International Journal of Research in Medical Sciences
Mallika DK et al. Int J Res Med Sci. 2022 May;10(5):1126-1131
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20221187

Original Research Article

Association of atherogenic indices with obesity and as biomarkers of cardiovascular risk

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Received: 21 March 2022
Revised: 11 April 2022
Accepted: 12 April 2022

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ABSTRACT

Background: Obesity, the new world syndrome is the major health problem pandemically. One of the causes of dyslipidemia is obesity. The study was aimed to detect the pattern and prevalence of dyslipidemia in obese persons.
Methods: Case control study included 70 subjects categorized into two groups based on BMI (body mass index) as cases (obese) with BMI >25 kg/m^2 (n=35) and controls (non-obese) with BMI <25 kg/m^2 (n=35). Anthropometric measurements such as waist and hip circumference and waist to hip ratio were measured. Fasting venous blood samples collected were estimated for total cholesterol, triglycerides, high density lipoprotein. Non-HDL-cholesterol, atherogenic indices such as atherogenic index of plasma, Castelli's risk index I and II and atherogenic coefficient were calculated from the estimated lipids.
Results: Dyslipidemia observed in obese cases was hypercholesterolemia, hypertriglyceridemia (28.57%), lowered HDL (57.14%) and increased LDL (65.71%). Significant lower HDL, elevated non-HDL cholesterol, CRI-I, II and AC were observed in cases compared to controls. BMI had a significant negative correlation with HDL and positive correlation with anthropometric measurements, TC, non-HDL cholesterol and atherogenic indices. TC and HDL were associated with all the atherogenic indices. CRI-I, CRI-II and AC have significant diagnostic utility, with CRI-I and AC having more sensitivity and specificity at cut off values of 3.85 and 2.85 respectively.
Conclusions: Decrease in HDL, elevated non-HDL cholesterol and atherogenic indices are associated with BMI. CRI-I and AC are indicative cardiovascular risk.

Keywords: Obesity, CRI-I, CRI-II, AIP, Atherogenic coefficient, Anthropometric indices

INTRODUCTION

Major cause of dyslipidemia is obesity, which is becoming a major health problem and is found to be prevalent in both developed and in developing countries.[1-5] Causes of obesity include factors such as overeating, diet high in simple carbohydrates, alcohol intake, frequency of eating, physical inactivity, psychological factors, medications like corticosteroids, beta adrenergic blockers, diseases like hypothyroidism, Cushing syndrome and also genetic factors.[5] Obesity is not an immediately lethal disease, but progressively it leads to serious non communicable diseases like type 2 diabetes mellitus (T2DM), heart failure, hypertension, polycystic ovarian syndrome, cancers of breast, gall bladder, colon, fetal defects associated with maternal obesity, osteoarthritis, hyperuricemia gout, breathlessness, sleep apnea and chronic airways passage obstruction.[4] Obesity in South Asians have characteristic features such as high prevalence of abdominal obesity with more intra-abdominal, truncal subcutaneous adiposity. In addition, there is greater accumulation of fat

at ectopic site such as liver and skeletal muscle. Dyslipidemia is a common feature in approximately 60-70% of obese patients and in 50-60% of overweight patients.[6] The dyslipidemia of obesity commonly noted is an increase in triglycerides (TG) and free fatty acids, decreased high density lipoprotein (HDL) and normal or slightly increased low density lipoprotein (LDL) and small dense LDL, with increase in apolipoprotein (apo) B.[7] Phase I of the Indian council of medical research india diabetes (ICMR-INDIAB) study was conducted in a representative population of Tamil Nadu, Maharashtra, Jharkhand and Chandigarh which found a high prevalence of dyslipidemia.[6] Dyslipidemia is known to play an important role in the pathophysiology of cardiovascular disease (CVD). There have been studies which have found apparently normal conventional lipid profile parameters such as total cholesterol (TC), triglycerides, high density lipoprotein and low-density lipoprotein. However, atherogenic ratios comprising of lipid ratios such as Castelli's risk index-I and II (CRI-I and II), atherogenic co-efficient (AC) and the atherogenic index of plasma (AIP) have been found to perform as the diagnostic alternatives in predicting cardiovascular risk.[8-10] In the present study, we analyzed the associations of anthropometric indices, lipids and atherogenic indices, in obese subjects. The diagnostic utility of the atherogenic indices was examined to assess the cardiovascular risk in the obese subjects.

METHODS

Study design and duration

A prospective case control study was conducted which included 70 subjects who attended outpatient department of obesity clinic and their accompanying attendants and the staff of Sri Venkateswara institute of medical sciences, Tirupati. The study was conducted between June 2019 to August 2019.

Inclusion criteria

The obese subjects attending the obesity clinic in the age group of 30-60 years were included into the study. Healthy age and gender matched non obese control subjects from among the accompanying attendants and from among the hospital staff were included into the study.

Exclusion criteria

Subjects with history of cardiovascular diseases, thyroid disorders, those taking lipid lowering drugs and oral hypoglycemic agents were excluded from the study.

Diagnostic criteria for obesity

The subjects were categorized as obese cases (BMI >25 kg/m^2) and non obese controls (BMI <25 kg/m^2) based on Asia-Pacific guidelines for South Asians.[11] Subjects were recruited into the study after obtaining a written informed consent.

Anthropometric measurements

Anthropometric measurements were made with the subject wearing minimal clothing, with no shoes and socks, with feet kept together, arms to the side, legs straight and shoulders relaxed and looking straight ahead. The heels, buttocks, shoulder blades and back of the head were placed against the vertical surface of a wall and measurement of height was taken at maximum inspiration. A right-angled headboard and a measuring tape were used to measure the height. An electronic scale was used to measure the weight. The electronic scale was brought to zero before measuring the weight. The subject was instructed to stand still with the weight equally distributed on both feet and without holding onto any support. The BMI was calculated as body weight (expressed in kilograms)/square of height (expressed in meters square). Waist circumference (WC) measured at the level of the navel, hip circumference (HC) measured at the level of the buttocks and the quotient between the WC and the HC was calculated as waist/hip ratio (WHR).

Laboratory methods

Six ml of venous blood was drawn from medial cubital vein from subjects after an overnight fast of 8-10 hours. The blood was transferred into additive free tubes which were allowed to stand for 30 minutes for clotting and then centrifuged at 2000 rotation per minute for 15 minutes to obtain serum. The separated serum was analyzed for total cholesterol, triglycerides, high density lipoprotein using standard methods on Beckman Synchron DXC 600 auto analyzer (Beckman Coulter, USA). Very low density lipoprotein and low density lipoprotein were calculated by Friedwalds formula (VLDL=triglyceride/5 and LDL=total cholesterol (HDL+very low density lipoprotein) and non HDL-cholesterol=TC-HDL. The prevalence of dyslipidemia was studied in the subjects according to national cholesterol education program (NCEP)-adult treatment panel (ATP) 3 guidelines.[12] The Atherogenic indices were calculated as: atherogenic index (AI)=log (TG/HDL), Castelli's risk index (CRI-I)=TC/HDL, Castelli's risk index (CRI-II)=LDL/HDL, Atherogenic coefficient (AC)=(TC-HDL)/HDL.[13-15]

Statistical analysis

Data distribution was studied by using Kolmogrov Smirnov test. Differences in the means of parameters among study and control groups were tested using parametric 't' test. Pearson's correlation or Spearman rank correlation analysis was done to study the correlations among the anthropometric measurements, lipids and atherogenic indices as appropriate. Receiver operative characteristic (ROC) curve analysis was performed to study the diagnostic utility of atherogenic indices for cardiovascular risk in the obese subjects.

RESULTS

In the present study no significant differences in the anthropometric measurements such as WC, HC, WHR between the obese subjects and non obese controls was observed (Table 1).

Among the lipids only a significant lower HDL levels and elevated non HDL cholesterol levels were observed in obese cases when compared to non-obese controls. The atherogenic indices CRI-I, CRI-II, AC were significantly elevated in obese subjects compared to controls (Table 2). The presence of dyslipidemia was higher in the obese subjects with elevated cholesterol, TGL, LDL and lowered HDL levels (Table 3).

Table 1: Base line characteristics of subjects.

Parameters	Controls (n=35) Mean±SD	Cases (n=35) Mean±SD	P value
Age (years)	41.05±8.76	37.97±7.12	0.236
Male/female (N)	19/16	20/15	
BMI (kg/m^2)	22.31±1.45	28.89±2.22	<0.001
Waist circumference (cms)	82.85±7.31	84±7.67	0.860
Hip circumference (cms)	92.28±7.00	94.82±5.58	0.109
Waist/hip ratio	0.89±0.02	0.88±0.06	0.714

Table 2: Lipids and atherogenic indices among subjects.

Lipid parameters	Controls (n=35) Mean±SD	Cases (n=35) Mean±SD	P value
Total cholesterol (mg/dl)	170.11±22.41	179.02±22.37	0.069
Triglycerides (mg/dl)	120.57±41.64	112.85±37.45	0.55
HDL (mg/dl)	51.40±6.81	42.28±9.02	<0.001
VLDL (mg/dl)	24.03±8.35	22.56±7.47	0.55
LDL (mg/dl)	103.79±19.27	105.06±25.38	0.492
Non HDL-C (mg/dl)	118.17±24.34	136.74±22.07	0.002
AIP	0.348±0.166	0.413±0.144	0.067
CRI-I	3.375±0.679	4.373±0.899	<0.001
CRI-II	2.052±0.463	2.555±0.739	0.008
AC	2.375±0.679	3.373±0.899	<0.001

Correlations between the anthropometric indices, lipids and atherogenic indices found positive correlations of BMI with WC, HC, WHR, and positive correlation of WC with HC and WHR. No association was found between WHR and HC. Among the anthropometric indices only BMI was found to have a significant positive association with TC, CRI-I, CRI-II, AC and non-HDL-C, with a significant negative correlation with HDL. And among the atherogenic indices only AIP showed no significant correlations with the anthropometric indices (Table 4).

The correlations among the lipids and atherogenic indices found total cholesterol to have a significant positive correlation with TGL, VLDL, LDL, AIP, CRI-I, CRI-II, AC and significant negative correlation with HDL. TGL and VLDL had significant positive correlation with AIP. HDL had significant negative correlation with AIP, CRI-I, CRI-II, AC and non-HDL-C. LDL was found to have significant positive correlation with CRI-I, CRI-II and AC (Table 5). The receiver operating characteristic (ROC) curve found CRI-I, CRI-II, AC and non-HDL-C to have significant areas under the curve. Among them CRI-I and AC at cutoff values of 3.85 and 2.85 respectively had higher sensitivity and specificity of 71% and 80% respectively (Table 6).

Table 3: Pattern of dyslipidemia.

Parameters	Controls (n=35) BMI <25 kg/m^2 % (N)	Cases (n=35) BMI ≥25 kg/m^2 % (N)
Total cholesterol (≥200mg/dl)[12]	11.42 (4)	28.57 (10)
Triglycerides (≥150 mg/dl)[12]	17.14 (6)	28.57 (10)
HDL (<40 mg/dl)[12]	2.8 (1)	57.14 (20)
LDL (≥100mg/dl)[12]	60 (21)	65.71 (23)

DISCUSSION

As the definition of obesity in the present study was based on BMI, among the anthropometric measurements a significant difference only in BMI was observed in cases compared to controls. This appears to be part of Asian Indian phenotype which includes a high body mass index (BMI). The anthropometric indicators most widely used in clinical practice are BMI and WC. WHR and WC is an indicator of visceral fat.[16] BMI is an index of relative weight and is said to have a consistent relationship with central obesity and cardiovascular risk and mortality.[17] Overweight and obesity are due to abnormal or excessive fat accumulation in the body which is in turn associated with higher metabolic risk. It has been hypothesized that BMI is a surrogate measure for prediction of body fat percentage as BMI is found to moderately correlate with more direct measures of body fat.[18] The dyslipidemia observed in the findings of the ICMR-INDIAB study found 13.9% of the population had hypercholesterolemia, 29.5% had hypertriglyceridemia, 72.3% had low HDL-C, 11.8% had high LDL-C levels and 79% had abnormalities in one of the lipid parameters. Low HDL-C was the most common lipid abnormality and in 44.9% of the population studied, it was present as an isolated abnormality.[6] The present study also found only a significant low HDL levels indicative of dyslipidemia in 57.14% of the obese cases.

Table 4: Correlations between the anthropometric indices, lipids and atherogenic indices.

Variables		WC	HC	WHR	TC	TGL	HDL	NON HDL-C	CRI-I	CRI-II	AC
BMI	**r**	0.542	0.322	0.365	0.321	-0.04	-0.556	0.241	0.578	0.473	0.578
	p	0.001	0.007	0.032	0.007	0.717	0.001	0.044	<0.001	<0.001	<0.001
WC	**r**	1	0.714	0.631	0.097	0.021	-0.119	0.043	0.159	0.116	0.159
	p	-	<0.001	<0.001	0.426	0.863	0.326	0.723	0.188	0.339	0.188

Table 5: Correlations between lipids and atherogenic indices.

Variables		TC	TGL	HDL	VLDL	LDL	CRI-I	CRI-II	AC
AIP	**r**	0.271	0.840	-0.445	0.843	-0.078	0.486	0.230	0.486
	p	0.023	<0.001	<0.001	<0.001	0.519	<0.001	0.056	<0.001
CRI-I	**r**	0.580	0.055	-0.815	0.059	0.401	1	0.901	1.000
	p	<0.001	0.654	<0.001	0.627	0.001	-	<0.001	<0.001
CRI-II	**r**	0.708	-0.090	-0.593	-0.086	0.710	0.901	1	0.901
	P	<0.001	0.450	<0.001	0.478	<0.001	<0.001	-	<0.001
AC	**r**	0.580	0.055	-0.815	0.059	0.401	1.000	0.901	1
	p	<0.001	0.654	<0.001	0.627	0.001	<0.001	<0.001	-
TC	**r**	1	.285	-0.038	0.288	0.875	0.580	0.708	0.580
	p	-	0.017	0.752	0.016	<0.001	<0.001	<0.001	<0.001
NON HDL-C	**r**	-0.062	-0.105	-0.320	-0.104	-0.177	0.227	0.067	0.227
	p	0.609	0.387	0.007	0.392	0.142	0.059	0.580	0.059

Table 6: Diagnostic utility of atherogenic indices in obesity.

Parameter	AUC	95% CI	Cut off value	Sensitivity (%)	Specificity (%)	P value
CRI-I	0.805	0.705-0.905	3.85	71	80	<0.001
CRI-II	0.683	0.558-0.809	2.11	63	57	0.008
AC	0.805	0.705-0.905	2.85	71	80	<0.001
NON HDL-C (mg/dl)	0.700	0.579-0.821	121	74	57	0.004

Low HDL levels have been reported to be an independent and major predictor of future cardiovascular events and were found to be positively associated with female gender, generalized obesity, abdominal obesity, sedentary lifestyle and diabetes.[6,19] Non-HDL cholesterol was significantly elevated in obese cases compared to controls. Non-HDL has been opined to have many advantages such as it does not deal with the relationship between VLDL and triglycerides, can be assessed in patients with triglyceride levels >400 mg/dl.

Non-HDL cholesterol calculation is an assessment of all atherogenic apolipoprotein B-containing lipoproteins such as VLDL, intermediate-density lipoprotein, LDL and lipoprotein (a) as well. The major advantage is non-HDL testing does not require the patient to be in a fasting state. The adult treatment panel III of the National cholesterol education program also recommends using non-HDL cholesterol in assessing CVD risk in patients with diabetes, and monitoring its levels as a secondary target of therapy in people with triglyceride levels >200 mg/dl.[20] Though no significant changes were observed in LDL levels in cases compared to controls, the elevated LDL levels were observed in 65.71% of obese cases.

It has been widely accepted that CVD risk mainly based on conventional lipid parameters, using either LDL-C alone or HDL-C alone is inadequate for prediction of cardiovascular risk, especially in individuals with intermediate risk. The importance of many lipid ratios have been reported, which were found to be strong indicators of the CVD risk.[21,22] The present study found atherogenic indices CRI-I, CRI-II and AC to be elevated in obese subjects compared to controls. AIP has been reported to be the most sensitive marker among the atherogenic indices, classified according to the values obtained: 0.3 to 0.1 for low risk, 0.1 to 0.24 for medium, and more than 0.24 for high risk of CVD. These lipid ratios were depicting the imbalance between atherogenic and antiatherogenic lipoproteins.[23] Similarly we found that 33 obese subjects (94%) had AIP of >0.24 indicating increased CVD risk among obese subjects. However no significant difference in AIP was found in obese subjects compared to controls. The positive association of BMI with TC and non-HDL-C, negative correlation with HDL indicate that alterations in lipids have an effect on BMI. Similar findings of higher BMI being inversely associated with HDL with no significant association between BMI and LDL have been reported.[24] Obesity is postulated to be an important risk factor for decrease in HDL, which predisposes to cardiovascular diseases.[15] Overweight or generally obese individuals were reported to have nearly 5 times greater odds, and centrally obese individuals were at nearly 4 times greater odds for

developing decreased HDL than non obese individuals.[25] The positive association of BMI with the atherogenic indices CRI-I, CRI-II, AC indicate the intricate relation of BMI with lipids and its ratios which are considered as indicators of atherogenic profile. The interactions among the lipids and atherogenic indices found HDL was associated negatively with all the calculated atherogenic indices. Cholesterol was positively associated with elevated AIP and AC; TG and VLDL were positively associated with elevated AIP and LDL was positively associated with elevated AC. The findings of the present study suggest that though no significant changes in TC, TG, VLDL and LDL were observed, their atherogenic ratios were significantly elevated in obese subjects. Further the lipids correlating with their atherogenic indices indicate the importance of the atherogenic indices as indicators of CVD risk in obesity.

In the present study, the diagnostic ability of the atherogenic indices in obesity analyzed by ROC curve found CRI-I, CRI-II, AC and non-HDL cholesterol had significant area under the curve. However among the atherogenic indices, CRI-I and AC were found to be have greater sensitivity and specificity in obesity. Both CRI-I and AC ratios deal with total cholesterol and HDL which were both found to have significant inverse association with each other and similarly both total cholesterol and HDL were associated with the atherogenic indices. CRI-I also known as cardiac risk ratio, has been particularly reported to be associated with the carotid intima media thickness and hence indicates the vulnerability to coronary plaques formation even in young adults.[22] AC is a measure of cholesterol in LDL, VLDL, IDL lipoprotein fractions with respect to HDL. It is reflective of the atherogenic potential of the lipoproteins. Hence the present findings suggest that elevated atherogenic indices are associated with obesity and are indicators of CVD risk.

Limitations

The sample size in the present study is small. The number of overweight subjects with BMI of 23-24.9 kg/m^2 in the non-obese control group were 18 (51%) which may be the probable reason for not observing significant changes in lipids and AIP between the groups.

CONCLUSION

The decreases in the HDL levels are indicative of an isolated abnormality of dyslipidemia along with elevated non HDL- cholesterol levels. The atherogenic indices were found to be associated with BMI. CR-I, CRI-II, AC and non-HDL cholesterol have significant diagnostic utility in obesity with CRI-I and AC found to have higher sensitivity and specificity as indicators of cardiovascular risk at cut off values of 3.85 and 2.85 respectively. The use of atherogenic indices should be encouraged to identify obese individuals at cardiovascular risk especially in the presence of normal cholesterol, TG or LDL levels. Lifestyle modifications or therapeutic interventions targeted towards the attenuation of atherogenic milieu will be the game changer in curtailing morbidity and mortality due to obesity related complications. The primary advantage is that dyslipidemia is an independent modifiable risk factor for CVD.

ACKNOWLEDGEMENTS

This study was approved by Indian Council of Medical Research (ICMR) for short term studentship.

Funding: Sri. Balaji Arogyavaraprasadini scheme of Sri Venkateswara Institute of Medical Sciences, Tirupati
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Mallika DK, Manohar SM, Arslan M. Association of atherogenic indices with obesity and as biomarkers of cardiovascular risk. Int J Res Med Sci 2022;10:1126-31.