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Original Article

Differential performance of surrogate indices of fasting insulin resistance in low-birthweight and normal-birth weight cohorts: Observations from Hyperinsulinaemic-Euglycaemic clamp studies in young, Asian Indian males

Riddhi Dasgupta [a, *], Shajith Anoop [a], Padmanaban Venkatesan [a], Mercy Inbakumari [a], Geethanjali Finney [b], Nihal Thomas [a, b]

[a] Department of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore (CMC), India
[b] Department of Biochemistry, Christian Medical College, Vellore, India

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ABSTRACT

Aim: To evaluate the predictive accuracy of surrogate measures of fasting insulin resistance/sensitivity like the Homeostasis model assessment for insulin resistance (HOMA −IR), Fasting glucose/insulin ratio (FG-IR), Quantitative insulin sensitivity check index (QUICKI), and the 20/fasting C peptide x fasting plasma glucose [20/(FCP × FPG)] index in comparison to M value derived from hyperinsulinaemic-euglycaemic clamp (HEC) studies in two birth weight based cohorts of Asian Indian males.
Methods: HEC studies were performed in non-diabetic Asian Indian males (n = 117), born of normal birth weight (n = 59, birth weight > 2.5 kgs) and low birth weight (n = 58, birth weight < 2.5 kgs). Anthropometry and biochemical analysis were done. Surrogate indices of fasting insulin resistance were calculated and data were analysed by Pearson's correlation and Random calibration model analysis.
Results: Amongst surrogate indices of fasting insulin resistance/sensitivity, the mean values for HOMA-IR, QUICKI, FG-IR, 20/(FCP × FPG) index and M value were similar between the two groups. Significant positive correlation was observed for FG-IR and QUICKI with M value (the gold standard measure of insulin sensitivity derived from HEC procedure) in the low birth weight cohort in contrast to the normal birth weight cohort, wherein no significant correlation was observed for any of the indices. Random calibration model analysis showed highest predictive accuracy for QUICKI in both the study groups.
Conclusion: The QUICKI index showed highest predictive accuracy in the normal birth weight and the low birth weight cohorts of Asian Indian males.

1. Introduction

Insulin resistance is a pivotal factor associated with the onset of metabolic syndrome, type 2 diabetes mellitus (T2DM) and cardiovascular diseases in South Asians, especially Asian Indians. Across populations worldwide, low birth weight is associated with an increased risk of insulin resistance and T2DM, irrespective of socioeconomic status [1]. As compared to other countries, nearly 30% of Asian Indian infants are born with low birth weight, due to poor maternal-foetal nutrition during pregnancy [2]. Low birth weight infants have an increased predisposition towards adiposity in early childhood, insulin resistance, hypertension and cardiovascular disease in adult life than those born with normal birth weight [3] Deranged insulin sensitivity has also been shown in lean normoglycaemic Asian Indians [4] and in children of women with gestational diabetes [5]. Low birth weight and increased risk of T2DM in adulthood have been attributed to alterations of the neuroendocrine system [6] deranged lipid metabolism [7] and pancreatic dysfunction [8], when compared to the increased risk of obesity alone [9].

The hyperinsulinemic-euglycemic glucose clamp (HEC) technique-the gold standard technique for measuring peripheral insulin resistance [10] is not feasible in large population based studies as it is labour-intensive, expensive and technically

* Corresponding author.
E-mail address: riddhi_dg@rediffmail.com (R. Dasgupta).

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demanding. Thus, a rapid, accurate, and low-cost method for assessing insulin resistance is essential in clinical practice and epidemiological studies [11]. Several surrogate measures of insulin resistance such as Homeostasis model assessment for insulin resistance (HOMA-IR), Quantitative insulin sensitivity check index (QUICKI), Fasting glucose to insulin ratio (FG-IR), amongst others are being used routinely in epidemiological studies across various populations [12]. Recently, C-peptide based novel insulin resistance indices such as the fasting/prandial C– peptide index, the 20/(Fasting C Peptide) (FCP) × Fasting Plasma Glucose (FPG) index and Insulin/C peptide ratio have garnered much research interest due to its sensitivity and specificity across various populations [13]. However, there is lack of data about the validity of surrogate fasting indices like the 20/(Fasting C Peptide (FCP) × Fasting Plasma Glucose (FPG) index in different ethnic populations including Asian Indians. Non-diabetic Asian Indians are predisposed to insulin resistance even at low BMI as compared to other ethnic groups [4]. The prevalence of T2DM is higher in subjects born with low birth weight as compared to normal birth weight [5]. We hypothesized that surrogate indices of insulin resistance/sensitivity would perform differently in normoglycaemic Asian Indians born with low birth weight or normal birth weight subject. In this study, we have measured different surrogate measures of fasting insulin sensitivity/resistance including the novel 20/(FCP × FPG) index and compared it with the M value of HEC studies separately in low-birth weight and normal birth-weight cohorts of healthy Asian Indian males. The validity of surrogate indices in comparison to the M value has been performed using correlation analysis and further the predictive accuracy of surrogate indices has been evaluated by random calibration model analysis in both the low birth weight and normal birth weight cohorts.

2. Methodology

This cross sectional study was approved by the institutional research Board and human ethics committee of Christian Medical College, Vellore, India (Research Committee Minute Number: 5879, 2006 and Administrative Committee Minute Number: 50-y: 6–2006) of Christian Medical College, Vellore (India) and the study was conducted in accordance to the guidelines mentioned in the declaration of Helsinki 2013. In the current study, the primary objective was to measure various surrogate measures of fasting insulin resistance *viz*: the 20/(FCP × FPG) index, HOMA-IR, FG-IR, QUICKI in comparison with M value derived from HEC studies and to check for the accuracy of these surrogate indices using random calibration model (RMSE) analysis in two birth weight based cohorts of Asian Indian males. Data was obtained from our previous cohort study entitled "*Born with low birth weight in rural Southern India: what are the metabolic consequences 20 years later?*" Details of study procedure and study subjects are available in a previous publication from the same cohort [3]. Briefly, subjects for this study were selected according to their birth weight as recorded in the birth registry for the years 1986–1990 at the Community Health and Development (CHAD) programme, Christian Medical College, Vellore, India which has a prospective surveillance system with a repository of updated population based data on infant births, deaths, pregnancies, deliveries, morbidity and immunisation status among mothers. The medical records were reviewed and a cohort of 117 non-diabetic men aged between 18 and 22 years, born of normal birth weight (n = 59, birth weight ≥2.5 kgs) or low birth weight (n = 58, birth weight < 2.5 kgs) with low BMI were recruited with informed, written consent. Anthropometry and biochemical assessment was performed and all subjects underwent the 120 min Hyperinsulinaemic-Euglycaemic clamp (HEC) procedure for evaluation of peripheral and hepatic insulin resistance [10]. In this procedure, a primed continuous infusion of insulin was initiated and the flow rate was fixed at 40 mU/kg/minutes for the entire duration of the two hour clamp. During the HEC procedure, a 25% glucose solution was infused and plasma glucose levels were measured every 5 min using a bedside glucose analyser (Analox GM-9D). An infusion of 25% dextrose was adjusted to maintain a stable plasma glucose concentration of 90 mg/dl (5 mmol/l) throughout the clamp procedure. Blood samples for biochemical estimation of insulin, C-peptide and plasma glucose were drawn at baseline and at the end of the steady state phase (*i.e* last 30 min of the basal phase and the last 30 min of the clamp period) [3]. Serum insulin and C-peptide levels were measured by the chemiluminescence method using kits supplied by Siemens, on the Immulite 2000 system (Siemens healthcare Diagnostic products Ltd., Llanberis, Gwynedd, UK). Chemistry and Immunoassay controls supplied by Bio-Rad were used as internal precision controls (CV 10.2% for insulin and 3.7% for C-peptide) [3]. In order to fulfill the objectives of the current study, the following surrogate indices of insulin resistance were calculated by using specific formulae as follows;

1. 20/(FCP × FPG); 20/(fasting C-peptide × fasting plasma glucose) [26]
2. QUICKI: 1/[log fasting insulin (mU/L) + log fasting glucose (mg/dL)] [28]
3. HOMA-IR: Fasting glucose (mmol/L) × fasting insulin (mU/L)/22.5 [11]
4. FG-IR: Fasting glucose (mg/dL)/Fasting insulin (mU/L) [29].

3. Statistical analysis

Continuous variables were summarised as Mean ± SD/, median (minimum & maximum) values. The values of skewed variables were log transformed and data were normalized for age, BMI and birth weight and Pearson's partial correlation analysis was applied to test for significance in correlation between indices of insulin resistance and the M value. A p value < 0.05 was considered statistically significant. Furthermore, to determine the predictive accuracy of the surrogate indices in comparison to the M value, the random calibration model analysis was performed by calculating the square root of the mean squared error of prediction (RMSE) and a leave-one-out cross validation type root mean squared error (CVPE) of prediction. The RMSE value was estimated by the formula $[\Sigma e_i^2/(n-2)]^{1/2}$, where e_i is the difference between observed and predicted M value. CVPE is calculated as $[\Sigma e_{(i)}^2/n]^{1/2}$, and the M value predicted by the model with the ith subject excluded. Further, the bootstrap percentile analysis was done to measure the confidence interval of the difference in RMSE and CVPE values between the surrogate measures in the two groups, to determine whether errors in predicting the M value among surrogate measures were statistically significant. The difference was considered statistically significant when the 95% confidence interval did not include zero. STATA 11.0 (College station, Texas, USA) was used for descriptive statistics and correlation analysis. RMSE and CVPE analysis were performed using the R statistical platform (http://www.r-project.org).

4. Results

The mean values of birth weight, body weight, height and total lean mass of the low birth weight cohort were significantly lower than that of the normal birth weight cohort whereas the mean age of the low birth weight cohort was significantly higher. However, no significant differences were observed for BMI and biochemical

parameters between the two groups. Further, no significant differences were observed in the mean value of M value (the gold standard measure of insulin sensitivity derived from HEC procedure) and surrogate indices of insulin resistance *viz* HOMA-IR, QUICKI, FG-IR, the 20/(FCP × FPG) index between the two groups (Table 1). Correlation statistics revealed significant positive correlation of FG-IR and QUICKI with the M value in the low birth weight cohort in the unadjusted form and after adjustment for age, BMI and birth weight in contrast to the normal birth weight cohort wherein no significant correlation was observed for any of the indices in the unadjusted and adjusted forms. In fact, the correlation coefficients were higher ($r = 37$) and significant for QUICKI ($P = 0.004$) in the low birth weight cohort as compared to the normal birth weight cohort (Table 2).

We applied the 20/(FCP × FPG) index as the outcome variable and observed no significant correlation for the 20/(FCP × FPG) index with the M value and surrogate fasting indices namely FG-IR, HOMA-IR and QUICKI in both the study groups (Table 3). Furthermore, the predictive accuracy of surrogate indices in the low birth weight and normal birth weight cohorts were analysed separately using RMSE and CVPE analysis, which showed lowest RMSE and CVPE values for QUICKI in the normal birth weight and the low birth weight cohorts (Table 4). On pairwise comparisons of RMSE and CVPE values between surrogate indices, no significant differences were observed in the confidence intervals of RMSE values for the normal birth weight and low birth weight cohorts (Table 5).

5. Discussion

Our study is the first amongst Asian Indians to have compared correlations and evaluated the predictive accuracy of established surrogate indices of insulin resistance including the novel 20/(FCP × FPG) index with the M value (a measure of whole body insulin sensitivity estimated as the rate of insulin stimulated glucose disposal) obtained from the HEC study in separate cohorts of males born with low birth weight and normal birth weight. In comparison to an earlier study from our group in 16 healthy Asian Indian males [14] the subjects of the present study are young (mean age: 19.5 ± 5 years) and lean (mean BMI: 19.5 kg/m^2). Amongst surrogate indices of insulin resistance, the mean values of HOMA-IR were comparatively lower than the cut-off value of 1.47 to define insulin resistance [15]. This is in contrast to the observations to our previous HEC study wherein increased HOMA-IR value was observed in 16 healthy Asian Indian males [14].

In a recent birth weight based study on healthy Finnish adults, it was observed that subjects born with very low birth weight (birth weight < : 1.5 kgs) had fasting insulin concentration (16.7%), higher (40.0%) insulin levels, higher post prandial blood glucose levels (6.7%), and HOMA-IR index (18.9%), when compared to normal birth weight subjects despite adjustment for body mass index [16]. Similarly a study on 111 lean Japanese subjects (BMI ≤ 21.2 kg/m^2) born of very low birth weight (birth weight < 1.5 kgs) and aged between 19 and 30 years, showed consistent association of insulin resistance (on HOMA-IR) with cardio-metabolic risk in the later stages of life [17]. In comparison to the Japanese study, the subjects in our study are younger with lower mean HOMA-IR values. Moreover, our study on Asian Indian males has validated surrogate indices of insulin resistance/sensitivity in comparison to the M value obtained from HEC procedure.

It has been reported that the FG-IR is better than HOMA-IR as a

Table 1
Anthropometry, biochemical profile and indices of fasting insulin resistance/sensitivity.

Variables	Normal birth weight cohort (59)	Low birth weight cohort (n = 58)	*P* value
Age (years)	19.5 ± 1.0	20.0 ± 0.9	**0.01**
Birth weight (kg)	3.2 ± 0.1	2.1 ± 0.2	**0.00**
Height (cm)	171 ± 5.5	166.5 ± 5.9	**0.001**
Weight (kgs)	55.4 ± 7.0	50.1 ± 8	**0.02**
Body mass Index (kg/m^2)	19.5 ± 2.6	19 ± 2.9	0.41
Total lean mass (kgs)	45.0 ± 3.8	41.1 ± 4.8	**0.001**
Waist circumference (cms)	70.9 ± 7.1	69.5 ± 7.6	0.30
Waist -to- hip ratio	0.82 ± 0.05	0.83 ± 0.04	0.58
Fasting plasma glucose (mg/dl)	87.3 ± 6.0	88.0 ± 6.9	0.53
120 min post prandial plasma glucose (mg/dl)	100.7 ± 17.2	102 ± 26.2	0.73
Fasting serum insulin (μU/ml)	4.3 ± 3.5[a] (0.5, 29.6)[b]	8.3 ± 4[a] (0.5, 57.1)[b]	0.09
120 min post prandial serum insulin (μU/ml)	36.2 ± 29.3[a] (1, 160)	41.8 ± 29.6[a] (0.4, 212.7)[b]	0.37
Fasting C-peptide (ng/ml)	1.5 ± 1.1[a] (0.1, 5)[b]	2.2 ± 1.4[a] (0.1, 34)[b]	0.25
120 min post prandial C-peptide (ng/ml)	4.9 ± 4.8[a] (0.1, 13)[b]	5.3 ± 5.4[a] (0.1, 11.7)[b]	0.43
Total cholesterol (mg/dl)	129.8 ± 27.3	133.7 ± 32.5	0.47
High density lipoprotein cholesterol (mg/dl)	31.0 ± 5.6	31.6 ± 8.2	0.65
Low density lipoprotein cholesterol (mg/dl)	80.0 ± 22.8	82 .0 ± 26.2	0.65
Serum triglycerides (mg/dl)	78.8 ± 32.4 74[a](32, 158)[b]	83.7 ± 47.6 70[a](20, 281.4)[b]	0.50
Indices of insulin sensitivity/resistance			
M value (mg/kg/min)	10.3 ± 3.8	10.2 ± 3.9	0.84
QUICKI index	0.41 ± 0.06	0.42 ± 0.08	0.95
HOMA-IR	0.97 ± 0.77 0.80[a] (0.2, 3.9)[b]	0.97 ± 0.90 0.80[a] (0.1, 5.5)[b]	0.96
20/(FCP × FPG) index	0.38 ± 0.2[a] (0.05,2.4)[b]	0.37 ± 0.6 0.16[a] (0.06, 2.46)[b]	0.96
Fasting insulin/glucose ratio	28.5 ± 18.4 24.8[a] (4.8, 170)[b]	31.0 ± 20.6 22.6[a] (0.7, 168)[b]	0.56

Bold indicates P value < 0.05.
Values are presented as Means and SD/median. *P* value < 0.05: Statistically significant.
[a] Indicates median values.
[b] Indicates indicate minimum and maximum median values respectively.

Table 2
Correlation of surrogate indices of insulin resistance with the M value in the study cohort.

Indices of insulin resistance/sensitivity	Normal birth weight (n = 59)				Low birth weight (n = 58)			
	Unadjusted		Adjusted for age, BMI and birth weight		Unadjusted		Adjusted for age, BMI and birth weight	
	r	P value	*r*	P value	*r*	P value	*r*	P value
FGIR	0.22	0.10	0.20	0.124	0.41	**0.001**	0.41	**0.002**
20/(FCP x FPG)	0.04	0.77	−0.03	0.818	0.08	0.52	0.09	0.49
HOMA-IR	0.04	0.76	0.12	0.382	0.11	0.39	0.09	0.49
QUICKI	0.20	0.11	0.20	0.128	0.37	**0.004**	0.37	**0.005**

Bold indicates P value < 0.05.
P < 0.05: Statistically significant.

Table 3
Correlation of 20/(FCP x FPG) index with M value and indices of insulin resistance/sensitivity in the study cohort.

Indices of insulin resistance/sensitivity	Normal birth weight (n = 59)				Low birth weight (n = 58)			
	Unadjusted		Adjusted for age, BMI and birth weight		Unadjusted		Adjusted for age, BMI and birth weight	
	r	P value	*r*	P value	*r*	P value	*r*	P value
M-value	0.04	0.77	−0.03	0.81	0.08	0.52	0.09	0.49
FGIR	0.06	0.63	0.08	0.53	0.25	0.05	0.25	0.06
HOMA-IR	0.02	0.85	0.09	0.49	0.07	0.58	0.04	0.74
QUICKI	0.04	0.76	0.07	0.61	0.25	0.05	0.24	0.07

P < 0.05: Statistically significant.

Table 4
Root Mean Squared Error (RMSE) and leave– one–out cross validation type of prediction (CVPE) calculated by calibration model for surrogate indices of insulin resistance.

Indices of insulin resistance	Normal birth weight cohort (n = 59)		Low birth weight cohort (n = 58)	
	RMSE value	CVPE value	RMSE value	CVPE value
HOMA- IR	3.8	15.3	3.9	19.3
QUICKI	**3.8**	**14.7**	**3.7**	**15.1**
Fasting glucose/insulin ratio	3.8	14.7	3.9	16.8
20/(FCP × FPG) index	3.8	15.1	3.9	16.8

Bold indicates P value < 0.05.

Table 5
Difference between RMSE & CVPE values for surrogate indices derived using boot strap percentile method.

Difference in RMSE & CVPE values between surrogate indices at 95% CI	Normal birth weight cohort (n = 59)	Low birth weight cohort (n = 58)
HOMA-IR *vs.* QUICKI	(-0.16, 0.23)[a]	(-0.27, 0.63)[a]
	(-1.65, 1.02)[b]	(-4.31, 3.24)[b]
HOMA-IR *vs.* FG-IR	(-0.16, 0.20)[a]	(-0.32, 0.47)[a]
	(-1.58, 1.03)[b]	(-3.68, 3.14)[b]
HOMA-IR *vs.* 20/FCP x FPG	(-0.16, 0.07)[a]	(-0.34, 0.27)[a]
	(-0.48, 0.53)[b]	(-1.8, 3.32)[b]
QUICKI *vs.* FG-IR	(-0.07, 0.03)[a]	(-0.23, 0.03)[a]
	(-0.43, 0.46)[b]	(-0.97, 1.51)[b]
QUICKI *vs.*20/FCP x FPG	(-0.83, 1.55)[a]	(-0.55, 0.15)[a]
	(-0.20, 0.06)[b]	(-1.38, 3.96)[b]
FG-IR *vs.* 20/FCP x FPG	(-0.20, 0.06)[a]	(-0.44, 0.23)[a]
	(-0.88, 1.43)[b]	(-1.53, 3.57)[b]

[a] Indicates upper and lower limits of RMSE values at 95 %CI.
[b] Indicates upper and lower limits of CVPE values at 95 %CI.

surrogate index of insulin resistance, when applied in normoglycaemic subjects [18] and compared to diabetic subjects [19]. An important observation in this study is the consistent positive correlations of FG-IR with M value in the low birth weight cohort before and after adjustment for confounders. This is similar to the observations of our earlier HEC based study in healthy South Indian males aged between 29.8 and 36 years wherein the highest degree of correlation and predictive accuracy was observed for FG-IR with M value when compared with other surrogate indices [14]. However, the correlation coefficient for FG-IR ($r = 0.41$) in the present study for the low birth weight cohort was less in comparison to an earlier study from our group [14]. Furthermore, another study on 70 Asian Indian males aged between 18 and 73 years (mean BMI: $21 \pm 4\ kg/m^2$) used fasting insulin glucose ratio (an inverse measure of FG-IR) and reported significant inverse correlation with the M value derived from HEC procedure, thus underscoring the utility of indices based on ratios of fasting insulin/glucose in Asian Indians [20].

The QUICKI is the inverse of HOMA-IR and a precise index of insulin sensitivity [21] showing better correlation with the M value derived from the HEC technique [22]. A meta-analysis on surrogate indices of insulin sensitivity has shown significant correlation of QUICKI with M value [23]. In a multi ethnic cohort of 116 subjects aged between 19 and 64 years, it has been shown the QUICKI correlates linearly and significantly with M value. We applied the QUICKI and FG-IR indices in a homogenous cohort of Asian Indian males and observed moderate but significant positive correlation ($r = 0.37$, $P = 0.004$) with the M value only in the low birth weight cohort after adjustment for confounders. Our results agree with the previous HEC based study in Asian Indian men from South India, wherein QUICKI correlated significantly with the M value [14]. In addition, our study results are in agreement with the results of an earlier study in Asian Indian men wherein significant positive correlation was observed for QUICKI with M value of the HEC study [21].

5.1. C peptide based indices and other surrogate indices of insulin resistance

Most surrogate indices of insulin resistance studied till date are based on fasting insulin and glucose levels. Such indices are used as measures of hepatic insulin sensitivity/resistance. Specifically, serum C-peptide level is a precise measure of endogenous insulin secretion when compared to fasting insulin levels [24] as C-peptide is physiologically much stable during hepatic clearance as compared to insulin. It shows a linear trend of metabolic kinetics at physiological and supra-physiologic plasma concentrations [25]. However, C-peptide based indices are sparsely researched and validated in comparison to the M value obtained from HEC studies especially in normoglycaemic subjects of low BMI. A few studies in different ethnic groups have demonstrated the correlation of the 20/(FCP × FPG) index with other surrogate indices. Specifically, the 20/(FCP × FPG) index has been sparsely researched in Asian Indians, despite high prevalence of insulin resistance, diabetes and cardiovascular diseases typical to this ethnic group. In this study, the 20/(FCP × FPG) index showed positive correlation with FGIR in the low birth weight cohort, but not in the normal birth weight cohort. In a pilot study on elderly obese Japanese patients with type 2 diabetes, the 20/(FCP × FPG) index correlated positively with glucose infusion rate and the insulin sensitivity index of HEC procedure but negatively with HOMA IR [26]. Similarly a pilot study from Iran on elderly diabetic subjects on metformin monotherapy showed significant correlation of the 20/(FCP × FPG) index with QUICKI. Contrastingly, no significant correlations were observed for the 20/(FCP × FPG) index in diabetic subjects on combined therapy [27]. It may be noted that the studies mentioned above were performed in obese diabetic subjects and comparative analysis with control groups was not performed. Further, the study observations were not validated in comparison to the M value, unlike the present study, thus limiting the applications of the study observations in the respective ethnic groups.

Importantly, it has been shown that the correlation between a surrogate index and the gold standard HEC technique can be strong despite poor predictive accuracy [28]. As correlation coefficients can sometimes be deceptive, we performed the random calibration model analysis has been performed. Random calibration model is the inverse of regression derived using the mean of square root (RMSE) of regression coefficients. RMSE and CVPE are measures of error of the linear regression model derived from surrogate indices in predicting the value of insulin sensitivity as measured by the clamp [14]. Extremities and errors in data can be well controlled by CVPE than RMSE. The CVPE value is highly reliable than RMSE as CVPE uses an estimate that excludes the ith subject when predicting results for the same subject. This reflects more closely a clinical scenario in which data for each new patient is predicted based on a model obtained from previous patients.

Surrogate indices with lower RMSE and CVPE values are considered to have superior predictive accuracy due to less random errors in regression coefficients [28]. In the present study, RMSE and CVPE analysis showed that the predictive accuracy was highest for QUICKI in the normal birth weight and the low birth weight cohort. Previously, using random calibration model analysis we had reported strong correlation of FG-IR with the M value in a cohort of non diabetic, South Asian males and that the FG-IR had higher predictive accuracy as compared to HOMA-IR and QUICKI [14]. As for other surrogate indices, the RMSE values were identical for QUICKI and the 20/(FCP x FPG), in the low birth weight cohort. This indicates that the distribution of residuals is homogenous in the cohort.

Furthermore, a study by Muniyappa and colleagues used random calibration model analysis to assess the predictive ability of surrogate indices namely fasting insulin levels, QUICKI and FIGR in young, non-obese Asian Indian men (mean BMI: $21 \pm 4\ kg/m^2$), irrespective of birth weight status. Their study observed no significant differences in RMSE and CVPE values of surrogate indices when compared with QUICKI [21]. Chen and colleagues performed random calibration model analysis to validate the predictive accuracy of surrogate indices in comparison to HEC procedures in a mixed cohort of 116 subjects comprising obese, non-obese subjects, normoglycaemic, hypertensive subjects and patients with T2DM. It was noted that the degrees of insulin sensitivity, as determined by surrogate indices *viz* QUICKI, HOMA, log (HOMA), were in good agreement with HEC procedure. Further, this study showed that QUICKI and log (HOMA) had better predictive accuracy than fasting insulin, HOMA-IR [28]. In comparison to the study by Chen et al. [28], our study on a homogenous cohort of young, non-diabetic Asian Indian males shows better predictive accuracy of QUICKI and FG-IR in the low birth weight and normal birth weight cohorts respectively. In the low birth weight cohort, the mean values of total fat mass, peripheral lean mass (lean mass in arms and legs) and total lean mass were significantly lower as compared to the normal birth weight cohort. As glucose disposal is majorly mediated by peripheral lean mass, it is important to note that reduced lean mass in low birth weight subjects predisposes them to insulin resistance and T2DM in late adulthood [3]. However, our study observations are limited to the use of “M” value which is a measure of whole body insulin sensitivity and there is no demarcation of hepatic and peripheral insulin resistance. Ideally, the use of stable-isotope based clamp studies to derive hepatic and peripheral insulin resistance separately would have added further significance to our results. Further, our study observations are restricted to Asian Indian males and needs to be validated in females. Nevertheless, the study observations have important clinical implications in population based surveillance programmes for prevention of diabetes and co-morbidities associated with insulin resistance in Asian Indians.

6. Conclusion

Our study, the first of its kind involving Asian Indians, clearly shows superior predictive accuracy of QUICKI over FGIR and the differences in predictive accuracy of established surrogates of insulin sensitivity in low and normal birth-weight cohorts. This indicates the importance of applying different sets of surrogate indices in birth weight based cohorts of Asian Indians.

Disclosure statement

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Conflicts of interest

The authors declare that no conflict of interest exist.

Data sharing statement

All data are presented in the article. No additional data are available.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2018.11.067.

References

[1] Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Anazawa S, et al. Birth weight and risk of type 2 diabetes: a systematic review. J Am Med Assoc 2008;300:2886–97. https://doi.org/10.1001/jama.2008.886. PMID:19109117.

[2] Yajnik CS. Nutrient-mediated teratogenesis and fuel-mediated teratogenesis: two pathways of intrauterine programming of diabetes. Int J Gynaecol Obstet 2009;104(Suppl 1):S27–31. https://doi.org/10.1016/j.ijgo.2008.11.034. PMID: 19152913.

[3] Thomas N, Grunnet LG, Poulsen P, Christopher S, Spurgeon R, Inbakumari M, et al. Born with low birth weight in rural Southern India: what are the metabolic consequences 20 years later ? Eur J Endocrinol 2012;166:647–55. https://doi.org/10.1530/EJE-11-0870. PMID:22250073.

[4] Liew CF, Seah ES, Yeo KP, Lee KO, Wise SD. Lean, non-diabetic Asian Indians have decreased insulin sensitivity and insulin clearance, and raised leptin compared to Caucasians and Chinese subjects. Int J Obes Relat Metab Disord 2003;27(7):784–9. https://doi.org/10.1038/sj.ijo.0802307. PMID: 12821962.

[5] Yajnik CS. Early life origins of insulin resistance and type 2 diabetes in India and other Asian countries. J Nutr 2004;134:205–10. https://doi.org/10.1093/jn/134.1.205. PMID: 14704320.

[6] Reynolds RM, Walker BR, Syddall HE, Andrew R, Wood PJ, Phillips DI, et al. Is there a gender difference in the associations of birthweight and adult hypothalamic-pituitary-adrenal axis activity? Eur J Endocrinol 2005;152:249–53. https://doi.org/10.1530/eje.1.01846. PMID: 15745933.

[7] Desai M, Guang H, Ferelli M, Kallichanda N, Lane RH. Programmed upregulation of adipogenic transcription factors in intrauterine growth-restricted offspring. Reprod Sci 2008;15:785–96. https://doi.org/10.1177/1933719108318597. PMID:19017816.

[8] Tarry-Adkins JL, Chen JH, Smith NS, Jones RH, Cherif H, Ozanne SE. Poor maternal nutrition followed by accelerated postnatal growth leads to telomere shortening and increased markers of cell senescence in rat islets. Faseb J 2009;23(5):1521–8. https://doi.org/10.1096/fj.08-122796. PMID:19126595.

[9] Ruiz-Narváez EA, Haddad SA, Rosenberg L, Palmer JR. Birth weight modifies the association between central nervous system gene variation and adult body mass index. J Hum Genet 2016;61(3):193–8. https://doi.org/10.1038/jhg.2015.139. PMID: 26582267.

[10] DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J physiol 1979;237:E214–23. https://doi.org/10.1152/ajpendo.1979.237.3.E214. PMID: 382871.

[11] Katsuki A, Sumida Y, Gabazza EC, Murashima S, Furuta M, Araki-Sasaki R. Homeostasis model assessment is reliable indicator of insulin resistance during followup of patients with type 2 diabetes. Diabetes Care 2001;24(2):362–5. PMID: 11213893.

[12] Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance *in vivo*: advantages, limitations, and appropriate usage. Am J Physiol Endocrinol Metab 2008;294:E15–26. https://doi.org/10.1152/ajpendo.00645.2007. PMID:17957034.

[13] World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Am Med Assoc 2013;310(20):2191–4. https://doi.org/10.1001/jama.2013.281053. PMID: 24141714.

[14] Venkatesan P, Tiwari A, Dasgupta R, Carey M, Kehlenbrink S, Wickramanayake A, et al. Surrogate measures of insulin sensitivity when compared to euglycemic hyperinsulinemic clamp studies in Asian Indian men without diabetes. J Diabet Complicat 2016;30(2):287–91. https://doi.org/10.1016/j.jdiacomp.2015.11.024. PMID: 26718937.

[15] Stern SE, Williams K, Ferrannini E, DeFronzo RA, Bogardus C, Stern MP. Identification of individuals with insulin resistance using routine clinical measurements. Diabetes 2005;54:333–9. PMID: 15677489.

[16] Hovi P, Andersson S, Eriksson JG, Jarvenpaa AL, Strang-Karlsson S, Mäkitie O, Kajantie E. Glucose regulation in young adults with very low birth weight. 356 N Engl J Med 2007;17(20):2053–63. https://doi.org/10.1056/NEJMoa067187. PMID: 17507704.

[17] Sato R, Maekawa M, Genma R, Shirai K, Ohki S, Morita H, et al. Final height and cardiometabolic outcomes in young adults with very low birth weight (< 1500 g). PLoS One 2014;9(11), e112286. https://doi.org/10.1371/journal.pone.0112286. PMID: 25397968.

[18] Disse E, Bastard JP, Bonnet F, Maitrepierre C, Peyrat J, Louche-Pelissier C, Laville M. A lipid-parameter-based index for estimating insulin sensitivity and identifying insulin resistance in a healthy population. Diabetes Metabol 2008;34:457–63. https://doi.org/10.1016/j.diabet.2008.02.009. PMID: 18922725.

[19] Zaletel J, Barlovic DP, Prezelj J. Adiponectin–leptin ratio: a useful estimate of insulin resistance in patients with Type 2 diabetes. J Endocrinol Invest 2010;33:514–8. https://doi.org/10.3275/6811. PMID: 20142631.

[20] Muniyappa R, Irving BA, Unni US, Briggs WM, Nair KS, Quon MJ, Kurpad AV. Limited predictive ability of surrogate indices of insulin sensitivity/resistance in Asian-Indian men. Am J Physiol Endocrinol Metab 2010;299(6):E1106–12. https://doi.org/10.1152/ajpendo.00454.2010. PMID: 20943755.

[21] Wallace TM, Matthews DR. The assessment of insulin resistance in man. Diabet Med 2002;19:527–34. https://doi.org/10.1046/j.1464-5491.2002.00745.x. PMID: 12099954.

[22] Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, Quon MJ. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000;85:2402–10. https://doi.org/10.1210/jcem.85.7.6661. PMID:10902785.

[23] Otten J, Ahren B, Olsson T. Surrogate measures of insulin sensitivity vs the hyperinsulinaemic-euglycaemic clamp: a meta-analysis. Diabetologia 2014;57(9):1781–8. https://doi.org/10.1007/s00125-014-3285-x. PMID: 24891021.

[24] Greenbaum CJ, Mandrup PT, McGee PF, Battelino T, Haastert B, Ludvigsson J. Type 1 Diabetes Trial Net Research Group; European C-Peptide Trial Study Group: mixed-meal tolerance test versus glucagon stimulation test for the assessment of beta-cell function in therapeutic trials in type 1 diabetes. Diabetes Care 2008;31:1966–71. https://doi.org/10.2337/dc07-2451. PMID: 18628574.

[25] Polonsky KS, Licinio-Paixao J, Given BD, Pugh W, Rue P, Galloway J, Karrison T, Frank B. Use of biosynthetic human C-peptide in the measurement of insulin secretion rates in normal volunteers and type I diabetic patients. J Clin Invest 1986;77:98–105. https://doi.org/10.1172/JCI112308. PMID: 3511094.

[26] Ohkura T, Shiochi H, Fujioka Y, Sumi K, Yamamoto N, Matsuzawa K, et al. 20/(fasting C-peptide × fasting plasma glucose) is a simple and effective index of insulin resistance in patients with type 2 diabetes mellitus: a preliminary report. Cardiovasc Diabetol 2013;12:21. https://doi.org/10.1186/1475-2840-12-21. PMID: 23339473.

[27] Ghaffari A, Payami SA, Payami SP, Payami SP, Larky DA, Nikzamir A, et al. Evaluation of insulin resistance indices in type 2 diabetic patients treated with different anti-diabetic drugs. Open J Endocr Metab Dis 2016;6:95–101. https://doi.org/10.4236/ojemd.2016.62013.

[28] Chen H, Sullivan G, Quon MJ. Assessing the predictive accuracy of QUICKI as a surrogate index for insulin sensitivity using a calibration model. Diabetes 2005;54:1914–25. https://doi.org/10.2337/diabetes.54.7.1914. PMID: 15983190.

[29] Legro RS, Finegood D, Dunaif A. A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome. J Clin Endocrinol Metab 1998;83(8):2694–8.