory state which is detrimental to endothelial function and may play an important role in mediating atherogenesis.Type 2 diabetes mellitus (DM) is a strong risk factor for coronary heart disease (CHD), which in turn is the leading cause of mortality and morbidity in diabetic patients[15,16]. Aging and rampant obesity underlie a current epidemic of type 2 diabetes mellitus, although this increased risk has been attributed primarily to hyperglycemia, dyslipidemia, and a pro thrombotic state, recent observations have focused attention on low-grade inflammation in the pathogenesis of type 2 DM and its complications . Studies in non diabetic patients or subjects with impaired glucose tolerance or impaired fasting glucose have confirmed that high concentrations of inflammatory markers predict the development of type 2 DM and are closely linked to insulin resistance[17].The ability of insulin to stimulate glucose disposal varies more than six-fold in apparently healthy individuals. The one third of the population that is most insulin resistant is at greatly increased risk to develop cardiovascular disease (CVD), type 2 diabetes, hypertension, stroke, nonalcoholic fatty liver disease, polycystic ovary disease, and certain forms of cancer.Homeostatic model assessment of insulin resistance (HOMA-IR) has emerged as a practical and simple method for estimating insulin resistance. This index was extensively validated in comparison with the gold-standard method for the evaluation of insulin resistance, the hyperinsulinemiceuglycemic glucose clamp technique. While this method is currently not routinely used as a cardiovascular risk marker, we hypothesized that it could be potentially useful since hyperglycemia and hyperinsulinemia are both related to cardiovascular disease.The present study was undertaken to identify the association of IR in high risk individuals without CHD and in CHD cases. The study includes 90 subjects divided into three groups healthy controls (n=30), high risk individuals without CHD (n=30) and CHD cases (n=30).In the present study the Mean±S.D of IR in controls was 0.7±0.3, in high risk individuals without CHD was 6.8 ± 4.1 and in CHD cases 6.3 ± 3.5. IR was increased significantly in high risk individuals without CHD cases and in CHD cases when compared with controls in accordance with Bertoluci et al. IR correlated positively with FPG, Fasting Insulin, TC, TG, LDL,

VLDL-C in all cases and controls. IR was positively correlated with Fasting Insulin which was significant in all the groups.IR was positively correlated with TG/HDL index in high risk individuals without CHD and is positively correlated with HS CRP in CHD cases.

Similar results were observed in Bertoluci et al. study[10] in which HOMA-IR were significantly increased in the CAD group as compared to the No CAD group, (p =0.0446 and p = 0.0152, respectively). Bertoluci et al. did a cross-sectional study, in 131 patients (57.0 ± 10 years-old, 51.5% men) who underwent clinical, laboratory and angiographic evaluation and were classified as No CAD (absence of coronary artery disease) or CAD (stenosis of more than 30% in at least one major coronary artery). Study showed an association between insulin resistance, with the presence of coronary artery disease in patients referred for coronary angiography. A HOMA-IR higher than and the TG/HDLc index above 8.5 were associated with the presence of coronary lesions, and it was independent of age, gender, body mass index, diabetes mellitus and systolic blood pressure.Framingham heart study[6]concluded that Plasma insulin values were higher in men, and the frequency of IR defined by the upper quartile of HOMA-IR, was also greater in men.

In this population, continuous values for HOMA-IR were significantly correlated with age (r=0.10), plasma insulin levels (r=0.98), glucose (r=0.52), HDL-C (r=0.34), triglycerides (r=0.36), LDL-C(r=0.07), systolic blood pressure (r=0.30), BMI (r=0.50), and waist circumference (r=0.49), all with P<0.001The San Antonio Heart Study have demonstrated significant associations between baseline levels of both HOMA-IR and insulin and subsequent risk of CVD outcomes in a large population-based study. HOMA-IR showed almost perfect correlation with fasting insulin concentration (r = 0.99). In addition, HOMA-IR was significantly associated with baseline fasting glucose (P = 0.0001), and cardiovascular risk factors HDL,TC ,SBP, DBP(P = 0.0001).The Bruneck study[18] concluded that levels of HOMA-IR were higher at baseline among subjects who developed CVD compared with those remaining free of CVD (P < 0.05). Levels of HOMA-IR also were significantly correlated (P < 0.05) with most CVD risk factors we evaluated.Andrew Selwyn[19] (Boston, MA) reviewed aspects of the relationship between insulin resistance syndrome(IRS) and CVD, noting the increasing prevalence of type 2 diabetes from the 1970s to the 1990s, with its far stronger association with CVD than with the traditional micro vascular complications such as visual loss, renal failure, and amputation. Analysis of individuals developing diabetes in the Nurses' Health Study led to the development of the ―ticking clock hypothesis,‖ in which the pre-diabetes state is one associated with increased CVD risk, with macro vascular atherosclerotic disease developing in many cases a decade before diabetes becomes manifest.There is increasing awareness of the clinical phenotype of metabolic syndrome/IRS based on glucotoxicity and lipotoxicity and of its association with a variety of abnormalities of inflammatory mediators. There is similarity of the pathways leading to insulin resistance and to atherosclerosis, with elevations both in glucose and in free fatty acids causing oxidant stress. Selwyn concluded by stressing the importance of control of all of these risk factors among individuals with diabetes.James Leiper[20] (London, U.K.) discussed endogenous inhibitors of nitric oxide (NO) synthesis in the setting of insulin resistance. NO regulates vasodilatation, synthesized by endothelial cells and diffusing into vascular smooth muscle cells, with NO production from L arginine, leading to production of citrulline as a side product, tightly regulated by endothelial NO synthase (NOS). There are two endogenous analogs of the competitive inhibitor of NOS, L-NMMA (L-Nmonomethylarginine), asymmetric and symmetric dimethyl arginine (ADMA and SDMA, respectively). Increased ADMA has been reported to be associated with hypercholesterolemia, hypertension, diabetes, and CVD, as well as with insulin resistance.Robert Chilton[21] (San Antonio, TX) discussed therapeutic implications of the relationship between insulin resistance and the development of atherosclerotic plaques. Among children, associations can be found between carotid intima media thickness and decreased flow mediated vasodilatation, increased C-reactive protein, increased triglyceride, decreased HDL cholesterol, and increased insulin levels. Endothelial dysfunction, as measured by flow-mediated vasodilatation, is strongly related to insulin resistance and to a family history of diabetes.

Insulin is a peptide hormone produced by beta cells in the pancreas. It regulates the metabolism of carbohydrates and fats by promoting absorption of glucose from the blood to skeletal muscles and fat tissue and by causing fat to be stored rather than used for energy. Insulin also inhibits the production of glucose by the liver[22]. Hyperinsulinemia is a condition in which there are excess levels of insulin circulating in the blood relative to the level of glucose. Hyperinsulinemia is associated with hypertension, obesity, dyslipidemia and glucose intolerance. Obese people have an excess of adipose tissue which secretes various metabolites, hormones and cytokines that may play a role in causing hyperinsulinemia. Specifically cytokines secreted by adipose tissue directly affect the insulin signalling cascade and thus insulin secretion[23]In the present study, the mean± SD of Fasting Insulin in controls was 3.3 ±1.7, in high risk individuals without CHD cases was 20±11 and in CHD cases was 19 ±11. Insulin levels were significantly increased in high risk individuals without CHD cases and in CHD cases when compared to controls with P-value of < 0.0001 which were in accordance with bertoluci et al. There was positive correlation between insulin values and HS CRP in both high risk individuals without CHD cases and in CHD cases.The greatest association of hyperinsulinemia with CAD has been found in Finland in a population with a very high frequency of CAD. Tapani Ronnemaa et,al[24]concluded that both diabetic and nondiabetic subjects with various manifestations of CHD had higher plasma insulin levels than did subjects free of CHD. The levels of insulin were elevated in CHD group with statistical significance (<0.005).Results of a prospective investigation of 2103 men from Quebec[25] clearly showed that high fasting insulin concentrations are an independent predictor of CAD. This important study used an insulin assay without cross-reactivity with proinsulin, thus avoiding that confounding influence.Diabetes mellitus is a strong risk factor for coronary heart disease (CHD), which in turn is the leading cause of morbidity in diabetic patients. In patients with non-insulin- dependent diabetes mellitus (NIDDM), there is a large variability in fasting and post glucose plasma insulin levels, and cross-sectional studies have demonstrated that NIDDM patients with atherosclerotic vascular disease have higher levels of fasting plasma insulin than do those without atherosclerotic vascular disease. Prediabetes is defined by elevations of plasma glucose concentration, and is aimed at identifying individuals at increased risk of type 2 diabetes and coronary heart disease (CHD)[26]

In the present study, the mean ± SD of FPG in controls was 84± 13., in in high risk individuals without CHD cases was 135 ± 21 and in CHD cases was 134 ±17.FPG levels were significantly increased in in high risk individuals without CHD cases and in CHD cases than in controls in accordance with Gerald reaven et.al[27]FPG correlated positively with IR and all the lipid parameters in both cases and controls. Correlation of FPG with insulin level was positive in high risk individuals without CHD cases and in CHD cases. It is negative in controls.Gerald reaven et.al concluded plasma insulin concentrations in patients with type 2 diabetes mellitus are more closely associated with hyperglycemia than with obesity. p value <0.005.In the present study, the mean ± SD of TG in controls was 80± 17., in in high risk individuals without CHD cases was 151 ± 80 and in CHD cases was 229 ±105.TG levels were significantly increased in in high risk individuals without CHD cases and in CHD cases than in controls with P-value of < 0.0001. Serum triglycerides, were significantly elevated in cases compared to controls with p value <0.001. and there were highly significant differences between cases and controls with respect to established coronary risk factors

such as smoking, body mass index, blood pressure, and other serum lipid concentrations.The Prospective Cardiovascular Münster (PROCAM) study involved 4849 middle-aged men who were followed up for 8 years to record the incidence of coronary heart disease (CHD) events according to the risk factors present at study entry. The study showed that fasting levels of TG were an independent risk factor for CHD events, independent of serum levels of HDL-C or LDL-C .In the 8-year Copenhagen Male Study, a prospective study including 2906 men who were free of cardiovascular disease at baseline, the risk for ischemic heart disease was 50% higher in those with TG levels in the middle tertile and 120% higher in the upper tertile as compared to those in the lowest TG tertile after adjustment for conventional risk factors such as age, body mass index (BMI), alcohol intake, smoking, physical activity, hypertension, diabetes, and LDL-C and HDL-C levels.The mean ± SD of Total cholesterol (TC) in controls was 123± 19, in in high risk individuals without CHD cases was 199 ± 60 and in CHD cases was 215 ±72.TC levels were significantly increased in in high risk individuals without CHD cases and in CHD cases than in controls with P-value of < 0.0001. The mean ± SD of VLDL in controls was 16± 3, in in high risk individuals without CHD cases was 30 ± 16 and in CHD cases was 45±21. VLDL levels were also significantly increased in high risk individuals without CHD cases and in CHD cases when compared to controls(P-value of < 0.0001).The mean ± SD of LDL in controls was 67± 14, in high risk individuals without CHD cases was 113 ± 58 and in CHD cases was 122±71. LDL levels were significantly increased in high risk individuals without CHD cases and in CHD cases when compared to controls with P-value of < 0.0003.The mean ± SD of HDL in controls was 46±5, in in high risk individuals without CHD cases was 39±7 and in CHD cases was 29±4. HDL levels were significantly decreased in high risk individuals without CHD cases and in CHD cases when compared to controls with P-value of < 0.0001in accordance with Framingham heart study[6].In the present study, TC, TG, VLDL and LDL cholesterol showed positive and HDL cholesterol negative correlation with IR and inflammatory marker HS CRP.In the present study, the mean ± SD of TG/HDL index in controls was 1.8 ± 0.4, in high risk individuals without CHD cases was 4.1 ± 3.2 and in CHD cases cases was 8.0±4 Insulin levels were significantly increased in in high risk individuals without CHD cases and in CHD cases cases compared to controls with P-value of < 0.0001 which were in accordance with bertuloci et al and Framingham heart study .Bertoluci et al concluded that TG/HDLc index were higher in the CAD vs No CAD group,TG/HDLc: 3.20 (2.38-5.59) vs. 2.80 (1.98-4.59) (p = 0.045) and showed a positive correlation with HOMA-IR and TG/HDLc with angiographic coronary artery disease.

TG/HDLc index and HOMA-IR were significantly increased in the CAD group , as compared to the No CAD group, (p = 0.0446 and p = 0.0152, respectively).After a ROC curve analysis, the highest positive predictive values were used as cut-off values. The cutoff value for HOMA-IR was 6.0, for TG/HDLc index was 8.5 and for the product [HOMA-IR × TG/HDLc] was 28.0. The positive predictive value for the presence of coronary artery disease with a HOMA-IR >6.0 was 82.6%, for a TG/HDLc> 8.5 was 85.7% and for [HOMA-IR×TG/HDLc]>28 was 88.0%In the present study, the mean ± SD of HSCRP in controls was 1.7±0.5, in high risk individual without CHD cases was 5.3±2 and in CHD cases was 11±2 .HSCRP levels were moderately elevated in high risk individuals without CHD(P value <0.0001) when compared to controls. HSCRP levels were grossly elevated in CHD cases (P value <0.0001) when compared to controls. Similar findings were found in Preethi et al. which are in accordance with other studies. HSCRP showed positive correlation with IR and TG/HDL index in CHD cases .In the present study, HSCRP showed positive association with insulin levels, total cholesterol, TG and LDL cholesterol and negative association with HDL cholesterol.Physicians health society(PHS)[28] demonstrated the role of HSCRP as a predictor of future coronary events. This study showed that those in the highest quartile of hs-CRP had a twofold higher risk of future stroke (RR 51.9; 95% CI, 1.1–3.3), threefold higher risk of future MI (RR 5 2.9; 95% CI, 1.8–4.6), and fourfold higher risk of future peripheral vascular disease (PVD; RR 5 4.1; 95% CI, 1.2– 6.0) (23, 28). The RRs were stable over a long period of time (6 years) and independent of other CHD risk factors.In 2003, Ishikawa et al[29] concluded that CRP is found inside atherosclerotic plaques and plays an important part in both plaque instability and post-angioplasty restenosis. Similarly, Inoue et al. demonstrated in 2005 that CRP is released by atherosclerotic plaques responsible for acute coronary syndromes (ACS).Several prospective trials in apparently healthy individuals have shown that elevated hs- CRP is positively correlated with cardiovascular morbidity and mortality.The present study demonstrated association between insulin resistance and CHD. Several mechanisms have been postulated to assess the role of insulin resistance in CHD, its association with atherogenic dyslipidemia consisting of elevated TG/HDL index in CHD and its relationship with HSCRP, a sensitive cardiac inflammatory bio-marker. These data suggest that HSCRP levels add prognostic value to classic risk factors including lipid parameters, and help identify patients at risk for cardiovascular events, even those previously classified as low or intermediate risk.

Limitations of the study

- Study should have been carried out on a larger group of population.
- Few subjects included in the study were on anti-hyperlipidemic treatment which resulted in bias.
- Glycemic control should have been assessed using HbA_{1c} levels rather than using FPG
- Factors like age, alcohol, smoking, diet and drugs (oral hypoglycemics) are found to affect IR activity which were not taken into account in this study.

Conclusion

In the present study Increased HOMA-IR, TG/HDLc and HS CRP are positively associated with coronary heart disease. There is positive correlation with statistical significance among all the three parameters in CHD cases. Our present study provides clear evidence that for the end points of MI and CHD death, the risk associated with lower and higher levels of HDL-C and triglycerides can be more precisely defined in conjunction with a measure of IR. Insulin resistance evaluated by the HOMA-IR and lipoprotein ratio i.e. TG/HDL index is usually not included in the recommendations for cardiovascular risk stratification. These conditions are generally considered emerging risk factors. They are linked to the patho-physiology of atherosclerosis, providing additional value in primary and secondary prevention.

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