

A Cross-sectional Study to Assess Insulin Resistance and Atherogenic Index of Plasma as Predictors of Risk of Cardiometabolic Disease among Undergraduate Medical Students at a Tertiary Care Teaching Hospital, Karnataka

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ABSTRACT

Background: Medical profession is known for stress and challenges due to hectic academic schedules which makes students, high-risk candidates for diabetes mellitus, hypertension and cardiometabolic disease (CMD). Surrogate markers such as homeostatic model assessment insulin resistance (HOMA-IR) and atherogenic index of plasma (AIP) along with routine parameters enable early prediction of the disease. Hence, this study aimed at determining HOMA-IR and AIP along with assessment of their correlation with anthropometric and biochemical parameters associated with CMD risk among undergraduate medical students. **Methodology :** 460 medical students consented to participate in the study. The data related to socio-demographic profile, anthropometry, blood pressure and biochemical parameters such as fasting plasma glucose (FPG), fasting plasma insulin (FPI) and lipid profile was collected and analyzed. HOMA-IR and AIP were calculated. The strength of association between study variables was determined by relevant statistics. **Results:** The study showed the prevalence of overweight (17.8%), obesity (20.4%), pre-hypertension (37.82%) and hypertension (3.47%). 98.5% of the participants had normal FPG and FPI, whereas 1.5% had impaired levels. Lipid profile analysis showed hypercholesterolemia (3.7%), hypertriglyceridemia (8.1%), increased LDL-c (33.7%) and reduced HDL-c (55.2%). High HOMA-IR and AIP were contributed by 28.9% and 73.3% respectively. HOMA-IR and AIP showed statistically significant positive correlation with CMD risk factors. **Conclusion:** HOMA-IR and AIP considered as the better predictors of CMD risk among apparently healthy medical students. Thus, incorporation of these surrogate markers along with routine parameters for regular screening can help in early prediction of the risk of CMD among undergraduate medical students.

KEY WORDS: Homeostatic model assessment insulin resistance, Atherogenic index of plasma, Cardiometabolic disease, Medical students.

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Introduction

In this present competitive world, there exists a great tendency for leading a better life by each and every person. Education serves an important role in providing an opportunity to settle down with a well-recognized profession. The commonest professions opted by are medicine, engineering, law, chartered accountancy, teaching among others.

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Medical profession is considered as, “The Noble Profession” for provision of health services, respect in society and in turn provides career satisfaction.^[1] During the course of medical training, factors such as prolonged lectures, frequent assessments and stress due to rigorous training results in intense sedentariness, physical inactivity, inadequate sleep, overeating and addictions. Thus, medical students are more vulnerable for development of stress, overweight, obesity, dyslipidaemia, insulin resistance (IR), diabetes mellitus (DM), hypertension and cardiometabolic disease (CMD).^[1,2]

According to World Health Organisation (WHO), in 2019 CMD took first position among top 10 causes of deaths, accounting for 16% of total deaths globally.^[3] India is in the phase of epidemiologic transition, in which the burden of communicable diseases has gradually reduced, with the prominent increase in burden of non-communicable diseases (NCD).^[4] Currently, studies have documented about 30 million cases of CMD in our country. India witnessed a 4-fold rise in CMD prevalence in past 40 years, mainly contributed by DM, hypertension, atherogenic dyslipidaemia, central obesity, physical inactivity, rapid urbanization and changes in lifestyle^[4].

Abdominal obesity shows an obvious role towards the development of IR and CMD. Prevalence of DM has increased drastically with proportionate increase of obesity, unhealthy diet, sedentary lifestyle, physical inactivity, urbanisation, economic development and aging of population. Considering this upsurge of IR and DM, International Diabetes Federation (IDF) predicted that, by 2040 about 642 million would have developed diabetes.^[5] There exists a strong relationship of IR with obesity, DM and cardiometabolic risk markers such as dyslipidaemia, hypertension and central adiposity resulting in atherogenesis.^[6] Thus, metabolic conditions related to IR are increasing at an alarming rate and a substantial proportion of apparently healthy people are found to be insulin resistant. Development of IR can be predicted by Homeostasis Model Assessment Insulin Resistance (HOMA-IR). HOMA-IR shows strong association between IR, obesity and other CMD risk factors which brings about early detection of IR and CMD in apparently healthy population.^[7,8]

INTERHEART- South Asia study concluded that, dyslipidaemia is the most important risk factor

for CMD.^[9] Dyslipidaemia is a widely accepted risk factor for cardiovascular disease and is characterized by lipid triad i.e., increased total cholesterol (TC), Low Density Lipoprotein Cholesterol (LDL-c) and triglyceride (TG) or decreased High Density Lipoprotein Cholesterol (HDL-c). This triad is most commonly witnessed in people with premature CMD, thus resulting in atherogenic dyslipidaemia.^[10] Atherogenic dyslipidaemia is determined by atherogenic index of plasma (AIP) and implicated as risk marker of CHD.^[11]

Medical profession is considered as stressful due to prolonged study hours, hectic academic schedules and sedentary lifestyle which lead to development of overweight, obesity and other CMD risk factors. Hence, medical students should be screened for CMD and IR. In early stages of CMD, the routine parameters [Fasting Plasma Glucose (FPG), lipid profile, blood pressure] are usually unaffected, whereas an obvious derangement is witnessed when cardiovascular dysfunction is already apparent and very little can be done to benefit the patient at this stage.^[12] So, this requires a valid marker which is simple and sensitive to recognize high-risk individuals even before dyslipidaemia, hyperglycaemia or hypertension are observed. Hence, the present study was undertaken to assess the usefulness of HOMA-IR and AIP as the early predictors of risk of CMD among undergraduate medical students at a Tertiary care teaching hospital, Karnataka.

Materials & Methods

This cross-sectional study was conducted for a period of 1 year on 460 consenting students from all phases of MBBS. Commencement of the study was made after obtaining approval from Institutional Scientific and Ethics Committee, vide letter no. MIMS/IEC/2018/258 dated 17/10/2018. Participant proforma was used to collect information regarding personal and family history. Anthropometric measurements like height, weight, waist circumference (WC), hip circumference (HC) and biochemical parameters like Fasting plasma glucose (FPG), Fasting Plasma Insulin (FPI), TC, TG, HDL-c and LDL-c. Body Mass Index (BMI), Waist to Hip ratio (WHR), HOMA-IR and AIP were calculated. Subjects with DM, endocrine dysfunction, CHD, females with polycystic ovarian syndrome, participants on medications like antipsychotics, cardiac drugs and glucocorticoids were excluded and subjects not consenting to take part in the study were excluded.

Collection of blood samples

Students were approached on the previous day and brief information regarding the study was provided and was also informed about the requirement of 8-10 hours of overnight fasting. Next day morning, subjects were instructed to report to Clinical Biochemistry Section, Central Diagnostic Laboratory of the Institution. After filling the details in proforma, anthropometry and blood pressure (BP) was measured. Under aseptic precautions, 3ml of venous blood was drawn into plain tubes for biochemical parameters and allowed to stand for 10-15 minutes and the samples were subjected to centrifugation for 15-20 minutes at 3500rpm. The serum separated was used to estimate FPG by Hexokinase method, FPI by Chemiluminescent Microparticle Immunoassay method, TC by Cholesterol Oxidase peroxidase (CHOD-POD) method, TG by Glycerol Phosphate Oxidase (GPO) method and HDL-c by Accelerated Selective Detergent method in the fully automated Abbott architect analyzers. The quality of reports was ensured by both internal and external quality control checks.

Calculated parameters

HOMA-IR and AIP were calculated using the values obtained by estimating biochemical parameters. HOMA-IR is a formal test and a validated method to assess hepatic IR and deficient β -cell function. It is given by the formula, $HOMA-IR = [FPG(\text{mmol/L}) \times FPI(\mu\text{IU/ml})] / 22.5$. HOMA-IR value of >2.5 is taken as an indicator of IR.^[13,14] AIP is considered as a strong marker for atherogenicity and a critical stand-alone index for CMD risk. AIP is given by the formula, $AIP = \text{Log}[TG(\text{mg/dl}) / HDL-c(\text{mg/dl})]$. AIP value <0.1 as low risk, $0.11-0.21$ as intermediate risk and >0.21 as increased risk for CMD.^[15,16]

Anthropometric measurements

Height (cm) and weight (kg) was measured using a stadiometer and analogue weighing scale respectively. WC and HC were measured using a non-stretchable tape and BMI was calculated as $\text{Weight (kg)} / \text{Height (m)}^2$. Systolic BP (SBP) and Diastolic BP (DBP) were measured using mercury sphygmo manometer. According to WHO, $WC \geq 90\text{cm}$ for males and $\geq 80\text{cm}$ for females and $WHR \geq 0.95$ and ≥ 0.85 for males and females respectively were categorised as obese.^[17] BMI was classified according to Indian Council of Medical Research (ICMR) and Association of Physicians (AOP) as follows; $18.0-22.9\text{Kg/m}^2$ as normal, $23.0-24.9\text{Kg/m}^2$ as overweight and $\geq 25\text{kg/m}^2$ as obese. As per, 7th Report of Joint

National Committee (JNC), BP $<120/80\text{mmHg}$ was considered normal, SBP between $120-140\text{mmHg}$ and DBP between $80-100\text{mmHg}$ as pre-hypertensive and $BP \geq 140/100\text{mmHg}$ as hypertensives.

Statistical analysis

Data was entered into Microsoft Excel sheets and analyzed by statistical software- IBM Statistical Package for the Social Sciences (SPSS) -22.0 and R environment version-3.2. Descriptive and inferential statistical analysis was used for Mean \pm Standard Deviation. Strength of association between variables was determined by Pearson's correlation. Correlation coefficient value close to $+1$ indicates strong positive correlation and value close to -1 indicates strong negative correlation. The statistical significance was evaluated at 95% confidence level and probability value (p) of <0.05 was considered statistically significant.

Results

In this study, out of 460 students, 228 (49.6%) were males and 232 (50.4%) were females. The mean age of the subjects was 19.73 ± 1.4 years. The baseline characteristics of the subjects are depicted in Table 1.

Among the total participants, 284 (61.7%) had normal BMI, 82 (17.8%) were overweight and 94 (20.4%) were obese. Out of 228 male subjects, 64.5% had normal BMI, 17.5% were overweight and 18% were obese. Whereas, among 232 female subjects, 59.1% had normal BMI, 18.1% were overweight and 22.8% were obese.

Abdominal adiposity can be predicted by measuring WC and WHR. According to present study, among males, 189 (41.1%) had $WC < 90\text{cm}$ and 39 (8.5%) had $WC \geq 90\text{cm}$. Whereas, amongst females, 150 (32.6%) had $WC < 80\text{cm}$ and 82 (17.8%) had $WC \geq 80\text{cm}$. Thus, according to WC, 8.5% males and 17.8% females showed the presence of abdominal obesity. Similarly, with WHR, 226 (41.1%) males had $WHR < 0.95$ and 2 (0.4%) had $WHR \geq 0.95$. Whereas 137 (29.8%) female subjects had $WHR < 0.85$ and 95 (20.7%) had $WHR \geq 0.85$. WHR indicated increased abdominal obesity in female subjects. Thus, in this study, female subjects showed increased prevalence of abdominal obesity compared to males.

According to 7th Report of JNC, the present study reported 37.82% of the subjects as pre-hypertensive and 3.47% of them as hypertensive.

Table 1: Baseline characteristics of the study subjects

Variables	Mean ± SD	Anthropometric measurements	Mean ± SD	Biochemical parameters	Mean ± SD
Total subjects (n)	460	Height (cm)	166.43±9.39	FPG (mmol/L)	4.62±0.39
No. of Males	228(49.6%)	Weight (kg)	62.74±10.46	FPI (μIU/ml)	10.54±5.56
No. of Females	232(50.4%)	BMI (kg/m ²)	22.63±3.17	TC (mg/dl)	149.27±26.87
Mean age (Years)	19.73±1.4	WC (cm)	78.60±9.31	TG (mg/dl)	91.14±37.79
		WHR	0.84±0.05	HDL-c (mg/dl)	38.87±7.74
		SBP (mmHg)	120.82±10.75	LDL-c (mg/dl)	92.35±21.97
		DBP (mmHg)	80.60±7.78	HOMA-IR	2.19±1.21
				AIP	0.35±0.20

BMI: Body Mass Index, WC: Waist Circumference, WHR: Waist Hip Ratio, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, FPG: Fasting Blood Glucose, FPI: Fasting Plasma Insulin, TC: Total Cholesterol, TG: Triglycerides, HDL-c: High Density Lipoprotein Cholesterol, LDL-c: Low Density Lipoprotein Cholesterol, HOMA-IR: Homeostatic Model Assessment Insulin Resistance, AIP: Atherogenic Index of Plasma.

Based on ADA criteria, considering their FPG values participants were categorized as normal, impaired and type-2 DM. 98.5% of the subjects had normal FPG and FPI values, while the remaining 1.5% had impaired or high levels of FPG and FPI.

According to National Cholesterol Education Program (NCEP)/Adult Treatment Panel (ATP)-III guidelines, based on lipid profile, participants were categorized as desirable, borderline and high risk for CHD. According to the present study results, dyslipidaemia was contributed as follows, hypercholesterolemia by 3.7%, hypertriglyceridemia by 8.1%, increased LDL-c by 33.7% and low HDL-c values by 55.2% which is depicted in Figure 1.

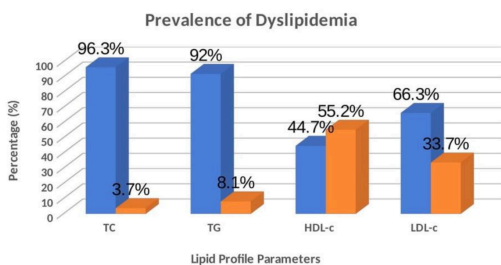


Figure 1: The prevalence of dyslipidaemia among the undergraduate medical student

As per ATP-III and IDF criteria, participants were classified based on HOMA-IR cut-off towards the diagnosis of IR. The mean HOMA-IR value of the participants was 2.19±1.2. It was observed that 71.1% had HOMA-IR value <2.5 and remaining 28.9% had ≥2.5 indicating the presence of IR. HOMA-IR showed a statistically significant positive

correlation with anthropometric measurements like, BMI, WC, WHR, SBP and DBP. Similarly, with respect to biochemical parameters, a statistically significant positive correlation was observed with all the biochemical parameters except for LDL-c, whereas HDL-c showed statistically significant negative correlation as depicted in Table 2 and Figure 2.

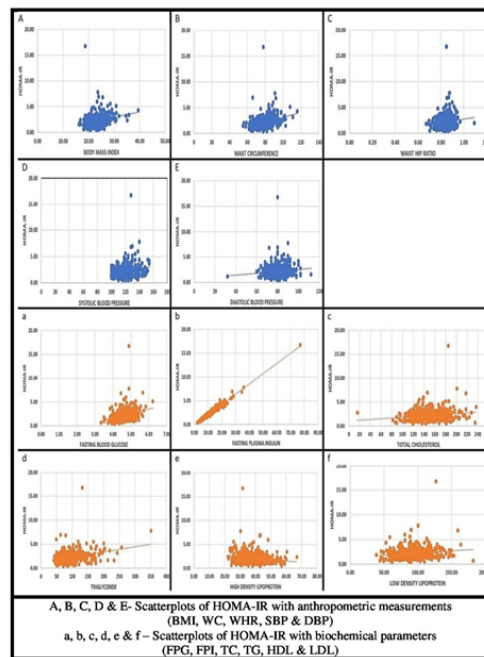


Figure 2: Scatterplots of HOMA-IR with anthropometric measurement and biochemical parameters

The risk of CMD as assessed by AIP showed that 8.5% of the subjects had low risk, 18.3% had

Table 2: The correlation analysis of HOMA-IR and AIP with anthropometric measurements and biochemical parameters

Correlation of HOMA-IR	r-value	p-value	Correlation of AIP	r-value	p-value
HOMA-IR vs BMI (kg/m ²)	0.274	<0.001**	AIP vs BMI (kg/m ²)	0.238	<0.001**
HOMA-IR vs WC (cm)	0.345	<0.001**	AIP vs WC (cm)	0.313	<0.001**
HOMA-IR vs WHR	0.150	0.001**	AIP vs WHR	0.173	<0.001**
HOMA-IR vs SBP(mmHg)	0.212	<0.001**	AIP vs SBP (mmHg)	0.227	<0.001**
HOMA-IR vs DBP(mmHg)	0.117	0.012*	AIP vs DBP (mmHg)	0.156	0.001*
HOMA-IR vs FPG(mmol/L)	0.311	<0.001**	AIP vs FPG (mmol/L)	0.121	0.009**
HOMA-IR vs FPI(μIU/ml)	0.986	<0.001**	AIP vs FPI (μIU/ml)	0.326	<0.001**
HOMA-IR vs TC(mg/dl)	0.170	<0.001**	AIP vs TC (mg/dl)	0.230	<0.001**
HOMA-IR vs TG (mg/dl)	0.339	<0.001**	AIP vs TG (mg/dl)	0.873	<0.001**
HOMA-IR vs HDL-c (mg/dl)	-0.196	<0.001**	AIP vs HDL-c (mg/dl)	-0.636	<0.001**
HOMA-IR vs LDL-c(mg/dl)	0.078	0.097+	AIP vs LDL-c (mg/dl)	0.099	0.034*

** Strongly significant (p-value: <0.01); * Moderately significant (p-value: 0.01 < to ≤ 0.05);

+ Suggestive significance (p-value: <0.05 to <0.10)

BMI: Body Mass Index, WC: Waist Circumference, WHR: Waist Hip Ratio, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, FPG: Fasting Blood Glucose, FPI: Fasting Plasma Insulin, TC: Total Cholesterol, TG: Triglycerides, HDL-c: High Density Lipoprotein Cholesterol, LDL-c: Low Density Lipoprotein Cholesterol, HOMA-IR: Homeostatic Model Assessment Insulin Resistance, AIP: Atherogenic Index of Plasma.

intermediate risk and 73.3% had high risk. AIP showed statistically significant positive correlation with all the anthropometric measurements (BMI, WC, WHR, SBP and DBP). AIP also showed statistically significant positive correlation with all the biochemical parameters except for HDL-c that correlated negatively as shown in Table 2 and Figure 3.

The correlation analysis between HOMA-IR and AIP revealed a statistically significant positive correlation (r=0.335; p=<0.001**) as depicted in Figure 4.

Discussion

Medical profession mainly targets protection and restoration of good health by proper diagnosis and treatment, also upholds the responsibility which promises the clinical standards and delivers care to the needy. Despite all these responsibilities, medical students are more prone to experience stress at every phase of professional course due to prolonged lectures, frequent assessments, inadequate sleep, physical inactivity, social isolation and addictions. Hence, medical students are vulnerable to many life-threatening NCDs such as overweight, obesity, dyslipidaemia, DM, hypertension, and CMD.

In recent days, the prevalence of obesity is on the increasing trend among medical students. BMI, WC, WHR serve as predictors of obesity. Present study

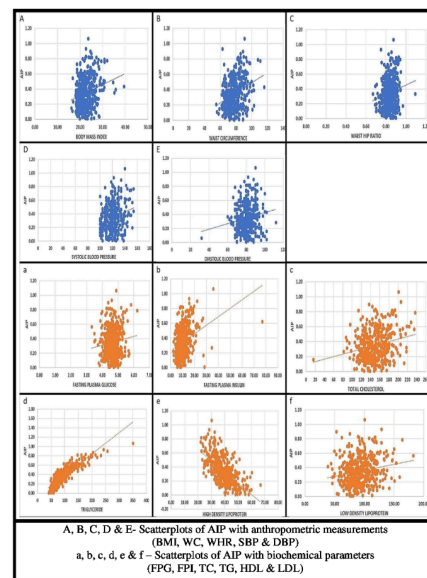


Figure 3: Scatterplots of AIP with anthropometric measurements and biochemical parameters

showed prevalence of overweight and obesity as 17.8% and 20.4% respectively and remaining 61.7% had normal BMI. Similar results were seen in a study conducted by Gudegowda KS et al., in which the prevalence of overweight and obesity was 14.6% and 11.3% respectively and remaining 60.85% had normal BMI. [18]

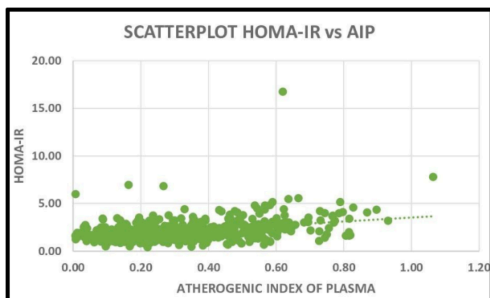


Figure 4: Scatterplots of HOMA-IR vs AIP

Present study reported 8.5% males and 17.8% female subjects had increased WC. Our results were in accordance with the study conducted by Thomas E et al., in which 24.6% male students and 44.3% female students showed increased WC.^[19] 0.4% of males and 20.7% of the female subjects of this study had increased WHR. Similar results were observed in a study conducted by Rachaconda P et al., in which, female students (30.3%) had increased WHR compared to male students (5.3%) indicating an increased visceral adiposity among female students.^[20] Prevalence of hypertension among medical students is considered a major risk factor for CMD, chronic renal disease, cerebrovascular disease and many other diseases. In this study, 37.82% subjects were pre-hypertensive and 3.47% were hypertensive. Our results were in accordance with the study conducted by Chitrapu et al., in which the prevalence of pre-hypertension among their medical students were found to be 37.45% and hypertension by 3.63%.^[21]

IR is often associated with visceral adiposity, glucose intolerance, hypertension, dyslipidaemia, hyperglycaemia, endothelial dysfunction, and increased inflammatory markers. The present study showed, 1.5% students had impaired FPG values and remaining 98.5% had normal values. A study conducted by Gopalakrishnan S et al. also showed similar results, in which 2% of the medical students had high risk and 57.4% had moderate risk and remaining 40.6% had low risk towards the development of DM.^[22]

According to the present study, 28.9% students had HOMA-IR value >2.5. Similar result was observed in a study conducted by Charpe C et al. in which 40% of the students showed IR.^[23] Many studies have shown that IR precedes and is considered as a strong predictor for development of DM. Hence, estimation of IR by HOMA-IR serves as the surrogate

marker towards early detection of DM and associated comorbidities even before the actual disease sets in.

HOMA-IR showed a statistically significant positive correlation with anthropometric measurements (BMI, WC and WHR). The present study results were consistent with a study conducted by Al-Farai H et al. According to them, medical students had increased tendency towards the development of obesity. High BMI values showed statistically significant association with IR.^[24] Many studies have evidently documented an interrelationship between obesity, BP and IR towards its adverse effect on human body.^[22,25,26] The present study reported a positive correlation between HOMA-IR and BP. This correlation was strongly significant for SBP and moderately significant for DBP as per Table 2. Similar results were seen in study conducted by Sinha et al., in which HOMA-IR showed a positive correlation for SBP and DBP but statistical significance was observed for SBP only.^[27] All the biochemical parameters were positively correlated with HOMA-IR, whereas HDL-c showed negative correlation as per Table 2. This correlation was statistically significant for all the parameters except for LDL-c. Present study results were in accordance with the results obtained by Singhal et al. in which IR was correlated positively with TC, TG, LDL-c and negatively with HDL-c and this correlation was statistically significant.^[28]

According to Figure 1, it was found that the presence of dyslipidaemia was prevalent among our medical students, in which 3.7% had hypercholesterolemia. Hypertriglyceridemia and increased LDL-c levels were observed among 8.1% and 33.7% of the subjects respectively, whereas 55.2% had low HDL-c values. The results of this study were in accordance with the results obtained by Goswami S et al. in which, the prevalence of dyslipidaemia among medical students of South Kolkata was as follows, with high serum TC (26%), high TG (10%) and low HDL-c (87%).^[29]

Routine parameters like blood glucose level, lipid profile and BP are usually unaffected in early stages. These are deranged when the cardiovascular dysfunction is already apparent and very little can be done to benefit the patient at this stage. So, this requires a valid marker which is simple and sensitive enough to recognize the high-risk obese individuals for the probable complications even before dyslipidaemia, hyperglycaemia or hypertension is observed. Apart from normal lipid profile

parameters, dyslipidaemia can be predicted by AIP. AIP is considered as a sensitive marker for the determination of underlying dyslipidaemia and CMD risk.

According to Table 2, AIP showed a statistically significant positive correlation with anthropometric measurements (BMI, WC and WHR). The results of the present study were in accordance with the study conducted by Shen *et al.* in which AIP was positively correlated with WC.^[30] AIP showed positive correlation with both SBP and DBP in our study as per the Table 2. This result was consistent with the results obtained by Niroumand *et al.*, in which AIP showed statistical significance positive correlation with SBP and DBP.^[31] AIP showed positive correlation with all the biochemical parameters except for HDL-c, in which negative correlation was witnessed. The results of the present study were in consistence with the study conducted by MyatSu Bo *et al.*, in which AIP showed a significant positive correlation with TC, LDL-c, TG, glucose, whereas a significant negative correlation with HDL-c was observed.^[32]

HOMA-IR and AIP are the early sensitive predictors of DM, dyslipidaemia and other risk factors associated with the development of CMD. According to the present study, HOMA-IR and AIP showed a statistically significant positive correlation with each other and was found to be in accordance with the study conducted by Sein *et al.* They also concluded that, HOMA-IR along with AIP can significantly contribute towards the assessment of CMD risk particularly in obese subjects as the degree of visceral adiposity have increased tendency to worsen IR and enhance CMD risk. Thus, incorporation of both HOMA-IR and AIP should be done as a standard risk assessment tool towards the development of atherosclerosis and to assess its relationship with IR.^[33]

When the individual parameters were used to quantify the burden of CMD risk among the study population, the obtained prevalence was comparatively less. On estimating IR by HOMA-IR with the help of FPG and FPI, 28.9% of them showed IR. Similarly, the individual lipid profile parameters reported less prevalence of CMD risk. When TG and HDL-c values were used together as AIP to classify the subjects on the basis of CMD risk, AIP categorized more cases with increased CMD risk. IR and dyslipidaemia as estimated by HOMA-IR and AIP showed statistically significant positive correlation

with other CMD risk factors.

Conclusion

The present study concludes that, HOMA-IR and AIP can be considered as the better predictors of CMD risk among apparently healthy medical students. Thus, incorporation of these surrogate markers along with routine parameters for regular screening can help in early prediction of increased risk of CMD in the initial phase of disease development at no extra cost.

Limitations of the study

Details on physical activity and diet were not taken into account. Participants with high FPG values were not confirmed with glycated haemoglobin for DM. High BP values were not confirmed with average readings of 3 consecutive days for hypertension. The gold standard hyperinsulinaemic euglycemic clamp method for IR estimation could not be incorporated due to cost-effectiveness. For detailed CMD risk assessment, the appropriate investigations such as echocardiography and 2-D echo were not done. Follow up of cases were not done to study the causal relation between anthropometric measurements and biochemical parameters towards the development of cardiovascular risk factors.

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Nil

Conflicts of interest

Nil

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