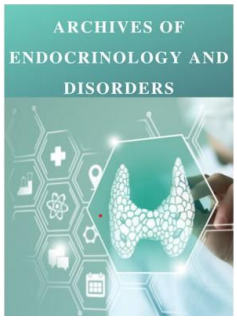

Archives of Endocrinology and Disorders

ATHENAEUM SCIENTIFIC PUBLISHERS

Research Article

Cardiometabolic Dysfunction and Insulin Resistance in Young and Middle-Aged Indian Adults: A Cross-Sectional Study Using Surrogate Biomarkers

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Citation: Desai S, et al. Cardiometabolic Dysfunction and Insulin Resistance in Young and Middle-Aged Indian Adults: A Cross-Sectional Study Using Surrogate Biomarkers. Arch Endocrinol Disord. 2025;1(2):1-12.

https://doi.org/10.46889/AED.2025.1206

Received Date: 10-12-2025

Accepted Date: 24-12-2025

Published Date: 31-12-2025

Abstract

Background: Atherosclerosis and cardiometabolic diseases are driven by insulin resistance, visceral adiposity, dyslipidaemia and chronic inflammation, all of which are highly prevalent in the Indian population. Simple indices such as the TG/HDL cholesterol ratio, Triglyceride-Glucose (TyG) index, monocyte to high-density lipoprotein cholesterol (HDL-C) ratio (MHR) and Visceral Adiposity Index (VAI) have emerged as practical, cost-effective markers reflecting metabolic dysfunction, inflammation and cardiovascular risk. This study therefore examines the association of these indices with anthropometry, body composition, HbA1c and HOMA-IR in healthy individuals aged 16-55 years.

Methods: This cross-sectional study included 431 apparently healthy adolescents and adults (16-55 years) from the Mumbai Metropolitan Region, recruited from academic institutions with informed consent and ethics approval. Anthropometry (weight, height, WC, HC, BMI, WHR, WHtR) and body composition (InBody 120) were measured. Fasting blood samples were analysed for CBC, glucose, insulin, HbA1c and lipid profile and used to compute TG/HDL ratio, TyG index, MHR and VAI. Data was analysed using SPSS 21, with $p<0.05$ considered significant.

Results: Middle-aged adults (35-55 years) had significantly higher HbA1c, lipids, TG/HDL, TyG index, MHR and VAI. Nearly half the sample was obese (48%) and increasing BMI category was associated with higher WHR, WHtR, body fat, visceral fat and lower muscle mass. Grade-2 obesity was linked with significantly higher glucose, insulin, HbA1c, HOMA-IR, TG/HDL, TyG index, MHR and VAI. Participants with insulin resistance (48.2%) or elevated HbA1c (45.2%) had significantly higher adiposity markers and adverse lipid-glycemic indices. ROC analysis showed TyG index as the strongest predictor of insulin resistance and elevated HbA1c in males, while VAI best predicted insulin resistance and TyG index best predicted HbA1c in females.

Conclusion: Therefore, simple, low-cost metabolic indices-TyG, TG/HDL ratio, MHR and VAI were strongly associated with adiposity, dysglycemia and insulin resistance even in apparently healthy adolescents and adults and incorporating these indices into routine screening may enable earlier detection and prevention of cardiometabolic disease.

Keywords: Surrogate Biomarkers; Cardiometabolic Dysfunction; Insulin; Visceral Adiposity Index

Introduction

Atherosclerosis is a complex proinflammatory and prothrombotic state, the pathophysiology being influenced by lipid metabolism, insulin resistance and inflammation [1]. Patients with Type 2 Diabetes Mellitus (T2DM) often display atherogenic dyslipidaemia and obesity, which greatly increases their risk for coronary artery disease [2,3]. Persistent hyperglycaemia and

Insulin Resistance (IR) are associated with damage to organs, especially eyes, kidney, nerves and the heart [4,5]. The ICMR - INDIAB study, 2017 report from India, observed that the overall weighted prevalence of diabetes, prediabetes, hypertension, generalised obesity, abdominal obesity and dyslipidaemia was 11·4%, 15·3%, 35·5%, 28·6%, 39·5% and 81·2% respectively [6]. It is noteworthy that even if they are not-obese, Asians especially Indians have a high propensity to develop insulin resistance [7,8]. Similarly, several epidemiological and cohort studies have established a strong association between LDL-cholesterol (LDL-c) or low HDL-cholesterol (HDL-c) and the incidence of atherosclerosis-related diseases, such as ischemic heart disease, stroke and peripheral vascular disease [9-12]. The key to reducing the burden of cardio-metabolic disorders is early detection of insulin resistance using simple markers and indices that are readily available and cost effective.

Increased Plasma Triglycerides (TG) and decreased High-Density Lipoprotein Cholesterol (HDL-C) levels has already been proposed in the diagnostic criteria for Metabolic Syndrome (MetS) [13,14]. More recently, the ratio of the two has been used to investigate the relationship of both factors with IR. The TG/HDL ratio was found to be more closely linked to the development of IR and central adiposity than either TG or HDL alone [15]. Further, it has been seen Triglyceride-Glucose (TyG) index which can be calculated using easily available laboratory data like fasting plasma triglycerides and glucose levels helps to indirectly assess IR through a mathematical model [16]. The TyG index has been shown to provide a relatively good accuracy in predicting cardiovascular events, with sensitivity and specificity values between 67 - 96% and 32.5-85%, respectively [17]. Monocyte to High-Density Lipoprotein Cholesterol (HDL-C) ratio (MHR) is another novel and simple measure associated positively with the body's inflammatory and oxidative stress status and reflects the balance between the two [18,19]. HDL-C could attenuate and reverse monocyte activation through apoA-I- mediated CD11b inhibition and its pro-inflammatory activity and therefore, assessing this ratio in community studies would be worthwhile [20].

Visceral obesity is well known to be associated with increased adipocytokine production, proinflammatory activity, increased insulin resistance with an increased risk of developing diabetes, "high-triglyceride/low-HDL cholesterol dyslipidaemia" hypertension, atherosclerosis and higher mortality rate [21]. Visceral adiposity index which takes into account routinely used measurements like Waist Circumference (WC), Body Mass Index (BMI) and lipids may help estimate the visceral adiposity dysfunction associated with cardiometabolic risk [21].

These simple measurements are promising, cost effective as well as practical tools for the assessment of inflammation, insulin resistance and associated CVD risk alternative to insulin assays and small dense LDL (sdLDL) in a large population or community studies. Evidence from Indian populations remains limited. Most existing studies from India are small, hospital-based or cross-sectional and lack community-level or prospective designs. As a result, it is important to study them in the Indian context, where unique metabolic phenotypes such as the "thin-fat" body composition and higher propensity for insulin resistance may influence their performance. Incorporating these indices into routine screening may enable earlier detection and prevention of cardiometabolic disease even in apparently healthy individual who may not be aware of their risks. Therefore, in the present study, we evaluated the relationship between TG/HDL cholesterol ratio, Triglyceride-Glucose (TyG) index, monocyte to High-Density Lipoprotein Cholesterol (HDL-C) ratio (MHR) and Visceral Adiposity Index (VAI) with anthropometric measurements, body composition, HbA1c and HOMA IR in young and middle- aged 16-55 years.

Methodology

Study Design and Sample Selection

This cross sectional study was done on 431 adolescents, young and middle-aged adults, 16-55 years residing in Mumbai Metropolitan Region (MMR region), India. The participants were both males and females who were a part of a larger clinical trial. All participants were enrolled after obtaining written informed consent and for those between 16-18 years informed written parental consent was obtained. The participants were recruited from various academic institutions as well as corporate and government offices. Data was collected by a trained researcher from these adults by face-to-face interview in local language at home/ the workplace of respondent after obtaining consent.

The study was approved by the Intersystem Biomedical Ethics Committee, Mumbai, India (ISBEC version 2 dated 12th Aug, 2017 and ISBEC, 21st October, 2022) and conducted according to Good Clinical Practices and the Declaration of Helsinki. The participants were included and excluded based on the given criteria:

Inclusion Criteria:

- Apparently healthy adolescents and adults in the age group of 16-55 years

Exclusion Criteria

- Pregnant and lactating women
- Presence of any known chronic disease, those on prescribed medications like steroids, hypoglycaemic agents, treatment of dyslipidaemia/lipid-lowering drugs or hypertension, for cardiac ailments
- Individuals suffering from/ suffered major depression, eating disorders and anxiety disorders
- Individuals with history of prior diagnosis of stroke, myocardial infarction or interventional cardiology procedures or other major mental illness or substance abuse as well as history of cognitive impairment and major neurological disorders
- Chronic pain conditions and taking sedatives, hypnotics and painkillers regularly

Anthropometric Measurements

Each participant was examined by a physician to assess the general health status. Weight, height, waist circumference and hip circumference were measured by trained research assistants. Body composition was measured using the InBody 120 body composition analyser.

Weight- Participants were weighed using InBody. It was ensured that they were wearing light clothing and no footwear at the time of measurement. The scale was zeroed before every measurement. Height was measured using a stadiometer (accuracy of 0.1 cm). Subjects were asked to remove their footwear, stand with their feet together, knees straight and chin parallel to the ground. Care was taken that the back of the head (occipital lobe), shoulder blades, buttocks and heels were in contact with the stadiometer surface.

Body Mass Index (BMI) was calculated as weight/height^2 (kg/m^2) and participants were classified as underweight, normal, overweight or obese based on the WHO criteria for Asians (2004) [22]. Waist Circumference (WC) and Hip Circumference (HC) were measured with a calibrated, non-extensible, flexible measuring tape. WC was measured at a level midway between the bottom of the rib cage and superior margin of iliac crests during inspiration and hip circumference at the maximal diameter of the buttocks. Waist-to-Hip Ratio (WHR) and Waist-to- Height Ratio (WHtR) was calculated using the waist and hip circumference and height.

Biological Samples, Collection, Storage and Biochemical Measurements

Blood samples of the participants were collected after an overnight fast of at least 12 hours. Venous blood (10 ml) was collected in fasting state. Two mL of fasting blood sample was immediately transferred to a BD vacutainer (spray-coated K2EDTA Tubes) for Complete Blood Count (CBC) and HbA1c, two ml of fasting blood sample was immediately transferred to a BD vacutainer (spray-coated sodium fluoride tubes) for estimation of plasma glucose levels and insulin. The remaining six ml of fasting blood was transferred into plain BD vacutainer for separation of serum. Fluoride and plain vacutainers were centrifuged, fluoride plasma was processed for estimation of plasma glucose levels and serum was processed for serum insulin levels and plain vacutainers were processed for lipid profile. The remaining fasting serum was divided into aliquots and stored at -70^{0}C until further analyses.

CBC was done for all 431 participants. Along with CBC, the following measurements were done: Glucose was measured by the GOD POD method (Accurex Biomedical Pvt Ltd), insulin was measured by radioimmunoassay using a Beckman Coulter Counter. HbA1c was measured using Nycocard reader (Alere Technologies, Norway). The lipid profile of these participants was measured using kits for total cholesterol, triglycerides, HDL-c, LDL-c and VLDL (Accurex Biomedical Pvt Ltd.).

- The TG/HDL cholesterol ratio was calculated after dividing absolute TG levels by absolute HDL cholesterol levels in peripheral blood with cut-offs (men: 2.6; women: 1.7) was used [23]
- The TyG index, calculated as TyG index = Ln [Fasting triglyceride (mg/dl) × fasting glucose (mg/dl)]/2, is a composite indicator composed of fasting Triglyceride (TG) and Fasting Glucose (FG) levels [24]
- Monocyte/HDL ratio is calculated by dividing the absolute number of monocytes by the absolute number of High-Density Lipoprotein (HDL) [25]

- VAI score was calculated as described using the following sex-specific equations, when *TG* is Triglycerides, levels expressed in mmol/l and *HDL* is HDL-Cholesterol levels expressed in mmol/l [21]

$$\text{VAI Men}: \frac{\text{Waist Circumference}}{39.68 + (1.88 \times \text{BMI})} \times \frac{\text{Triglyceride}}{1.03} \times \frac{1.31}{\text{HDL}}$$

$$\text{VAI Women}: \frac{\text{Waist Circumference}}{39.58 + (1.89 \times \text{BMI})} \times \frac{\text{Triglycerides}}{0.81} \times \frac{1.52}{\text{HDL}}$$

Statistics

Descriptive data of participants are reported as mean ±SD and 95% Confidence Interval (CI) for continuous variables. Independent student t-test and ANOVA tests were done to study the associations. Pearson's Chi Square analysis was done to study the correlation. Receiver Operating Characteristic (ROC) curves were to study the sensitivity and specificity for TyG index, TG/HDL ratio, monocyte/HDL ratio, visceral adiposity index. Analysis was done using SPSS 21. A p-value <0.05 was set to determine statistically significant differences.

Results

Among 431 participants, 93 (21.6%) were males and 338 (78.4%) were females, with an overall mean age of 29.2 ± 12.2 years. Age-wise comparison showed that young adolescents aged 16-20 years had significantly higher WBC and fasting insulin compared to older adults. HOMA-IR although not significantly different among age groups, was higher in the young adolescents. Adults in the middle- age group (35-55 years) had significantly higher HbA1c, total cholesterol, triglycerides, LDL-c, VLDL, TG/HDL, TyG index, monocyte/HDL ratio and higher visceral adiposity index compared to younger age-group (Table 1).

Table 2 shows that among the 431 participants aged 16-55 years, only 116 (26.9%) had normal BMI, whereas, 207 (48.0%) were obese with BMI>25 kg/m^2. It was observed that mean age, WHR, WHtR, % body fat and visceral fat were significantly higher in those with grade 1 and grade 2 obesity compared to individuals with normal BMI. Participants with grade 1 and grade 2 obesity also had significantly lower muscle mass. When biochemical measurements were compared, it was observed that fasting blood sugar, fasting insulin, HbA1c, HOMA IR, TG/Glu Index, TG/HDL ratio, Monocyte/HDL ratio and visceral adiposity index were significantly higher in those with grade 2 obesity compared to underweight, normal and overweight participants (Table 2).

Table 3 shows the comparison between anthropometric and biochemical parameters in participants with insulin resistance (HOMA IR>2.0) and HbA1c >5.7. Nearly half of the participants (48.2%, n=208) had HOMA IR>2.0 and 195 (45.2%) had HbA1c>5.7. In these participants, it was observed that mean BMI, WHR, WHtR, % body fat and visceral fat were significantly higher. Also, they had significantly higher levels of triglycerides, TyG index, TG/HDL and visceral adiposity index. In those with insulin resistance, mean HDL-c was significantly lower, while those with higher HbA1c had significantly higher total cholesterol and LDL-C.

Receiver Operating Characteristic (ROC) curves were plotted based on the sensitivity and specificity for TyG index, TG/HDL ratio, monocyte/HDL ratio, visceral adiposity index with HOMA IR and HbA1c (Fig. 1). The ROC analysis showed that for males, the TyG index (AUC 0.685, cut off value 4.41) was the best marker for identifying insulin resistance (HOMA IR>2.5) and identifying those with HbA1c>5.7 (AUC 0.710, cut off value 4.48).

In females, the ROC analysis showed that visceral adiposity index (AUC 0.638, cut off value 3.37) was the best marker for identifying insulin resistance (HOMA IR>2.5) and TyG index was a better marker for identifying those with HbA1c>5.7 (AUC 0.627, cut off value 4.30). Areas under the curve for TyG index, TG/HDL, monocyte/HDL and Visceral adiposity index are shown in Table 4.

Table 5 shows that all the indices i.e. TyG index, TG/HDL, Monocyte/HDL and VAI showed a significant positive correlation with measures of obesity and biochemical measurements and a significant negative correlation with muscle mass and HDL-c levels. However, Monocyte/HDL did not show any significant correlation with fasting insulin and HOMA IR and TyG index did not show a correlation with WBC count.

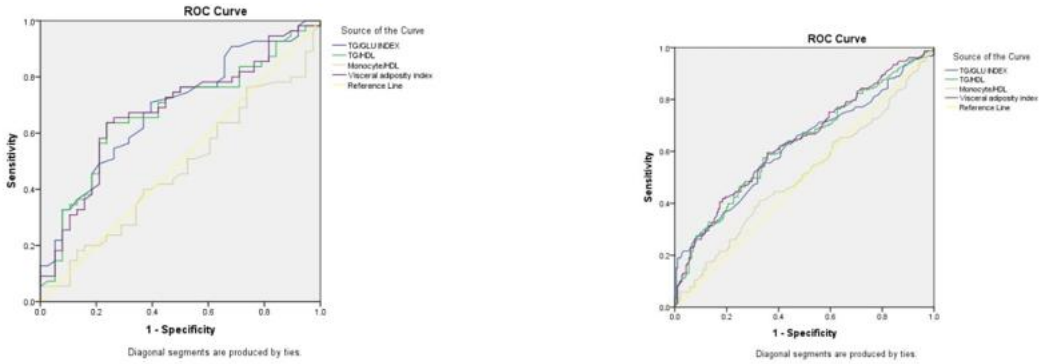

Figure 1.1a: Receiver operating characteristic curve for TyG index, TG/HDL, Monocyte/HDL , visceral adiposity index and Insulin Resistance (HOMA IR>2.5)

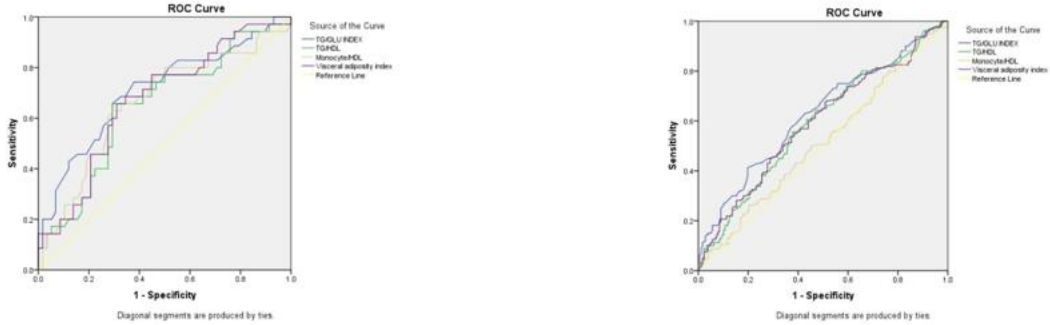

Figure 1.1b: Receiver operating characteristic curve for TyG index, TG/HDL, Monocyte/HDL, visceral adiposity index and HbA1c>5.7

	Gender				Age groups			
	Males (n=93)	**Females (n=338)**	**t**	**p**	**16-20 years (n=151)**	**21-35 years (n=151)**	**35-55 years (n=129)**	**F P**
Haemoglobin	14.4± 1.3	11.9± 1.4	15.111	**0.000**	12.4±1.9	12.3±1.5	12.6±1.7	0.265
WBC	7521± 1739	7739± 1799	-1.042	0.298	7948± 1752	7814± 1871	7249± 1650	**0.003**
Platelet Count	283538± 71650	310887± 78119	-3.041	**0.003**	292980± 80375	312940± 79582	309744± 70180	0.058
Fasting Blood Sugar	87.6± 14.3	86.9± 16.6	0.370	0.712	83.8±10.2	82.6±8.3	95.9±23.5	**0.000**
Fasting Insulin	10.9± 4.6	10.4± 5.7	0.383	0.429	11.8±6.3	10.2±4.7	9.4±5.0	**0.001**
HbA1c	5.4± 0.6	5.5± 0.7	-1.511	0.131	5.35±0.49	5.33±0.50	5.93±0.94	**0.000**
Cholesterol	156.5± 42.3	162.4± 35.0	-1.357	0.175	140.6±27.5	158.7±30.5	187.9±36.5	**0.000**
Triglycerides	103.4± 55.9	97.3± 54.2	0.942	0.347	73.5±32.5	94.0±54.9	133.5±56.9	**0.000**
HDL-C	38.1± 8.3	44.8± 9.8	-6.077	**0.000**	42.0±10	44.2±11.0	44.1±8.1	0.096
LDL-C	101.0± 36.9	101.0± 30.8	0.074	0.941	84.2±24.2	98.4±28.7	122.7±31.7	**0.000**
VLDL	20.1± 10.0	19.1± 9.7	0.916	0.360	14.7±6.5	18.2±8.9	26.1±10.3	**0.000**

HOMA-IR	2.34± 1.09	2.25± 1.38	0.688	0.492	2.5±1.4	2.1±1.0	2.2±1.5	0.051
TG/glucose Index	4.49± 0.27	4.45± 0.28	1.007	0.315	4.3±0.2	4.4±0.2	4.7±0.2	**0.000**
TG/HDL ratio	2.84± 1.67	2.37± 2.0	2.128	**0.034**	1.9±1.1	2.4±2.4	3.2±1.8	**0.000**
Monocyte/HDL ratio	9.43± 4.77	8.37± 4.75	0.939	0.059	5.7±3.0	9.0±5.2	11.6±3.9	**0.000**
Visceral Adiposity Index	3.54± 2.14	4.13± 3.51	-1.530	0.127	2.83± 1.44	3.96± 4.05	5.42± 3.25	**0.000**

Table 1: Mean biochemical measurements and cardio-metabolic indices with respect to gender and age groups.

	BMI Mean (SD)						
	Underweight (<18.50) (n=44)	**Normal (18.50-22.9) (n=116)**	**Overweight (23.0-24.9) (n=64)**	**Obese (25.0-26.9) (n=54)**	**Grade 1 obese (27.0-29.9) (n=67)**	**Grade 2 obese (>30.0) (n=86)**	**P**
Anthropometric Measurements							
Age	20.1(3.5)	23.4(8.3)	28.9(12.0)	33.2(11.9)	33.2(11.9)	36.0(12.7)	**0.000**
WHR	0.76(0.05)	0.78(0.07)	0.81(0.07)	0.81(0.07)	0.84(0.07)	0.82(0.07)	**0.000**
WHtR	0.39(0.03)	0.44(0.04)	0.49(0.03)	0.50(0.03)	0.55(0.04)	0.59(0.06)	**0.000**
% Body fat	19.8(5.3)	27.9(6.4)	34.1(7.2)	36.2(7.0)	38.8(6.7)	45.4(5.0)	**0.000**
Visceral fat	1.06(0.32)	3.04(1.40)	5.92(1.51)	7.82(2.07)	10.42(2.73)	14.82(4.39)	**0.000**
Muscle Mass	30.7(5.0)	32.2(8.2)	30.7(9.3)	28.5(10.7)	31.3(13.1)	26.6(11.7)	**0.005**
Biochemical Measurements							
Fasting Blood Sugar (mg/dL)	82.8(11.0)	82.9(13.1)	86.5(15.5)	87.2(9.9)	89.9(20.6)	92.8(19.4)	**0.000**
Fasting Insulin (Miu/l)	8.0(4.0)	9.3(4.6)	10.3(4.7)	9.5(3.4)	12.2(5.4)	12.9(7.4)	**0.000**
HbA1c	5.4(0.5)	5.4(0.6)	5.5(0.7)	5.3(0.5)	5.6(0.8)	5.8(0.8)	**0.000**
HOMA-IR	1.66(0.88)	1.91(1.00)	2.18(1.03)	2.05(0.82)	2.65(1.14)	2.97(1.97)	**0.000**
TG/glucose Ratio	4.27(0.22)	4.33(0.24)	4.45(0.26)	4.51(0.23)	4.56(0.28)	4.63(0.25)	**0.000**
TG/HDL ratio	1.56(0.94)	1.96(2.43)	2.36(1.37)	2.78(2.04)	2.87(1.48)	3.21(1.68)	**0.000**
Monocyte/HDL ratio	5.14(2.79)	6.90(4.13)	8.51(4.19)	9.93(4.26)	9.30(4.55)	11.34(5.34)	**0.000**
Visceral Adiposity Index	2.37(1.28)	3.13(4.15)	3.83(2.34)	4.45(3.68)	4.52(2.20)	5.46(2.95)	**0.000**

Table 2: Mean anthropometric and biochemical measurements by BMI categories.

	HOMA-IR			HbA1c		
	Normal Insulin (HOMA-IR<2.0) (n=223)	Insulin Resistant (HOMA-IR>2.0) (n=208)	p	HbA1c <5.7 (n=235)	HbA1c>5.7 (n=195)	P
BMI (kg/m²)	23.4(4.9)	26.9(5.2)	**0.000**	24.2(4.9)	26.3(5.6)	**0.000**
WHR	0.78(0.07)	0.82(0.07)	**0.000**	0.80 (0.07)	0.81(0.08)	**0.023**
WHtR	0.47(0.07)	0.52(0.08)	**0.000**	0.48(0.07)	0.52(0.08)	**0.000**
% Body Fat	32.5(10.0)	36.0(9.7)	**0.000**	32.2(9.6)	36.7(9.8)	**0.000**
Visceral fat	6.1(5.0)	8.9(5.4)	**0.000**	6.3(4.7)	8.9(5.7)	**0.000**
Muscle Mass	27.7(7.8)	32.5(11.9)	**0.000**	31.0(10.2)	29.0(10.2)	**0.048**
Fasting sugar (mg/dL)	82.6(8.3)	91.8(20.5)	**0.000**	83.1(8.8)	91.8(20.9)	**0.000**
Fasting Insulin (mIU/L)	6.9(1.7)	14.4(5.5)	**0.000**	9.9(4.8)	11.2(6.2)	**0.021**
HOMA IR	-	-	**-**	2.05(1.02)	2.53(1.58)	**0.000**
HbA1c	5.37(0.51)	5.67(0.85)	**0.000**			
Cholesterol (mg/dl)	159.0(34.1)	163.4(39.3)	0.216	154.1(34.5)	169.5(37.7)	**0.000**
Triglycerides (mg/dl)	87.0(41.3)	111.1(63.6)	**0.000**	89.2(49.8)	110.1(58.0)	**0.000**
HDL-C (mg/dl)	45.2(9.8)	41.4(9.5)	**0.000**	43.2(10.5)	43.6(9.0)	0.686
LDL-C(mg/dl)	98.7(30.1)	102.9(34.1)	0.182	96.0(30.1)	106.6(33.6)	**0.001**
VLDL (mg/dl)	17.1(7.7)	21.6(11.1)	**0.000**	17.4(8.5)	21.4(10.7)	**0.000**
TG/glucose Ratio	4.39(0.23)	4.54(0.30)	**0.000**	4.39(0.24)	4.54(0.30)	**0.000**
TG/HDL ratio	2.07(1.38)	2.90(2.28)	**0.000**	2.27(1.97)	2.72(1.81)	**0.014**
Monocyte/HDL ratio	8.47(4.47)	8.73(5.08)	0.569	8.30(4.64)	9.0(5.0)	0.140
Visceral Adiposity Index	3.36(2.43)	4.69(3.86)	**0.000**	3.58(3.32)	4.51(3.14)	**0.003**

Table 3: Comparison between anthropometric measurements, biochemical parameters and indices of insulin resistance and average glucose.

	Insulin Resistance HOMA IR>2.5				HbA1c HbA1c>5.7			
Variable	**Area**	**95% CI**		**P value**	**Area**	**95% CI**		**P value**
		Lower bound	**Upper bound**			**Lower bound**	**Upper bound**	
In Men								
TG/Glu Index	0.685	0.577	0.794	0.002	0.710	0.597	0.822	0.001
TG/HDL	0.672	0.560	0.783	0.005	0.647	0.531	0.764	0.018
Monocyte/HDL	0.472	0.353	0.590	0.642	0.662	0.544	0.780	0.009
Visceral adiposity Index	0.678	0.567	0.788	0.004	0.670	0.557	0.783	0.006
In Females								
TG/Glu Index	0.621	0.560	0.682	0.000	0.627	0.567	0.686	0.000
TG/HDL	0.629	0.569	0.689	0.000	0.592	0.531	0.653	0.004
Monocyte/HDL	0.508	0.445	0.570	0.806	0.519	0.457	0.580	0.554
Visceral adiposity Index	0.638	0.578	0.698	0.000	0.595	0.534	0.655	0.003

Table 4: Area under the curve of different parameters in predicting insulin resistance and HbA1c >5.7.

	TyG index		TG/HDL		Monocyte/HDL		Visceral adiposity Index	
	r	p	r	p	r	p	R	p
Anthropometric Measurements								
BMI	0.427**	0.000	0.277**	0.000	0.395**	0.000	0.296**	0.000
WHR	0.260**	0.000	0.214**	0.000	0.206**	0.000	0.195**	0.000
WHtR	0.458**	0.000	0.300**	0.000	0.423**	0.000	0.350**	0.000
%Body Fat	0.417**	0.000	0.212**	0.000	0.371**	0.000	0.320**	0.000
Visceral Fat	0.528**	0.000	0.340**	0.000	0.505**	0.000	0.328**	0.000
Muscle mass	-0.288**	0.000	-0.107**	0.000	-0.482**	0.000	-0.190**	0.000
Biochemical Measurements								
WBC	0.093	0.055	0.177*	0.015	0.262**	0.000	0.126**	0.009
Fasting Sugar	0.543**	0.000	0.192**	0.000	0.218**	0.000	0.213**	0.000
Fasting Insulin	0.112*	0.020	0.170*	0.000	-0.008	0.863	0.165*	0.001
HbA1C	0.399**	0.000	0.178**	0.000	0.162**	0.001	0.214**	0.000
Total Cholesterol	0.586**	0.000	0.300**	0.000	0.216**	0.000	0.317**	0.000
Triglycerides	0.910**	0.000	0.904**	0.000	0.459**	0.000	0.890**	0.000
HDL-c	-0.227**	0.000	-0.453**	0.000	-0.351**	0.000	-0.398**	0.000
LDL-c	0.503**	0.000	0.243**	0.000	0.269**	0.000	0.247**	0.000
VLDL	0.935**	0.000	0.921**	0.000	0.418**	0.000	0.911**	0.000
HOMA IR	0.254**	0.000	0.194**	0.000	0.055	0.257	0.198**	0.000

Table 5: Correlation Of TyG index, TG/HDL, monocyte/HDL And VAI with anthropometric and biochemical measurements.

Discussion

Dyslipidaemia and insulin resistance play an important role in development of micro- and macrovascular complications posing a major global health problem. Lipid profile measurements have been used to assess predisposition to cardiovascular diseases on a routine basis. Lipid ratios may be an accepted alternative to associate and identify at-risk individuals, but there is paucity of information regarding the implications of these lipid ratios in cardiovascular associated risk. In the present study, novel indices like TG/HDL cholesterol ratio, TyG index, MHR and VAI were measured and all these indices were found to be significantly higher in those aged 35-55 years compared to younger age groups like 16-20 years and 21-35 years. It was observed that the fasting insulin, WBC count and HOMA IR were significantly higher in the youngest age group studied i.e. 16-20 years. This is of concern, because higher levels of both these markers indicate the start of underlying inflammation at this young age. It indicates that they might be at-risk in future and vulnerable to developing type 2 diabetes as well as cardiovascular diseases. An earlier study by our group on 1313 young adolescents and adults aged 16-25 years, reported that 9.0% (n=118) had higher fasting insulin > 15 m IU/ L and nearly 30.5% (n=400) had stimulated insulin more than 80 m IU/ L [26]. It is important to address that insulin resistance is no longer a concern for only older adults but is showing up more and more in younger people.

In the present study, we observed that TyG index, TG/HDL ratio and VAI were significantly higher in those with HOMA IR > 2.0 and HbA1c >5.7. There are not many studies looking at TyG index, TG:HDL ratio, MHR and VAI in the Indian population. It is important to study these novel markers particularly for Asian population because of the variability in their body phenotypes, propensity towards lower HDL levels, a higher body fat percentage, a prominent abdominal obesity, a higher intramyocellular lipid and/or a higher liver fat content compared to Caucasians [27]. Cut offs established for Caucasians may not be appropriate for Asian population which are at much higher risks of cardiovascular diseases.

In the present study, the diagnostic accuracy of these novel tools of measurement of insulin resistance were compared to HOMA-IR, which is a recognised measurement of IR as well as with HbA1c. TyG index is a surrogate marker for insulin resistance and elevated TyG index is positively associated with increased arterial stiffness and increased incidence of diabetes, CE, stroke and all-cause and cardiovascular mortality [28]. In this study, the TyG index was the best marker for identifying insulin resistance (HOMA IR>2.5) in men (AUC 0.685, cut off value 4.41) and also for identifying those with HbA1c>5.7 in men (AUC 0.710, cut off value 4.48) and female (AUC 0.627, cut off value 4.30). In a Prospective Urban Rural Epidemiology (PURE) on 141243 individuals

aged 35-70 years from 22 countries particularly, Low-Income Countries (LICs) and Middle-Income Countries (MICs), the highest tertile of the TyG index was associated with increased hazards for the composite outcome, cardiovascular mortality, myocardial infarction, stroke and incident diabetes [29]. In a large cross-sectional study of apparently healthy individuals in Mexico, the pearson correlation between TyG index and HOMA-IR (r =0.322) was higher than correlation between HOMA-IR and hyper triglyceridemic. Further, reducing the cut point of TyG to 4.60 increases the sensitivity to 91.3%, improving the validity of the test for the early detection of subjects with insulin resistance [16]. In a study on 4820 patients of the Vascular-Metabolic CUN cohort (VMCUN cohort), reported that the TyG index had better predictive power (AUC: 0.75, 95% CI 0.7-0.81) in diagnosing subjects with DM than Fasting Blood Glucose (FBG) measurement (AUC: 0.66, 95% CI 0.60-0.72) and TG levels (AUC: 0.71, 95% CI 0.65-0.77) and therefore, this may help to identify individuals at risk of developing DM in the future so that early interventions can be provided [30]. TyG index and its related parameters like TyG-BMI, TyG-WC, TyG-WHpR and TyG-WHtR can be used as a predictor in identifying diabetes mellitus along with IDRS score assessment in low-cost clinical settings like primary healthcare centre [31].

Visceral adiposity index (AUC 0.638, cut off value 3.37) was the best marker for identifying insulin resistance (HOMA IR>2.5) in females. Over the last few years, VAI derived from anthropometric and biochemical measurements has gained importance. VAI is a simple clinical algorithm developed as a surrogate marker for characterizing Visceral Adiposity Dysfunction (VAD) and can be used for initial screening to replace expensive Magnetic Resonance Imaging (MRI). It is important to evaluate its merit in predicting the Cardiometabolic Risk (CMR) in apparently healthy population and in the current study it showed a better indicator to diagnose insulin resistance in women. Although VAI was modelled in Caucasian population, several studies have been carried out in different races (Chinese, Sicilian, Japanese and Caucasians) to explore and validate VAI cut -offs in determining metabolic risk. However, there are very few studies done in context to the Indian population. In the present study the mean VAI for males was 3.96(4.05) and for females was 5.42(3.25). In another cross-sectional study on South Asian population, it was observed that mean VAI in males was 3.49 (0.85) and that for females was 1.53 (1.01) [32]. In another study, it was observed that VAI cut-off of 2.0 predicted VAD with sensitivity and specificity of 73.21% and 71.23% respectively [33].

The physiological functions of insulin are to inhibit the release of free fatty acids from adipose tissue and promote the storage of triglycerides in adipocytes. However, in insulin resistance, this mechanism is hampered and the FFA are released into the bloodstream because of unchecked lipolysis. Also, the excess FFA in the liver increases triglyceride production, packaging them into Very Low-Density Lipoprotein (VLDL) particles, resulting in hypertriglyceridemia [34-36]. Additionally, HDL levels decrease because of the increase in catabolism of HDL particles, partly due to the heightened activity of hepatic lipase, an enzyme that hydrolyzes HDL triglycerides and phospholipids [37]. This may lead to rapid clearance of HDL from circulation. Also, it has been hypothesized that this subfraction of LDL, particularly small dense LDL (sdLDL), possesses increased atherogenic potential [38]. However, small dense Ldl-c is not routinely done in lipid profile because of the laborious and complex technique and cannot be done on a large sample. It has been observed that in patients with diabetes mellitus or metabolic syndrome, sdLDL has been associated with high triglycerides [39]. A ratio of Triglyceride/High-Density Lipoprotein Cholesterol (TG/HDL-C) ratio showed a strong correlation with Insulin Resistance (IR) and central obesity, both of them being aspects of the MetS, which can enhance the risk of CVD. Also, it has been reported that triglyceride/HDL ratio > 2 on translation into the presence of small dense lipoproteins (sdLDL), help us measure global lipid risk regardless of LDL levels [40]. In the present study, 10.7%(n=46) males and 44.1% (n=190) females had TG/HDL above the cut off value (Men 2.6, female 1.7) and the mean ratio in males was 2.84± 1.67 and that in females was 2.37± 2.0 both above the cut off value, which is of concern [23]. Also, TG/HDL showed a significant correlation with indices of overall and central adiposity and with fasting sugar and insulin as well as lipid profile.

It was observed that fasting blood sugar, fasting insulin, HbA1c, HOMA IR, TG/Glu index, TG/HDL ratio, Monocyte/HDL ratio and visceral adiposity index were significantly higher in those with grade 2 obesity compared to underweight, normal and overweight participants and showed a strong significant positive correlation with measures of overall and central adiposity. Studying these markers with respect to obesity can be helpful to understand the patients inflammatory state and also their risk for insulin resistance and cardiovascular health. It is well known that with higher fat mass accumulation, there is a higher frequency of atherogenic lipid profile, diabetes mellitus, metabolic syndrome and arterial blood pressure. Central adiposity, visceral fat plays a key role in insulin resistance because adipocytes are more hormonally and metabolically active and regulate numerous signal pathways. It has been observed that VAI shows a strong positive correlation with peripheral glucose utilization during euglycemic hyperinsulinemic clamp and seems to be independently associated with cardio- and cerebrovascular events

[26]. In Caucasians, VAI has shown a strong independent association with both cardiovascular [odd ratio (95% CI): 2.45 (1.52-3.95)] and cerebrovascular events [odd ratio (95% CI): 1.63 (1.06-2.50] [21]. Studies have reported that VAI showed good predictive power regarding the visceral adiposity-related risk of type 2 diabetes and hypertension [41-44]. A recent study reported a strong significant association of TyG with BMI, WHR, WHtR and further stated that assessment of TyG, TyG-WC, TyG-BMI and TyG-WHtR can predict the risk of hypertension among middle-aged and elderly individuals [45]. One of the Indian studies on South Indians observed that mean values of HOMA-IR, TyG index, TG:HDL ratio and Lipid Accumulation Product (LAP) was significantly higher in patients with MetS than in patients without MetS [46].

The gold standard method to measure IR is by use of the hyperinsulinemic euglycemic clamp, rarely performed because of its complexity, invasiveness, time- consumption [47,48]. This technique is also cumbersome and need high technical expertise and high costs. Therefore, lipid-based indices confer the advantage of being based on a fasting lipid profile and anthropometric measurements. This study studied the TG/Glu Index, TG/HDL ratio, Monocyte/HDL ratio and visceral adiposity index in 431 individuals spread over a wide age range from 16-55 years and is one of the largest studies looking at these indices in an Indian population.

Conclusion

Lipid-based indices such as TyG index, TG:HDL ratio, monocyte: HDL ratio and visceral adiposity index are novel biomarkers of IR and cardiometabolic risks which additionally show a strong correlation with measures of overall and central adiposity. TyG index and visceral adiposity index better predicts those with insulin resistance as well as those with HbA1c above 5.7 i.e. in prediabetic range and above particularly in urban population. Therefore, these indices can be used in routine clinical practice for early diagnosis of IR and timely interventions for primary prevention.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Financial Disclosure

This paper is from the data collected during screening for clinical trials which were supported by Almonds Board of California.

Authors Contributors

All the authors have made contributions in their own way.

Acknowledgment

The authors thank the investigators, coordinators and participants who participated in this study.

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