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Original article

The waist-height ratio is a potential anthropometric index of insulin resistance: Observations based on oral glucose tolerance test in lean, normo-glycaemic, Asian Indian males from Southern India

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ABSTRACT

Aims: To correlate the waist-to-height ratio (WHt-R) with Matsuda index of the Oral Glucose Tolerance Test (OGTT) and other surrogate indices of fasting insulin resistance/sensitivity and to derive a cut-off value for the WHt-R in lean, normoglycaemic males from Southern India.

Methods: A cohort of 105 lean, normoglycaemic males (mean BMI: 19.2 ± 2.6 kg/m^2) underwent OGTT. Surrogate indices of insulin resistance *viz,* the Homeostatic model assessment of Insulin Resistance (HOMA-IR), the Quantitative Insulin sensitivity Check Index (QUICKI), the Fasting glucose to insulin ratio (FG-IR), the McAuley's index and the Triglyceride/HDL-C ratio were correlated with the Matsuda and the Insulinogenic indices. The cut-off value for WHt-R to predict insulin resistance was obtained using Receiver operating characteristics (ROC) with Area under curve (AUC) at 95% confidence interval (CI). The P value < 0.05 was considered statistically significant.

Results: The ROC analysis at 95% confidence interval (CI), showed an AUC of 0.58 for the WHt-R cut-off value $\geq$ 0.39 with 69.4% sensitivity and 57.1% specificity. On pooled ROC analysis, significantly higher AUC was observed for the WHt-R (0.90) when compared to BMI (0.83) and waist-to-hip ratio (0.83). Paired wise comparison analysis of ROC curves revealed significant differences for AUC of WHt-R when compared to waist circumference ($p < 0.01$), but not for BMI and WHR.

Conclusion: The WHt-R can be used as a potential anthropometric index to screen for insulin resistance, when compared to BMI and WC in lean, normoglycaemic males from Southern India.

1. Introduction

The South Asian ethnicity is unique for its high propensity to develop insulin resistance when compared to the White Caucasians. Insulin resistance and its related metabolic disturbances are major contributory factors to the higher risk for type 2 diabetes mellitus (T2DM) and its associated morbidity and mortality in South Asians.[1] The prevalence of insulin resistance is higher in Asian Indians and South Asians residing across the globe. Notably, variable degrees of insulin resistance are prevalent even in lean, non-diabetic Asian Indians. Lean Asian Indians have elevated fasting insulin, triglyceride, adiponectin, higher body fat percentage, and lower leptin levels, when compared to other South Asian ethnic groups.[2,3] Numerous studies using anthropometric indices in obese subjects have demonstrated the relationships of total and/or regional adiposity to insulin resistance and metabolic abnormalities.[4] However, such studies done specifically in individuals of low body mass index (BMI) are sparse.

Anthropometric indices such as Body Mass Index (BMI), waist circumference (WC), neck circumference, waist-to-hip ratio (WHR) are universally used in population based studies for the non-invasive

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estimation of whole body obesity and abdominal obesity, irrespective of their metabolic status.[5] The structural and biochemical characteristics of subcutaneous and visceral adipose tissue depots are dissimilar between non-obese and obese subjects, leading to differentials in metabolic risk between lean and obese individuals. In this regard, anthropometric indices need to be validated in lean and obese subjects, as there is wide phenotype and metabolic variation amongst such phenotypes, and BMI has limited accuracy for the prediction and identification of fat distribution.

WHR is a robust predictor of acute myocardial infarction and insulin resistance, especially in South Asians.[6] However, the WHR is limited in its predictive accuracy for metabolic risk in an individual, as it does not account for the height of an individual and the WHR may potentially lead to a discrepant risk ratio for tall and short individuals.[7] In this scenario, the waist-to-height ratio (WHt-R) has been proposed to be a better anthropometric index to determine the cardiometabolic risk and abdominal obesity with respect to the height of an individual.[7]

Notably, the WHt-R has not been validated in individuals with low BMI (BMI < 20 kg/m^2), against established standards such as the oral glucose tolerance test (OGTT), and other surrogate indices of fasting insulin resistance based on biochemical variables. Secondly, appropriate cut-off values for the WHt-R need to be defined in low BMI individuals to screen them for risk of developing insulin resistance in future. The receiver operating characteristic (ROC) with Area under curve (AUC) is a universally used method to test the ability of an index to discriminate whether a specific risk factor is present or not. An AUC of 0.50 indicates that a test represents no discriminating ability while an AUC of 1.0 indicates that a test has robust discrimination,[8] with optimal sensitivity and specificity for a cut-off value nearest to the top-left most corner of the ROC curve.[9]

In a recent prospective cohort study from Vellore, India, it has been reported that weight gain relative to height during childhood or adolescence was associated with an adverse cardiovascular disease risk profile in adulthood.[10] In the current study, we compared the predictive accuracy of WHt-R, against BMI, WHR, and correlated the WHt-R against surrogate indices of insulin resistance. Furthermore, we derived cut-off value for the WHt-R with optimal sensitivity and specificity for prediction of risk of insulin resistance in normoglycaemic Asian Indian males with low BMI.

2. Methodology

The data for this study was obtained retrospectively from a previous cohort study entitled *"Born with low birth weight in rural Southern India: what are the metabolic consequences 20 years later?*[11] The study was approved by the institutional review board (IRB) for ethics in research on humans at the Christian Medical College (CMC), Vellore, India (Research Committee Minute Number: 13348/RETRO/28/08/2020). The sample size was calculated using the formula

$$n = \frac{Z^2_{1-\alpha/2} p(1-p)}{d^2}$$

wherein n denotes number of participants, p denotes expected proportion, d denotes absolute precision and 1 -α/2 denotes desired level of confidence interval. The sample size for this study was calculated as a minimum of 91 subjects with absolute precision of 0.70 with an anticipated standard deviation of 3.41 at 95% confidence interval. This study is exclusively based on male subjects who were recruited from the birth registry at the Community Health and Development (CHAD) programme, Christian Medical College (CMC), Vellore, India. The participants were identified from 23 randomly selected villages in Vellore district, Tamilnadu, Southern India. Briefly, a cohort of 105 lean men aged between 18 and 22 years, were recruited for the study with informed written consent. The primary study was exclusively on male subjects with an intent to look at body composition in a single group. The variables of body composition differ between males and females and therefore females were not recruited as per the study design. The objectives of the study methodology were explained to the participants in the local language and informed written consent was obtained. Participants diagnosed with pre-diabetes, impaired glucose tolerance, infectious diseases, other ailments or those unwilling to participate (n = 12) were excluded from the study as per protocol.

All the participants underwent anthropometric and biochemical assessment, followed by an Oral Glucose Tolerance Test (OGTT) after an overnight fast lasting 8 hours. Blood samples for biochemical estimation of plasma insulin, C-peptide and glucose were drawn at baseline, 30, 60 and 120 min of the OGTT. Subjects were classified as normal glucose tolerant or impaired glucose tolerant according to the American Diabetes Association (ADA) criteria (Fasting plasma glucose $\geq$ 7.0 mmol/l or 2 hours plasma glucose $\geq$ 11.1 mmol/l and impaired glucose tolerance (IGT) between $\geq$7.8 and $<$11.1 mmol/l). Plasma glucose levels was measured by the glucose oxidase-peroxidase method using reagents supplied by Roche, on Roche Modular P 800 system (Coefficient of Variation(CV:3.6%). Serum insulin and C-peptide levels were measured by the chemiluminescence method using the IMMULITE 2000 system (Siemens healthcare Diagnostic products Ltd., Llanberis, Gwynedd, UK). For the insulin and C-Peptide assays, controls supplied by Bio-Rad were used as internal precision controls (CV): 10.2% for insulin and 3.7% for C-peptide).[11] The following surrogate indices were calculated by using specific formulae mentioned below:

1. Homeostasis model for assessment of insulin resistance (HOMA-IR): Fasting glucose (mmol/L) × fasting insulin (mU/L)/22.5 [12]
2. Quantitative Insulin sensitivity Check Index (QUICKI): 1/[log fasting insulin (mU/L) + log fasting glucose (mg/(mg/dL)][13]
3. Fasting Glucose- Insulin ratio (FG-IR): Fasting glucose (mg/dL)/ Fasting insulin (mU/L)[14]
4. Triglyceride-HDL-C ratio: Triglyceride (mg/dL)/HDL-C (mg/dL)[15]
5. McAuley's index: = exp[2.63−0.28 x (fasting insulin in μU/ml)− 0.31x (fasting triglycerides in mmol/l)[16]
6. Matsuda index, Insulinogenic index and disposition index were calculated online from the weblink http://mmatsuda.diabetes-smc.jp/MIndex.html, based on formulae mentioned below:
   a. Matsuda index: $10000/\sqrt{(\textit{fasting glucose x fasting insulin})(\textit{mean glucose x mean insulin})}$
   b. Insulinogenic index: (Ins30 − Ins0)/(Gluc30 − Gluc0) or ΔIns0–30/ΔGlu0–30, where Insy and Gluy represent values at time (y: min) during the OGTT[17]

2.1. Statistical analysis

Continuous data were summarized as Mean ± standard deviation (SD) or median with interquartile ranges. Pearson's correlation analysis was performed with the waist-height ratio as the dependent variable against independent variables namely BMI, WHR and WC. Receiver operating characteristic (ROC) with area under curve (AUC) analysis was used to assess the ability of the WHt-R to diagnose insulin resistance. P values < 0.05 were considered as statistically significant.

3. Results

The mean values of fasting, post prandial glucose levels and fasting lipid profile were in normal range. Amongst surrogate indices of insulin resistance, the mean ± SD was significantly higher for fasting glucose to insulin ratio (FG-IR) when compared to HOMA-IR and QUICKI. Amongst triglyceride based surrogate indices, the mean ± SD was significantly higher for the McAuley's index than the triglyceride to HDL ratio. The mean value of the Matsuda index was higher when compared to the insulinogenic index (Table 1). On OGTT, the mean glucose, insulin and

Table 1
Baseline characteristics of the cohort.

Variables (n = 105)	Mean ± SD	Median with IQR
Age (years)	19.7 ± 0.9	20 (19, 20)
BMI (kg/m^2)	19.2 ± 2.6	19 (17.5, 20.4)
Waist circumference (cm)	70.1 ± 7.7	68 (65, 73)
Waist-hip ratio (WHR)	0.82 ± 0.04	0.82 (0.80, 0.86)
Waist-height ratio (WHt-R)	0.4 ± 0.04	0.40 (0.38, 0.43)
Fasting glucose (mg/dL)	87.7 ± 6.3	89 (83, 92)
Fasting insulin (pmol/L)	6.5 ± 13.4	1.1 (2, 5.2)
Fasting C-peptide (ng/mL)	1.8 ± 3.4	1.1 (0.7, 2.2)
Post prandial blood glucose (mg/dL)	102.3 ± 22.3	101 (90, 114)
Post prandial Insulin (pmol/l)	40.4 ± 35.2	30 (16.4, 52.2)
Post prandial C- peptide (ng/mL)	5.1 ± 3.0	5.1 (2.6, 7.1)
Total cholesterol (mg/dL)	131.5 ± 31.1	130 (114, 146)
Low density lipoprotein cholesterol (mg/dL)	81.2 ± 25.5	78 (68,92)
High density lipoprotein cholesterol (mg/dL)	31.4 ± 7.2	31 (28, 34)
Serum Triglycerides (mg/dL)	82.8 ± 41.2	74 (58, 103)
Indices of insulin sensitivity/resistance		
Fasting glucose insulin ratio	35.8 ± 32.1	23.4 (15.3, 41.7)
HOMA-IR	1.0 ± 0.8	0.8 (0.4, 1.2)
QUICKI (index of insulin sensitivity)	0.4 ± 0.07	0.4 (0.3,0.44)
McAuley's index	6.6 ± 1.9	6.4 (5.2, 7.6)
Triglyceride/HDL ratio	2.6 ± 1.2	2.4 (1.8, 3.3)
Surrogate indices on OGTT		
Matsuda index	10.2 ± 7.4	8.3 (5.4, 13.2)
Insulinogenic index	1.2 ± 1.5	0.9 (0.5, 1.4)

Values are presented as Mean ± SD. Median values are presented with 25th and 75th IQR.
HOMA-IR: Homeostatic Model Assessment of Insulin Resistance.
QUICKI: Quantitative Insulin sensitivity Check Index.
IQR: Interquartile range.

C-peptide levels were higher at 30 min when compared to the mean values at 60 and 120 min (Table 2). The correlation statistics demonstrated highly significant, positive correlation of the WHt-R with BMI, waist circumference (WC) and the waist-hip ratio (WHR). Amongst the surrogate indices of fasting insulin resistance, WHt-R demonstrated a significant negative correlation with FG-IR, QUICKI and McAuley's index. Significant negative correlation was noted for the WHt-R with Matsuda index but not with the insulinogenic index (Table 3). The ROC analysis at 95% confidence interval (CI), showed an AUC of 0.58 for the WHt-R cut-off value $\geq$ 0.39 with 69.4% sensitivity and 57.1% specificity (Positive predictive value (PPV): 10.5 and Negative predictive value (NPV): 96.5 (Fig. 1). Based on the Matsuda index cutoff value $\leq$ 2.5 to define insulin sensitivity, the proportion of individuals classified as insulin resistant (*i.e.* Matsuda index value > 2.5) was lower (n = 30; 28.5%) in comparison to the proportion of insulin sensitive individuals (n = 75%; 71.4%). On pooled ROC analysis, a significantly higher ($p < 0.05$) Area Under Curve (AUC) was observed for the waist-height ratio (0.90) when compared to BMI (0.83) and waist-to-hip ratio (0.83)

Table 2
Glucose, insulin and C- peptide levels at specific time points on OGTT.

Variables	Mean ± SD	Median with IQR
0 min Glucose (mg/dL)	88.2 ± 15.7	89 (85, 95)
30 min Glucose (mg/dL)	150.3 ± 27.6	150 (132, 223)
60 min Glucose (mg/dL)	126.2 ± 36.1	122 (97,149)
120 min Glucose (mg/dl)	100.3 ± 21.0	100 (90, 113)
0 min Insulin (pmol/L)	5.0 ± 5.0	3.7 (2.1, 5.9)
30 min Insulin (pmol/L)	63.5 ± 41.2	58.6 (34.7,83.2)
60 min Insulin (pmol/L)	57.6 ± 40	45.3 (78, 222)
120 min Insulin (pmol/L)	37.9 ± 30.7	30 (16, 48)
0 min C- peptide (ng/mL)	1.8 ± 3.3	1.3(0.8, 2.2)
30 min C-peptide (ng/mL)	5.7 ± 3.2	5.4 (3.2,7.0)
60 min C- peptide (ng/mL)	5.6 ± 3.0	5.8 (3.7, 7.0
120 min C-peptide (ng/mL)	5.2 ± 3.0	5.2 (3.1, 7)

HOMA-IR: Homeostatic Model Assessment of Insulin Resistance.
QUICKI: Quantitative Insulin sensitivity Check Index.
IQR: Inter-quartile range.

Table 3
Correlation of waist-height ratio with anthropometric measures and surrogate indices of insulin sensitivity/resistance.

Variables	*Correlation coefficient*	*P* value
Body mass index (kg/m^2)	0.81	<0.001
Waist-hip ratio (WHR)	0.60	<0.01
Waist circumference (WC)	0.89	<0.01
TG/HDL ratio	0.17	0.07
HOMA-IR	−0.07	0.43
QUICKI (index of insulin sensitivity)	−0.25	<0.01
Fasting glucose-insulin ratio (FG-IR)	−0.25	<0.01
McAuley's index	−0.28	<0.01
Surrogate indices on OGTT		
Matsuda index	−0.27	<0.05
Insulinogenic index	0.06	0.47

P value < 0.05: Statistically significant.
HOMA-IR: Homeostatic Model Assessment of Insulin Resistance.
QUICKI: Quantitative Insulin sensitivity Check Index.
TG/HDL ratio: Triglyceride/High density lipoprotein cholesterol ratio.

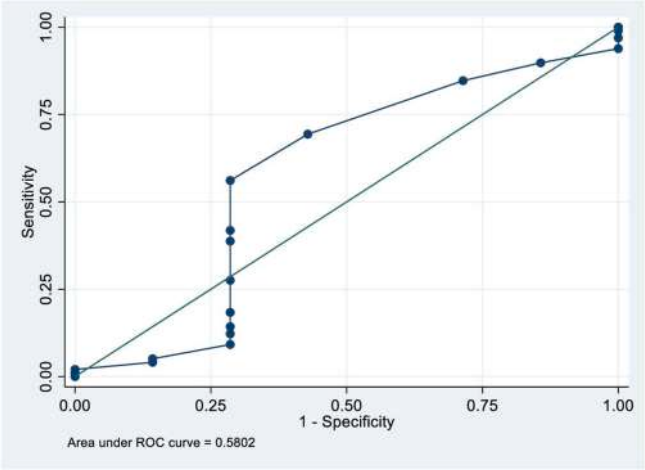

Fig. 1. Receiver Operator Characteristic (ROC) Area under curve (AUC) for WHt-R cut-off value.

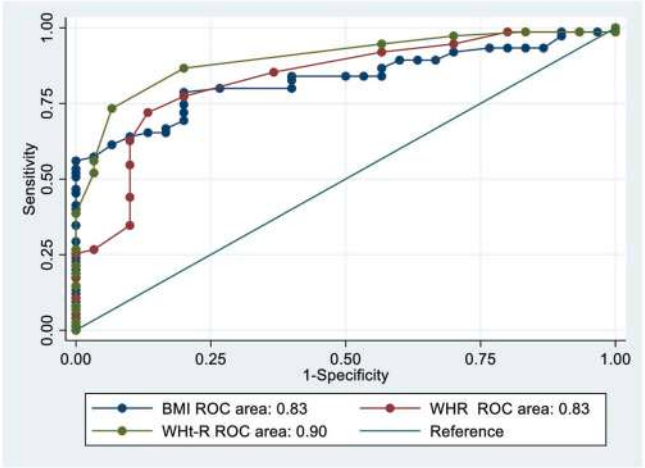

Fig. 2. Pooled receiver operator characteristic (ROC) area under curve (AUC) for WHt-R with BMI and WHR

(Fig. 2). Paired wise comparison analysis of ROC curves revealed significant differences for AUC of waist-height ratio only when compared to waist circumference ($p < 0.01$).

4. Discussion

The WHt-R is a simple anthropometric index to predict insulin resistance and cardiovascular risk in young individuals.[18] In this study on normoglycaemic individuals with low BMI, we have demonstrated the waist-to-height ratio (WHt-R), to have a better predictive accuracy for risk of insulin resistance in the future, when compared to BMI, and WHR. We observed a significant negative correlation of WHt-R with surrogate indices of insulin resistance namely FG-IR, and QUICKI (both as surrogate measures of insulin sensitivity) suggesting the existence of insulin resistance of a certain degree in the study cohort. However, in a cross sectional study in normal weight, (mean age: 33.5 ± 9.1 years, mean BMI: 22.6 ± 1.5 kg/m^2), normoglycaemic men, a significantly positive correlation was noted for the WHt-R with the triglyceride-HDL ratio and the triglyceride-glucose index.[19] However, in this study, we did not observe any significant correlation of the WHt-R with the triglyceride-HDL ratio, despite the mean TG/HDL ratio (2.6 ± 1.2) in our study being higher than the former,[19] probably due to significant differences in mean age and BMI. It may be noted that in the former study, the WHt-R was not validated against surrogate indices such as HOMA-IR, FG-IR, Matsuda index or the disposition index. We have addressed this lacuna in the current study in normoglycaemic Asian Indian males from southern India.

An ethnicity-specific validation of any surrogate index against an established index is essential prior to its application in population-based studies.[20] The Matsuda index is an indirect measure of hepatic and peripheral insulin sensitivity calculated from fasting and post prandial insulin and glucose values of the OGTT and has been validated against the gold standard Hyperinsulinemic-euglycaemic clamp. The insulinogenic index is a measure of beta cell function in the pancreas. It is a composite index calculated from insulin and glucose values at specific time points from an OGTT and remains constant in individuals with normal glucose tolerance.[21] We correlated the WHt-R against the Matsuda and the insulinogenic index derived from OGTT and noted a significant negative correlation for the WHt-R with Matsuda index, but not with the insulinogenic index.

An earlier study validated the WHt-R against two-sample OGTT and lipid profiles, and demonstrated better predictive accuracy of WHt-R for diabetes and hypertension, when compared to BMI and WHR.[22] However, the WHt-R was not correlated with plasma insulin and glucose-based indices such as HOMA-IR, Matsuda index, QUICKI and FG-IR. Furthermore, the cut-off values for WHt-R to predict the risk of diabetes and hypertension were not derived.

The results from a meta-analysis across different ethnic groups have shown a superior predictive accuracy of the WHt-R for cardiometabolic risk in comparison to BMI and WC. Specifically, the WHt-R had up to 5% higher predictive accuracy for risk of diabetes, hypertension, cardiovascular diseases (CVD), in comparison to BMI and WC. The AUC for WHt-R to predict the risk of diabetes, hypertension and cardiovascular diseases were 0.70 and 0.72 in men and women respectively.[5] In population based studies, anthropometric indices with predictive accuracy ranging between 60% and 70% are considered as ideal screening indices.[5]

In this study, the WHt-R predictive cut-off value ≥ 0.39 with 69.4% sensitivity and 57.1%, was lower when compared to the WHt-R cut-off value of ≥ 0.50 from a cross sectional study on metabolic syndrome and cardiometabolic risk factors from North India.[7] The differences in the cut-off values are plausible as our study included young, normoglycaemic individuals with a low BMI (≤ 20 kg/m^2), whereas the former study[8] included non-obese subjects (BMI ≤ 25 kg/m^2) with metabolic syndrome. The mean BMI and WC were 24.3 ± 4.1 kg/m^2 and 89.6 ± 11 cm in males and 25.2 ± 4.7 and 82.8 ± 12.4 cm in females in the former, were significantly higher when compared to the mean BMI and WC of individuals in our study, leading to the lower cut-off for WHt-R.

In a cross-sectional study on children aged between 4 and 18 years of age, the WHt-R cut-off value ≥ 0.5 was predictive of dyslipidemia and insulin resistance. Specifically, normal weight children with WHt-R ≥ 0.5 were 1.66, 2.01, 1.47 and 2.05 times more likely to have elevated levels of LDL cholesterol, low HDL cholesterol, high triglycerides and insulin, respectively.[23] In a population-based study in Korean adolescents aged between 10 and 19 years, it has been demonstrated that the WHt-R was significantly associated with cardiovascular risk factors, despite adjustment for confounders. Specifically, in normal weight adolescents, the prevalence of multiple cardiometabolic risk factors were 7.9% in those with the WHt-R ≤ 0.5, whereas it was 17.8% in those with WHt-R ≥ 0.5 ($p < 0.05$). Moreover, the prevalence of metabolic syndrome was higher in those with WHt-R ≥ 0.5 than in those with WHt-R < 0.5 in both non-overweight and overweight adolescents (both: p value < 0.001).[24] In the current study on lean, normoglycaemic males from Southern India, the WHt-R cutoff value ≥ 0.39 with 69.4% sensitivity and 57.1%, is significantly lower than the former and would be ideal in view of the high propensity of this ethnic group to develop insulin resistance at an early age, when compared to other ethnic groups.

The mean value of Matsuda index derived from OGTT in the current study (10.2 ± 7.4) is comparable to an earlier study on young Asian Indians with diabetes and normoglycaemic individuals (age: 21.5 ± 3.7 years). The Matsuda index mean value (10.2 ± 4.5) in individuals with normal glucose tolerance and high visceral fat was significantly higher than the mean value in subjects with normal glucose tolerance and normal visceral fat.[25] In the current study, we classified insulin sensitivity individuals based on a cut-off value < 2.5 of the Matsuda index when compared to the cut-off value < 4.3 established previously in a Japanese cohort.[26] We validated the cut-off value for WHt-R ≥ 0.39 against the Matsuda index cut-off value < 2.5 and have shownthe utility of WHt-R as an ideal index to screen for insulin resistance in individuals with low BMI. Using the lower cut-off value for WHt-R in this cohort, we classified thirty participants (28.5%) as insulin resistant, irrespective of their BMI.

Surrogate indices such as BMI and WHR may be deceptive in lean and normal weight individuals. In such cases, the WHt-R is an ideal index to predict metabolic risk due to abdominal adiposity.[27] Currently, the cut-off values for BMI, WC and WHR[28] do not discriminate between individuals based on their height. In such cases, the WHt-R is the ideal anthropometric index to screen for metabolic risk especially in lean individuals. The observations in low BMI (≤ 20 kg/m^2) normo-glycaemic, lean Asian Indian males in the current study, demonstrate better predictive accuracy of the WHt-R to screen for risk of insulin resistance, when compared to BMI and WC. We have derived a population specific cut-off value for the WHt-R and validated against the Matsuda index derived from the OGTT. Using the Matsuda index cutoff value ≤ 2.5 derived in this study, 28.5% of the normoglycaemic individuals were classified to be at risk of developing insulin resistance. These individuals need to be evaluated prospectively for manifestation of features of metabolic syndrome. Life style modification, increased physical activity and healthy dietary interventions will be the first line of therapy in such individuals.

5. Merits and limitations of the study

Firstly, this cross-sectional study was done in homogenous group of young, normoglycaemic and lean male subjects from Southern India. We derived a cohort specific WHt-R cut-off value and the Matsuda index cutoff value ≤ 2.5, which can be applied in prospective studies to screen low BMI individuals for insulin resistance. The limitations of the study are acknowledged. As this study is based in an exclusive cohort of males, gender-based comparisons could not be made with females. In this scenario, studies on representative samples of males and females across varied age groups, BMI and metabolic status, from different parts of India are required to ascertain the validity of the WHt-R over BMI, WC and WHR and to derive population specific cut-off values for the WHt-R. In addition, prospective studies would be required in the same cohort to study the changes in metabolic status with respect to age and BMI.

Author's contributions

SA and FJ conceptualized, performed the study and drafted the manuscript, DMP analysed and interpreted the data, MEK contributed to discussion, GF supervised the biochemical assays, VR and NT supervised the study, SA, FJ and NT reviewed and edited the manuscript.

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Declaration of competing interest

The authors have no conflicts of interest to disclose.

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