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Original Research Article

A mandatory practice in type 2 diabetes mellitus to maintain quality of life

Sadikshya Shrestha[1]*, Pradeep Krishna Shrestha[2], Binod Kumar Yadav[1]

[1]*Dept. of Biochemistry, Institute of Medicine, Tribhuvan University, Kathmandu, Nepal*
[2]*Dept. of Internal Medicine, Institute of Medicine, Tribhuvan University, Kathmandu, Nepal*

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ABSTRACT

Background: Nepalese owing to modern lifestyle and processed food are racially at an elevated risk of acquiring central obesity-related insulin resistance (IR) and thus Type 2 diabetes mellitus (T2DM) and Diabetic Kidney Disease (DKD). Low birth weight in utero and later becoming obese risks the development of T2DM.

Materials and Methods: In a total of eighty-four newly diagnosed treatment-naive Nepalese T2DMs, incidence of IR, percentage beta-cell function (%BCF) and percentage insulin sensitivity (%IS) were determined using Homeostatic Model Assessment 2 (HOMA2-IR). Association of HOMA2-IR with albuminuria, kidney function, hs-CRP, fatty liver, fatty pancreas, several anthropometric and biochemical parameters were analyzed. Among the eighty-four T2DMs, fifty-four agreeing regular follow-ups were prescribed a low-carbohydrate diet (<130gm/day). At 6 months, their glycemic controls were monitored.

Results: From 84 newly diagnosed T2DMs, 56 (66.7%) were insulin resistant and 28(33.3%) insulin-sensitive on HOMA2-IR. There was a significant association of HOMA2-IR with albuminuria and declining kidney function (p=0.006 and 0.034 respectively) and most of them were at reversible stages. Waist circumference (WC), waist-hip ratio (WHR), lipid profile ratios, fatty liver and fatty pancreas were elucidated as potential markers for IR. The IS group (ISG) had significantly inadequate %BCF (p=0.001) but high %IS (p<0.001) has healthier WHR (p=0.001) and lipid profile ratios which are opposite to IR group (IRG). 13 ISG had raised hs-CRP and 15 normal and 21 IRG had normal hs-CRP and 35 raised. At 6 months, the IRG achieved significantly better postprandial glycemic goals (p=0.04) and significant improvement in WC and WHR (p=0.008 and 0.03 respectively) with a low-carbohydrate diet as compared to ISG.

Conclusion: Severe insulin resistance and IR-associated DKD, fatty liver and fatty pancreas are highly prevalent from the time of diagnosis of T2DM in the Nepalese population. Thus inspecting for IR and its consequences mandatorily at diagnosis and applying precision therapies like adjustments in the quality and quantity of staple food carbohydrates significantly improves IR-related parameters and glycemia.

1. Introduction

As underdeveloped and developing nations endeavor ahead for a better quality of life through westernized diet and lifestyle, the health demographics in them seem to be evolving from inexpensive short duration communicable diseases to expensive life-long chronic non-communicable diseases (NCDs) along with even more expensive chronic complications.[1] This not only compromises the quality of life of individuals with NCDs and their complications but also incurs an economic burden to the family resulting in compromises, hardships and depression.[2]

* *Corresponding author*.
E-mail address: sadikshyasth5@gmail.com (S. Shrestha).

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Asians with a long history of a physically active lifestyle and occupation like agriculture and other manual works, which demand short duration high burst of calories provided by eating their staple unprocessed high carbohydrate foods straight from the fields, are genetically more prone to develop insulin resistance (IR) upon shifting to modern-day processed equally high carbohydrate diet with much less calorie demanding lifestyle and occupation.[3] We have already demonstrated previously that majority of Nepalese with type 2 diabetes mellitus (T2DM) at diagnosis had IR, unlike the Caucasians as in the Swedish study.[4–6]

The German study after the Swedish study showed similar results to the Swedish study reemphasizing the association of IR with DKD, NAFLD and diabetic neuropathy.[4–7] IR has been recognized as the common risk factor for the development of most NCDs like T2DM, atherosclerosis leading to coronary and cerebral vascular diseases, non-alcoholic fatty liver disease (NAFLD) and in-fact the pandemic of metabolic syndrome.[8] Furthermore, IR in renal podocytes has been shown to have a critical role in the development of albuminuria of Diabetic Kidney Disease (DKD), despite euglycemia.[9,10] IR in skeletal muscle resulting in defective muscle glucose uptake along with increased lipolysis from IR in visceral adipocytes causing an increase in hepatic gluconeogenesis, glucose and VLDL output due to hepatic IR along with IR in β cell leading to β cell dysfunction and loss of β cell mass are understood to be the major factors in the pathogenesis of T2DM.[11]

Nepalese seem to be genetically more prone to develop IR with carbohydrate-dense processed food, modern-day lifestyle and occupation and bear its costly morbid consequences. Lower carbohydrate dietary intake befitting lower physically active occupation and lifestyle of today could easily prevent IR and NCDs development in us.[12,13]

A study looking into the role of IR in Nepalese T2DM and IR, associated chronic complications right at diagnosis to individualize treatment regime from start could help in developing the countries specific treatment guidelines. Therefore, we carried out this study aiming to see if our previous study was reproducible. We also aimed to evaluate the association of IR and DKD in them. Homeostatic Model Assessment 2 (HOMA2) was used for calculating IR, percentage beta-cell function(%BCF) and percentage insulin sensitivity (%IS). Spot Urine Albumin to Creatinine ratio (ACR) and estimated Glomerular Filtration Rate (eGFR) were used for diagnosis of DKD and staged. Ultrasonography was used to evaluate fatty liver and pancreas which were correlated with IR. Eye fundoscopy was carried out to evaluate the association of DKD with diabetic retinopathy. Various cheaper and easily available HOMA2-IR indicating parameters were assessed for IR indication.

Since IR can be reversed by diet and physical activity, we designed the Nepalese diet-specific low carbohydrate (CHO) diet and prescribed this diet and recommended to continue their usual physical activity. We followed 54 of the 84 who had agreed to follow-up in the hospital for control of their glycemia and assessed reduction of IR by improvement in various anthropometric parameters associated with IR at 6 months on dietary treatment and their usual physical activities. If glycemic targets were not achieved at 6 months, a pharmacological intervention was added accordingly. We also evaluated the association of T2DM with inflammation with the aid of hs-CRP to see if we can sub-cluster them into T2DM with and without inflammation. With these aims, we present our country or race-specific findings.

2. Materials and Methods

2.1. Study populations

Eighty-four newly diagnosed treatment-naive Nepalese T2DMs visiting the Endocrinology Unit of Tribhuvan University Teaching Hospital (TUTH), a tertiary care center in Kathmandu, Nepal from February 2019 to November 2019 were enrolled using WHO diagnostic criteria for DM. Exclusion criteria included patients with Type 1 diabetes, T2DMs already on lifestyle modification or drug treatment, gestational or secondary diabetes mellitus, diabetic ketoacidosis, known kidney disease, hypertension, patients on ACE/ARB, trauma, toxins, infections, immune system disorders. Study protocols were approved by Institutional Review Board (IRB), Institute of Medicine. All participants gave written informed consent and all underwent the following investigations in the hospital.

2.2. Measurements

Blood pressure (BP) measurement was done using a recently calibrated aneroid sphygmomanometer with an adequate cuff size after a participant had rested for at least 5 minutes and the average of three BP readings was the patient's BP. Weight was taken using a platform digital 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. WHO's Asian parameters were used for categorization.

2.3. Collection and processing of samples

Five milliliters of blood were drawn after an overnight fast (8-12 hours) by the venous puncture method. Serum samples were separated, within half an hour, by centrifugation at 1500-3000 rpm for 5 minutes. Routine investigations were done on the same day of sample collection, which included blood glucose, creatinine, Total Cholesterol (TC), HDL-cholesterol and triglyceride (TG), which were measured in a fully-automated biochemistry analyzer, BT 1500, Italy. An aliquot of each sample was then stored at -80°C for the test of C-peptide and hs-CRP. EDTA anticoagulated blood was used for a determination of HbA1c. Spot urine samples collected from the patients were used for estimation of urinary albumin to creatinine ratio (ACR).

2.4. Procedures

Laboratory standard operating procedures were maintained for all laboratory analyses. 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 the glucose oxidase method, as described by Trinder, using commercial kit Biolabo Reagents, France. (Normal reference range: 3.5-6.1mmol/l)

Serum creatinine was measured by modified Jaffe reaction, Biolabo Reagents, France. (Normal reference ranges for creatinine Male: 60 130μmol/L, Female:40-110μmol/L).

Total cholesterol (TC) was estimated by CHOD/PAP method, Human, Germany. (Normal reference range: 3.5-5.1 mmol/L).

Triglyceride (TG) was measured by GPO/PAP method, Human, Germany. (Normal reference range: 0.5-1.8 mmol/L).

HDL-C was measured by PEG/CHOD-PAP method, Human, Germany. (Normal reference range: 0.8-1.6mmol/L).

LDL-C was calculated using the Friedewald's formula: -(Normal reference range: up to 4 mmol/L).

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. (Normal reference range: 0.1-1.7mmol/L).

Lipid profile ratio was calculated for an individual patient with their obtained values of TC, LDL, HDL and triglyceride.

Normal reference ranges

TC/HDL< 3.37

LDL/HDL < 3.5

TG/HDL< 3.0

HbA1c was measured by Hb-Vario Analyzer which uses pressure cation-exchange high-performance liquid chromatography (HPLC) in conjunction with gradient elution to separate human hemoglobin subtypes and variants from hemolyzed whole blood. (Normal Reference Range: 4.5-6.4%).

hs-CRP was measured using a solid phase enzyme-linked immunosorbent assay (ELISA) kit. (Normal Reference Range-: Neonatal serum: 10 to 350 ng/ml, Adult serum: 68 to 8200 ng/ml).

The C-peptide was measured using Sandwich Chemiluminescence assay performed by MAGLUMI 800 (Normal Reference Range; 0.929-3.73ng/ml). HOMA2 calculator was downloaded from Oxford University and was used for calculating IR. 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).[14] %BCF and %IS were also calculated with HOMA2 calculator and were compared between IRG and ISG T2DM. HOMA2-IR was used to compare and correlate various anthropometric and biochemical parameters between the insulin resistance and insulin sensitivity group of the diabetic cases in this study.

Urinary ACR was calculated by dividing albumin concentration in milligrams by creatinine concentration in millimoles per liter (Urine ACR reference range <3 mg/mmol). Glomerular filtration rate (GFR) was estimated using an abbreviated MDRD (Modification of Diet in Renal Disease) formula incorporating serum creatinine in people over 18 years.[15]

$eGFR = 186 \times (Creatinine \times 88.4)^{-1.154} . (Age)^{-0.203} . (0.742$ if female) x (1.210 if black)

The KDIGO 2012 guideline was followed to classify albuminuria and kidney damage stage in patients.[16]

Abdominal ultrasound was performed and graded by a single experienced radiologist to monitor fatty liver and fatty pancreas.

Fatty liver grading: Fatty liver was diagnosed as well as graded according to the severity of fat deposition into three grades. Grade 1 was characterized by a minimal diffuse increase in the fine echoes. The liver appeared bright compared to the cortex of the kidney. Normal visualization of the diaphragm and intrahepatic vessel borders. Grade 2 was characterized by a moderate diffuse increase in the fine echoes. Slightly impaired visualization of the intrahepatic vessels and diaphragm. Grade 3 was characterized by a marked increase in fine echoes. Poor or no visualization of intrahepatic vessels and diaphragm and poor penetration of the posterior segment of the right lobe of the liver.[17]

The fatty pancreas was diagnosed in the presence of increased echogenicity of the pancreatic parenchyma over that of the kidney with mild fatty pancreas categorized in grade 1 and fatty pancreas in grade 2. As the pancreas couldn't be compared with the kidney in the

same window ultrasound, the radiologists compared the difference between hepatic and renal echogenicity, and between hepatic and pancreas echogenicity, to have an objective ultrasound contrast between the pancreas and kidney.

Eyes fundoscopy after dilatation of pupil was performed by a single experienced ophthalmologist to see for the presence of diabetic retinopathy and their grading.

A low carbohydrate (CHO) (<130gm/day) diet,[18] with liberal calories from other macronutrients, was prescribed to the patients using exchangeable food models along with the recommendation of continuation of their usual physical activity. An inquiry was made at every visit for compliance and motivated for continuation with well-being and observed checklist.

2.5. Statistical analysis

Statistical analyses were done by SPSS 21.0 version (Statistical Package for Social Science for Window version; SPSS, Inc., Chicago, IL). The mean comparison was done by the Man Whitney U test. A Chi-square test was used to evaluate the association between categorical variables.6 months of follow-up data were utilized to perform pre and post-test analysis using repeated-measures ANOVA.

3. Results

The age distribution of the patients enrolled ranged from 25 to 78 years with a mean age of 47.70 years and IR was present in all age groups with no significant association (p= 0.79) (Table 1), denoting that T2DM in Nepalese are less commonly mild age-related diabetes. IR was observed in the majority of new T2DM patients, 66.7% (n=56 with 28 males and 28 females) making up IRG and only 33.3% (n=28 with 14 males and 14 females) ISG. ISG had a significantly lower mean %BCF(p=0.001) but very high mean %IS (p<0.001) when compared to IRG in whom the mean %BCF was significantly high and mean %IS low. These findings show that in the IR state, β cells have to have a super function to maintain euglycemia whereas in IS state β cells are inadequate to maintain euglycemia. BMI was not significantly different with both groups being in the Asian obese range. However, significant mean differences were found between IRG and ISG in terms of WC (p=0.008) and WHR (p<0.001) emphasizing the increased propensity for South Asians to develop IR owing to greater accumulation of inflammatory visceral fat. (Table 2)

Regarding biochemical measurements, the fasting blood glucose (FBG) was high and not significantly different between IRG and ISG denoting hepatic IR and raised fasting hepatic glucose output but postprandial blood glucose (PPBG) was significantly higher (p=0.031) in IRG reflecting muscle and other tissue IR besides hepatic IR thus overstimulating the β cells to secrete higher amounts of insulin to counter resultant hyperglycemia due to IR as reflected by significantly higher fasting c-peptide levels (p<0.001) but still unable to achieve glycemic control as indicated by significantly raised HbA1c (p=0.04). HDL was low, below 1 mmol/l in both groups but significantly lower in IRG (p=0.025) along with raised triglyceride, total cholesterol and LDL without significant difference between the groups. However, lipid ratios, TC/HDL, TG/HDL, LDL/HDL were significantly raised in the IRG (p=0.009, 0.024 and 0.03 respectively) suggesting that IR is more widespread in the IRG and mostly hepatic in ISG. Even though both had ACR in the microalbuminuric stage, IRG were having significantly greater microalbuminuria (p=0.03) in the background of mildly decreased eGFR, stage 2 in both. These findings can be instrumental in defining a panel of biochemical tests in detecting IR among Nepalese T2DM patients at diagnosis (Table 2).

The IR was significantly associated with albuminuria and declining eGFR (p=0.006 and 0.034 respectively). IRG had higher rates of microalbuminuria and greater progression into stages 2 and 3 of DKD than ISG which could justify that individuals with IR may be at elevated risk for developing structural changes in the kidney and eventual decline in GFR (Table 3). Despite the high prevalence of DKD, diabetic retinopathy was a very rare finding in patients (2.4%).

An ultrasound examination of the liver and pancreas revealed a significant association of fatty liver and fatty pancreas with IR. IRG had higher index of fatty liver (77% versus 23%, p=0.001) and fatty pancreas (84% versus 16%, p=0.009) than ISG. (Figure 1)

The hs-CRP was elevated in the 35 but normal in 21 IRG indicating not all had inflammation at the time of diagnosis. Sub-analysis of the 33.3% (n= 28) ISG revealed that 13 had raised hs-CRP and 15 had normal hs-CRP. Can hs-CRP levels indicate sub-cluster within clusters? However, we didn't get a clear-cut association between hs-CRP and ACR in T2DMs.

T2DMs (54, 36 IRG and 18 ISG) who were under a low-carbohydrate diet were followed up for the first month twice and every 3 months for 6 months. Their usual exercise, BMI, WC, WHR, FBG, PPBG and HbA1c were assessed. IRG showed significant improvement in their WC, WHR and PPBG levels (p=0.008, 0.03, and 0.04) respectively) which are known to be markers of IR as compared to ISG. HbA1C came below 7% in both but towards 6.5% in ISG. None required continuous pharmacological intervention to achieve glycemic goals recommended by WHO even at 6 months. (Table 4) All continued to strictly maintain taking the low-carbohydrate diet was counseled to them without complaints, motivated by their glycemic results and overall feeling of well-being.

Table 1: Association of insulin resistance with age groups

Age groups	HOMA2-IR≤ 1.8 n= 28		HOMA2-IR>1.8 n=56		p-value
	No	%	No	%	
25-35	5	17.9	8	14.3	
36-45	7	25.0	19	34.0	
46-55	10	35.7	14	25.0	0.79
56-65	4	14.3	11	19.6	
>65	2	7.1	4	7.1	

Table 2: Comparison of physical and biochemical parameters between ISG and IRG

	HOMA2-IR ≤1.8 n=28		HOMA2-IR >1.8 n=56		p-value
	Mean	± SD	Mean	± SD	
Age (years)	47.50	11.64	47.80	11.65	0.93
BMI	25.89	3.05	27.44	3.76	0.08
WC (cm)	90.57	8.67	96.64	8.36	0.008*
WHR	0.95	0.06	1.00	0.05	<0.001*
FBG (mmol/l)	9.83	2.16	11.35	4.01	0.17
PPBG (mmol/l)	14.22	4.13	17.74	7.00	0.031*
HbA1c (%)	8.68	2.07	9.54	2.00	0.04*
Fasting C-peptide (ng/ml)	1.30	0.51	2.86	0.88	<0.001*
%BCF	29.82	14.84	49.32	27.75	0.001*
%IS	93.66	40.46	35.95	10.56	<0.001*
hs-CRP (ng/ml)	7699	4319	8497	4519	0.61
Total Cholesterol (mmol/l)	4.92	0.91	5.52	1.45	0.11
HDL Cholesterol (mmol/l)	0.99	0.30	0.88	0.26	0.025*
LDL Cholesterol (mmol/l)	2.99	0.77	3.43	1.26	0.16
Triglyceride (mmol/l)	2.56	1.36	3.03	1.62	0.18
VLDL (mmol/l)	1.16	0.62	1.38	0.74	0.17
TC/HDL ratio	5.11	0.97	6.67	2.58	0.009*
TG/HDL ratio	2.62	1.45	3.71	2.12	0.024*
LDL/HDL ratio	3.17	1.04	4.16	2.01	0.033*
Creatinine(mmol/l)	80.25	12.74	85.25	15.98	0.10
ACR	4.22 3.73		6.14 4.66		0.03*
eGFR	85.28 15.71		79.27 16.89		0.10

* Statistically significant at p<0.05; Independent Sample t test (Mann Whitney U)
**Statistically significant at p<0.01; Independent Sample t test (Mann Whitney U)

Table 3: Association of IR with ACR and eGFR

		HOMA2-IR≤1.8 n=28		HOMA2-IR>1.8 n=56		Total	p-value
		No	%	No	%		
ACR	Normoalbuminuria	13	56.5	10	43.5	23	0.006*
	Microalbuminuria	15	24.6	46	75.4	61	
eGFR	Stage 1	12	50	12	50	24	
	Stage 2	16	30.2	37	69.8	53	0.034*
	Stage 3	0	0	7	100	7	

* Statistically significant at p<0.05; Chi-square test

Table 4: Analysis at diagnosis and after 6 months follow up with implemented dietary intervention (n=54)

	At diagnosis				After 6 months				p-value
	HOMA2-IR≤1.8 n= 18		HOMA2-IR>1.8 n= 36		HOMA2-IR≤1.8 n= 18		HOMA2-IR>1.8 n= 36		
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	
WC	91.33	8.28	98.22	8.72	85.00	7.07	89.59	6.05	0.008*
WHR	0.96	0.04	1.01	0.05	0.89	0.04	0.92	0.05	0.03*
BMI	26.87	2.58	28.19	3.41	25.36	2.26	26.30	3.02	0.06
FBG	9.56	1.97	10.88	4.03	6.01	0.99	6.37	1.09	0.16
PPBG	14.33	3.85	17.99	6.70	7.77	1.19	8.18	1.67	0.04*
HbA1C	8.93	2.26	9.33	1.80	6.62	1.03	6.99	1.07	0.35

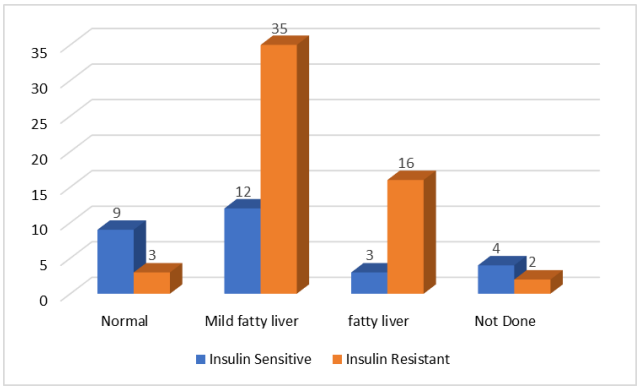

Figure 1: Association of IR with fatty liver

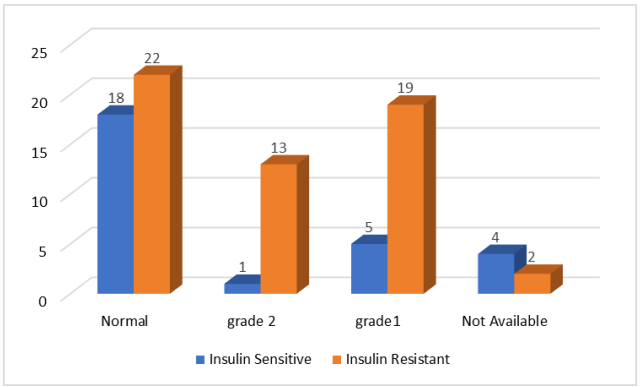

Figure 2: Association of IR with fatty pancreas

4. Discussion

This study reproduced the findings of the previous study published in 2018[4] confirming that IR (71.6% and 66.7% respectively in previous and present findings) has a dominant role in the pathogenesis of T2DM irrespective of age and sex in the Nepalese population unlike in the Caucasians. Excess calories intake from carbohydrates are stored mostly as white fat which may result in the development of IR and its morbid consequences in South Asians as revealed by IR-associated NCD epidemic studies in comparison to Caucasian dominant regions.[19] Waist circumference (p= 0.008) and more emphatically waist-hip ratio (p< 0.001) as shown by Table 2 have been reidentified by this study to be very sensitive and inexpensive anthropometric parameters for IR due to visceral adiposity. This coincides with World Health Organization (WHO) guideline stating that alternative measures that reflect abdominal obesity such as WC and WHR are superior to BMI in predicting IR.[20] Hence WC and more so WHR needs to be relied upon and popularized in a finance constrained situations to identify IR.

Significant biochemical parameters such as TC/HDL or TG/HDL or LDL/HDL ratios as illustrated in Table 2 further reinforce IR if used together with anthropometric parameters instead of expensive HOMA2-IR in clinical settings. Significantly high PPBG initially signifies skeletal muscle IR.[21] High BMI of 33.3% was found in ISG (n=28). But WC and WHR which signify visceral obesity were raised but significantly lower (p=0.008 and <0.001 respectively) than in IRG. This suggests that ISG are obesity-related T2DM with significantly lower visceral obesity.[5,6] As Nepal is one of the poorest countries in the world, many are born in poverty from undernourished mothers. These neonates are of low birth weight with small pancreas who may later gain weight and become obese in adulthood. Such situations of β cell inadequacy, owing to adulthood weight gain can also create ISG cluster in obesity-related T2DM.[22,23] The hs-CRP levels may be able to differentiate T2DMs with and without inflammation which may be indicating gestational nutrition and susceptibility to chronic complications of T2DM calling for targeted precision pharmacological treatment variation between and within the clusters beyond lifestyle modification for weight loss.[24]

Of the 66.7%(n=56) IR, 82.1% (n=46) as depicted by Table 3 had microalbuminuria. This finding emphasizes that T2DM patients are already in a serious chronic complication of DKD and if not looked for and treated from diagnosis could end up with expensive DKD treatments and loss of quality of life. However, 17.9%(n=10) of IRG (Table 3) did not have albuminuria but their eGFR was lower than 90(mean 83.9) signifying that T2DM could have decreased in GFR <90 despite normoalbuminuria. 53.6%(n=15) of

ISG (Table 3) also had albuminuria irrespective of hs-CRP levels. However, the etiology couldn't be identified but further workup of such cases needs to be pursued to prevent probable non-diabetic chronic kidney disease (CKD). The majority (91.7%) were having eGFR stages 1 and 2 depicting that T2DMs are mostly in a reversible stage. This underlines the importance of investigating for DKD at diagnosis. IRG had a higher index of fatty liver (77%) and fatty pancreas (84%) on ultrasound compared to ISG denoting greater metabolic derangement in IR. (Figures 1 and 2)

There was no significant association of diabetic retinopathy (DR) with albuminuria and declining eGFR. DR was a very rare finding in our study at diagnosis of T2DM irrespective of IR or IS suggesting DR be less related to IR and more related to the duration of hyperglycemia. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), among younger-onset patients with diabetes, the prevalence of any retinopathy was 8% at 3 years, 25% at 5 years, 60% at 10 years, and 80% at 15 years suggesting duration of diabetes to be the strongest predictor for development and progression of retinopathy.[25]

At 6 months, both groups showed a positive response to the low-carbohydrate diet but significant improvement was seen among IRG in regards to postprandial glycemic control and reduction in IR as demonstrated by anthropometric parameters such as WC and WHR which are markers of IR. This adherence to dietary measures though considered by the majority as short-lasting and poor compliance was not so in our cases who continued to be on it despite usual counseling.

5. Conclusion

In conclusion, our study demonstrates the higher prevalence of IR among Nepalese T2DM patients. IR-induced DKD is significantly present right at diagnosis but luckily at the reversible DKD stage, emphasizing the fact that our T2DM patients have more severe T2DM. We need to treat IR very vigorously with field-to-meal food without refining and processing leaving the fiber and low normal carbohydrate content intact along with a usual physical activity to burn the excess calories to prevent their storage in the belly and thus, remain free from IR, common to most NCDs. Drugs that target IR or prevent a surge in glucose absorption to match β cell function and decrease albuminuria need to be used for the remission of T2DM, DKD and other IR-associated NCDs. Maybe T2DM clusters can be subclustered based on hs-CRP and selection of precision treatment made accordingly.

6. Conflict of Interests

We declare no competing interests.

7. Contributors

PKS contributed to the conception of the work. SS researched data and contributed to data analysis. SS and AK contributed to data collection. AK formulated a standard low-carbohydrate diet prescribed to patients. BKY arranged the setup to run the biochemical tests. BKY and MR contributed to financial aid. UMP carried out ultrasound on our patients and SMS helped with eyes fundoscopy. PKS drafted the article and contributed to the discussion. SS contributed to the revision of the report. All authors gave final approval of the version to be published.

8. Patient Consent for Publication

All participants gave written informed consent and all underwent the necessary investigations in our hospital.

9. Ethics Approval

The study protocols were approved by Institutional Review Committee (IRC), Institute of Medicine, Kathmandu, Nepal.

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Author biography

Sadikshya Shrestha, Assistant Professor

Pradeep Krishna Shrestha, Professor and Head

Binod Kumar Yadav, Associate Professor

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