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Better Approach to Type 2 Diabetes Mellitus

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Abstract

Background: South East Asia with its developing countries is a megacenter for Type 2 Diabetes Mellitus (T2DM) which is one of the biggest hurdles in its economic growth. Combating T2DM needs a better approach in an event of its diagnosis to reduce its future exorbitant complications.

Methods: We carried out this study to determine insulin resistance (IR) and beta-cell function using Homeostatic Model Assessment (HOMA) in T2DM at diagnosis. We also analyzed which routinely investigated parameters at diagnosis of T2DM had the strongest association to predict IR as accurately as HOMA2IR, for cost saving clinical use by the treating physicians.

Results: Among the 60 newly diagnosed T2DM patients, 43 were insulin resistant and 17 were non-insulin resistant. Waist-Hip ratio (WHR) and LDL-C/HDL-C ratio together predicted IR most accurately with a cut-off of 2.49. Waist circumference, BMI, visceral adiposity indicators, and TyG index could not predict IR on their own.

Conclusion: IR should be identified with affordable surrogates and offset with targeted anti-IR treatment right from the initial diagnosis of T2DM.

Keywords: Anti-IR treatment; LDL-C/HDL-C ratio; Type 2 diabetes mellitus; Waist-hip ratio

Abbreviations: %B: Beta-Cell Function; %S: Insulin Sensitivity; AUC : Area under the Receiver Operating Characteristic Curve; BCF: Beta-Cell Function; BMI: Body Mass Index; CAD: Coronary Artery Disease; DKD: Diabetic Kidney Disease; HDL-C: High-Density Lipoprotein Cholesterol; HOMA: Homeostasis Model Assessment; IR: Insulin Resistance; IRG: Insulin Resistant Group; ISG: Insulin Sensitivity Group; LAP: Lipid Accumulation Product; LDL-C: Low-Density Lipoprotein Cholesterol; MARD: Mild Age-Related Diabetes; MOD: Mild Obesity-Related Diabetes; NASH: Non-Alcoholic Steatohepatitis; ROC : Receiver Operating Characteristic; SGPT: Serum Glutamate Pyruvate Transaminase; SIRD: Severe insulin resistant diabetes; T2DM: Type 2 Diabetes Mellitus; TC: Total Cholesterol; TG: Triglyceride; TUTH: Tribhuvan University Teaching Hospital; TyG index: Triglyceride Glucose index; VAI: Visceral Adiposity Index; WHR: Waist-Hip Ratio

Background

Diabetes mellitus (DM) is a metabolic disorder with adverse consequences in multiple organ systems. Type 2 DM is projected to be a leading cause of morbidity and mortality for the foreseeable future. South East Asians ethnically are more prone to develop central obesity and thus significant insulin resistance (IR) which puts them in the group for high risk for development of Type 2 DM that too 5 to 10 years earlier than in Caucasians i.e. the time to make ones career and take responsibilities to contribute to the family and nation economically [1]. This region has the highest number of Type 2 DM which is putting tremendous burden individually in those with the disease. Once the chronic complications set in, their families have no option but to make huge sacrifices due to the drastic rise in the out of pocket cost incurred [2].

Increased insulin resistance with resultant increase in hepatic gluconeogenesis and hepatic glucose output along with beta-cell dysfunction and failure is the central occurrence in the development of Type 2 DM [3]. Insulin resistance which is modifiable, is being emphasized as one of the major factor in the development of diabetic kidney disease (DKD) and non-alcoholic steatohepatitis (NASH), the major cause of cirrhosis and hepatocellular carcinoma in the developed world and an important cause in the developing world [4,5].

Fortunately the development of clinically overt nephropathy and NASH affects only about 30% and 34% of patients with DM respectively [6,7]. The majority escapes renal failure, and although some histologic damage occurs in the kidneys, their renal function remains essentially normal until death. It therefore appears that in humans, hyperglycaemia is necessary but not sufficient to cause renal damage to cause renal failure. This shows that inherited factors play an important role in determining the development to DKD and probably NASH too [8]. Finding out at diagnosis of Type 2 DM, the significant presence of IR and addressing its management therefore could delay or even prevent these complications and thus reduce the out of pocket expenditure and maintain the quality of life for all involved.

We carried out this study to determine insulin resistance and beta-cell function using Homeostatic Model Assessment (HOMA) in Type 2 DM at diagnosis. We also analysed which routinely investigated parameters at diagnosis of T2DM had the strongest association to predict IR as accurately as HOMA2IR, for cost saving clinical use by the treating physicians. Based on IR in this study, we sub classified Type 2 DM to highlight the importance of concerted treatment to modify IR when present at diagnosis.

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Materials and Methods

Place and duration of study

This study was conducted at Department of Endocrinology and Biochemistry Laboratory of Tribhuvan University Teaching Hospital (TUTH), a tertiary care center in Kathmandu, Nepal from February 2016 to January 2017.

Study population, inclusion and exclusion criteria

Sixty newly diagnosed treatment naive T2DM patients who provided written consent were enrolled in this study. Exclusion criteria included patients at diagnosis with evident diabetic complications, suffering from chronic illness, chronic liver and/or renal diseases, already receiving lipid-lowering medications, and pregnant women.

Anthropometric measurements

Weight was taken using a platform weighing scale. Standing height measurement was done with participants in bare foot, eyes looking ahead. The waist circumference (WC) was measured at the midpoint between the lowest rib and iliac crest at the end of expiration. The hip circumference was taken at the widest area of the hips at the greatest protuberance of the buttocks. Body mass index (BMI) was calculated by weight in kilograms divided by square of height in meters. Waist-Hip ratio (WHR) was calculated by simply dividing the waist measurement by the hip measurement. Blood pressure (BP) measurement was done using a recently calibrated aneroid sphygmomanometer with an adequate cuff size after participant had rested for at least 5 minutes.

Collection and processing of the sample

Five milliliter of blood was drawn after an overnight fast (8-12 hours) by venous puncture method. Serum samples were separated, within half an hour, by centrifugation at 1500-3000 rpm for 5 min. Routine investigation were done on the same day of sample collection, which included blood glucose, creatinine, SGPT, TC, HDL-cholesterol and TG, which were measured in fully-automated biochemistry analyser, BT 3000, Italy. An aliquot of each sample was then stored at -20°C for the test of C-peptide. EDTA anticoagulated blood was used for determination of HbA1c.

Laboratory standard operating procedures were maintained for all laboratory analysis. Internal quality control sera, both normal and pathological, were also run for each lot, for the validation of the results.

Fasting serum glucose (FSG) was measured by glucose oxidase method, as described by Trinder, using commercial kit Biolabo Reagents, France. Serum creatinine was measured by modified Jaffe reaction, Biolabo Reagents, France. SGPT was measured by IFCC recommended kinetic method. Total cholesterol (TC) was estimated by CHOD/PAP method, Human, Germany. Triglyceride (TG) was measured by GPO/PAP method, Human, Germany. HDL-C was measured by PEG/CHOD-PAP method, Human, Germany. LDL-C was calculated using the Friedewald's formula:-

LDL-C (mmol/L)=TC (mmol/L)-HDL-C (mmol/L)-TG (mmol/L)/2.2

When TG concentration exceeded 4 mmol/L, LDL-C was estimated by direct homogenous method, Biolabo Reagents, France. VLDL-C (mmol/L) was calculated as TG (mmol/L)/2.2. HbA1c was measured by boronate affinity assay using NycoCard reader. Lipid parameters like LAP (Lipid Accumulation Product), VAI (Visceral Adiposity Index), and TyG (Triglyceride Glucose index) were calculated by using following formulae [9,10]:

LAP for men: (WC in cm-65) × TG in mmol/L

LAP for women: (WC in cm-58) × TG in mmol/L

VAI for men: [WC in cm/(39.68+1.88 × BMI)] × (TG in mmol/L/1.03) × (1.31/HDL-C in mmol/L)

VAI for women: [WC in cm/(36.58+1.89 × BMI)] × (TG in mmol/L/0.81) × (1.52/HDL-C in mmol/L)

TyG index: Ln [TG in mg/dL × FSG in mg/dL/2]

TyG-BMI: TyG index × BMI

TyG-WC: TyG index × WC

TyG-WHR: TyG index × WHR

C-peptide was measured using a solid phase enzyme-linked immunosorbent assay (ELISA) kit, DRG, Italy. IR and BCF values were calculated using the HOMA2 calculator software. HOMA2 calculator was downloaded from university of oxford. Patients with HOMA2-IR > 1.8 were defined as insulin resistant group (IRG) whereas those with HOMA2-IR ≤ 1.8 were defined as insulin sensitivity group (ISG) [11]. HOMA2 was used to compare and correlate various routinely measured physical and laboratory parameters between the insulin resistant and insulin sensitivity group of the diabetic cases in this study.

Diabetic patients were also classified based on insulin resistance given by HOMA2IR, obesity defined by WHR (abdominal obesity being defined in Asians as a waist-hip ratio >0.90 for males and >0.85 for females [12], and age above 60 years into the following three clusters [13]:

Cluster 1: Severe insulin resistant diabetes (SIRD), characterised by insulin resistance and obesity.

Cluster 2: Mild obesity-related diabetes (MOD), characterised by obesity but not by insulin resistance.

Cluster 3: Mild age-related diabetes (MARD), representing diabetic patients older than 60 years of age.

Data processing and analysis

The data were entered in Microsoft Excel program (Microsoft Office 2010). Statistical analyses were done by SPSS 23.0 version (Statistical Package for Social Science for Window version; SPSS, Inc., Chicago, IL). Mean comparison was done by T-test. Chi square test was used for comparison of dichotomous variables. Pearson correlation was used to evaluate the correlations. P value ≤0.05 was considered to be statistically significant.

Evaluations of serum lipid parameters were done by constructing receiver operating characteristic (ROC) curve. Values for the area under the ROC curve of 0.5, ≥ 0.7 but < 0.8, ≥ 0.8 but < 0.9, and ≥ 0.9 were taken as suggestive of reflecting the following levels of discrimination: none, acceptable, excellent, and outstanding [14].

Results

Significant number i.e. 23 (38.33%) of T2DM patients were below 45 years of age (Table 1), emphasizing that Nepalese like other Asians develop type 2 DM 5 to 10 years earlier than Caucasians. Insulin resistance was prevalent in majority (n=43) of our Type 2 DM cases throughout the age group but a subgroup (n=17) had no insulin resistance in spite of having type 2 DM. Diagnoses of T2DM after 60

Age (<45 years)	Frequency (n=60)	Age (≥ 45 years)	Frequency (n=60)
33	1	45	5
34	2	46	1
35	4	47	8
36	1	48	2
38	4	49	3
39	2	50	3
40	5	51	1
42	3	52	2
43	1	53	1
		54	1
		55	2
		56	1
		57	3
		58	1
		59	1
		64	1
		66	1
Total	**23** (38.33%)	**Total**	**37** (61.67%)

Table 1: Age distribution of the 60 diabetes cases.

years of age were mainly insulin sensitive (Table 2).

We analyzed the physical risk factors BMI, waist circumference and waist-hip ratio that were mostly associated with IR in the 43 with IR and found that waist-hip ratio had the most significant correlation with IR (Table 3). Using WHR, all the new diabetic cases in our study were abdominally obese. Majority without IR had WHR just above the normal whereas the WHR was much above normal in the IR group (Table 4). Thus higher WHR reflects IR.

Analysis of biochemical indicators of insulin resistance in the 43 IRG and 17 ISG was done and LDL-C/HDL-C together with WHR was the most predictive of IR followed by LDL-C/HDL-C ratio alone. Visceral adiposity indicators and TyG index could not predict IR in our population (Table 5). The strongest predictor of IR was LDL-C/HDL-C ratio together with WHR with a cutoff of 2.49 and p-value 0.009, followed by WHR alone with a cutoff of 1.015 and p-value 0.014 and LDL-C/HDL-C ratio alone with a cutoff of 2.42 and p-value 0.015 (Table 6 and Figure 1). The cut-off for IR by BMI or WC was not definable in our study group of Nepalese (Table 6). Only LDL-C/HDL-C ratio and LDL-C/HDL-C ratio together with WHR were significantly correlated with IR (with confidence interval of 90%) and beta-cell function (with confidence interval of 95%) (Table 7).

Cluster classification of the 60 T2DM patients using WHR and IR showed the frequency of distribution and mean values as shown in Table 8 and Figure 2. All were abdominally obese by WHR.

Discussion

This study demonstrates that insulin resistance is present in majority (71.6%) of T2DM at diagnosis in Nepal and as Nepalese are ethnically similar to Indians on the south and Chinese on the north due to the unique location of Nepal, the same can be extrapolated for them who represent 33% i.e. one-third of world's T2DM [15,16].

HOMA2IR is the best way to detect IR but may not be possible routinely. WHR and LDL-C/HDL-C ratio together predicted IR most accurately in this study with a cut-off of 2.49. This could be used to predict the dominant presence of IR in our region. The assumption of IR is lower if WHR or LDL-C/HDL-C ratio is taken alone. Waist circumference or BMI could not predict IR on their own.

Age Group	HOMA2-IR ≤ 1.8 (n=17)		HOMA2-IR>1.8 (n= 3)		*p*-value
	No.	%	No.	%	
<36	3	17.6	4	9.3	0.032*
36-40	4	23.5	8	18.6	
41-45	1	5.9	8	18.6	
46-50	7	41.2	10	23.3	
51-55	0	0.0	7	16.3	
56-60	0	0.0	6	14.0	
>60	2	11.8	0	0.0	
*Statistically significant at p<0.05; Chi-square test					

Table 2: Relation between insulin resistance and age group.

	HOMA2-IR	
	Pearson's Correlation Coefficient	*p*-value
Body Mass Index (BMI)	0.141	0.283
Waist circumference (WC)	-0.120	0.362
Waist Hip Ratio (WHR)	0.274	0.034*

Table 3: Correlation of insulin resistance with physical risk factors.

WHR	ISG i.e. HOMA2-IR ≤ 1.8, frequency	IRG i.e. HOMA2-IR >1.8, frequency
0.93	0	1
0.95	3	1
0.96	2	1
0.97	2	3
0.98	1	2
1.00	1	1
1.01	1	5
1.02	1	4
1.03	2	3
1.04	1	4
1.05	2	2
1.06	0	2
1.07	0	7
1.08	0	4
1.10	1	0
1.11	0	1
1.12	0	1
1.16	0	1
Total	**17**	**43**

Table 4: WHR distribution in the ISG and IRG.

Insulin resistance and hypertension have been shown to be most strongly associated with diabetic kidney disease than hyperglycemia [17,18]. Identifying IR and addressing it aggressively by weight reduction and selecting anti-hyperglycemic medications that address IR right from diagnosis could prevent diabetes kidney disease in significant numbers. Hepatic insulin resistance is thought to cause non-alcoholic steatohepatitis [19], thus treating IR will also address prevention of NASH in this region too.

Seventeen (i.e. 28.3%) of the newly diagnosed diabetes who were abdominally obese by WHR did not show insulin resistance by HOMA2IR. They also had lower HbA1c at diagnosis. This group may be at lower risk of DKD and NASH but monitoring should continue. Follow up of both groups of IR and non-IR could assess the present

	HOMA2-IR ≤ 1.8 (n = 17)		HOMA2-IR >1.8 (n = 43)		*p*-value
	Mean	± SD	Mean	± SD	
Lipid ratios					
TC/HDL-C ratio	4.32	0.84	4.71	0.95	0.149
TG/HDL-C ratio	2.19	0.83	2.44	1.83	0.484
LDL-C/HDL-C ratio	2.35	0.89	2.86	0.87	0.047*
LDL-C/HDL-C and WHR	2.36	0.92	2.96	0.93	0.027*
LDL-C/HDL-C and TC/HDL-C	10.80	6.97	14.19	6.99	0.096
LDL-C/HDL-C and TC/HDL-C and WHR	10.85	7.16	14.69	7.48	0.075
Visceral adiposity indicators					
LAP	97.45	61.69	102.28	86.3	0.83
VAI	3.73	1.74	4.32	3.76	0.54
TyG related parameters					
TyG index	9.45	0.54	9.75	0.72	0.08
TyG-BMI	260.60	45.97	281.03	44.59	0.12
TyG-WC	986.42	135.32	1002.11	147.24	0.71
TyG-WHR	9.47	0.90	10.09	0.95	0.024*
*Statistically significant at p<0.05; Independent Sample *t* test					

Table 5: Mean comparison of lipid parameters between patients with HOMA2-IR ≤ 1.8 and >1.8.

	Area under the ROC curve	95% Confidence interval	*p*-value	Optimal cutoff for predicting IR	Sensitivity (%)	Specificity (%)
Physical parameters						
BMI	0.622	0.459–0.784	0.144 (NS)	Indefinable (27.75)	62.8	64.7
WC (cm)	0.449	0.288–0.610	0.544 (NS)	Indefinable (104.5)	41.9	52.9
WHR	0.705	0.559–0.851	0.014*	1.015	67.4	58.8
Lipid ratios						
TC/HDL-C ratio	0.661	0.509–0.812	0.054 (NS)	Indefinable (4.47)	65.1	76.5
TG/HDL-C ratio	0.477	0.329–0.625	0.787 (NS)	Indefinable (2.1)	48.8	64.7
LDL-C/HDL-C ratio	0.702	0.542–0.863	0.015*	2.42	69.8	76.5
LDL-C/HDL-C and WHR	0.718	0.557-0.879	0.009*	2.49	72.1	70.6
LDL-C/HDL-C and TC/HDL-C	0.677	0.520-0.835	0.034*	11.83	67.4	76.5
LDL-C/HDL-C and TC/HDL-C and WHR	0.689	0.532-0.847	0.023*	11.52	69.8	76.5
LDL-C/HDL-C and TG/HDL-C	0.576	0.432-0.720	0.363 (NS)	Indefinable (4.52)	58.1	52.9
LDL-C/HDL-C and TG/HDL-C and WHR	0.579	0.433-0.724	0.346 (NS)	Indefinable (4.66)	58.1	47.1
Visceral adiposity indicators						
LAP	0.460	0.306 – 0.615	0.634 (NS)	Indefinable (79.65)	46.5	47.1
VAI	0.482	0.332 – 0.631	0.825 (NS)	Indefinable (3.44)	48.8	41.2
*Statistically significant at p ≤ 0.05; NS: Non-significant						

Table 6: Serum lipid parameters and the areas under ROC (receiver operating characteristic) curve for detection of insulin resistance (HOMA2-IR).

	HOMA2-IR		HOMA2 %B	
	Pearson's Correlation Coefficient	*p*-value	Pearson's Correlation Coefficient	*p*-value
TC/HDL-C	0.203	0.120	-0.223	0.087
TG/HDL-C	0.144	0.272	0.117	0.372
LDL-C/HDL-C ratio	0.222	0.088*	-0.267	0.040**
LDL-C/HDL-C and WHR	0.241	0.063*	-0.269	0.038**
LDL-C/HDL-C and TC/HDL-C	0.195	0.136	-0.231	0.076
LDL-C/HDL-C and TC/HDL-C and WHR	0.203	0.120	-0.229	0.079

LAP	0.132	0.315	0.052	0.695
VAI	0.133	0.311	0.135	0.304
*Statistically significant at p<0.10; **Statistically significant at p<0.05				

Table 7: Correlation of IR and beta-cell function with anthropometric/metabolic variables.

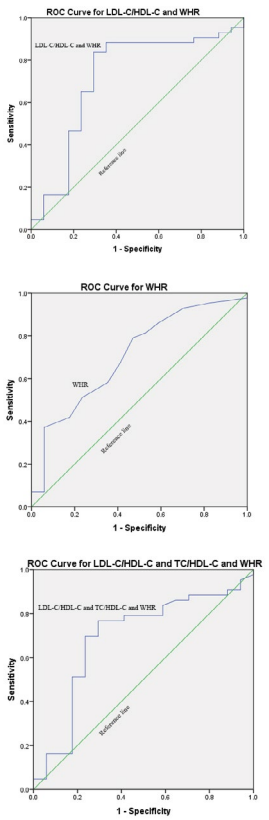

Figure 1: ROC curves of significant anthropometric/metabolic variables for prediction of IR.

	SIRD (Obese, IR)	MOD (Obese, Non-IR)	MARD (Obese) (Age>60yrs)
Frequency (n)	43 (71.6%)	15 (25.0%)	2 (3.3%)
HOMA2-IR	3.11	1.36	1.33
HOMA2 %B	46.79	47.44	51.4
Age at diagnosis, years	46	42	65
Osmotic symptoms (Yes/No)	37/6	1/14	1/1
Family history (Yes/No)	19/24	2/13	0/2
BMI, kg/m^2	28.8	27.5	27.4
WHR	1.04	1.00	1.00
WC (cm)	103	103	113
HbA$_1$c at diagnosis, %	10.34	7.2	9.3
TC/HDL-C	4.71	4.45	3.41
TG/HDL-C	2.44	2.24	1.86
LDL-C/HDL-C	2.86	2.45	1.57
LDL-C/HDL-C and WHR	2.96	2.46	1.57

Table 8: Cluster classification of the 60 T2DM patients using WHR and IR.

notion about IR in our region and if true helps reduce the out of pocket expenditure incurred and maintain the quality of life of all.

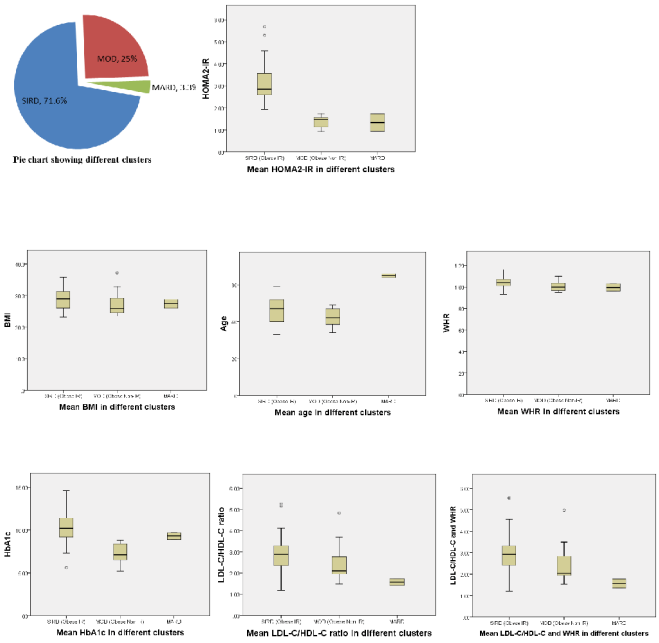

Figure 2: Classification of diabetic cases into three clusters and mean values of various parameters in those clusters.

Conclusion

In conclusion, our finding has emphasized that IR is significantly present and identifying IR at diagnosis or T2DM and treating it right from the initial diagnosis aggressively is equally if not more important than just targeting the blood glucose. To identify IR, the routinely measured parameter LDL-C/HDL-C ratio and WHR together should be used (cut-off of 2.49) to identify its presence in Asians. Multicenter trial is important in this region and is the need of the hour to better analyze the importance of IR and incorporate IR in the diagnostic criteria and classification of T2DM (with IR and without IR) for individualized management and focused monitoring to cut cost and preserve quality of life of the T2DM patients by preventing chronic complications.

Authors' Contributions

PKS conceptualized and designed the study, supervised the work and drafted the manuscript. PB carried out the study, analyzed the data and helped to prepare the manuscript. All authors have read and approved the manuscript.

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Ethics Approval and Consent to Participate

Written permission to conduct the study was obtained from Institutional Review Board, Research Department, Institute of Medicine. Informed written consent was explained and obtained from the all participants.

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