Table S1.A. Total Insulin secretion shown by area under curve (AUC) on MMTT across groups

AUC (pmol/kg)	LD (n=17)	T1D (n=5)	T2D (n=11)	Lean diabetics (n=13)	Overweight non-diabetics (n = 7)
0-15 min	27.6 (19.4, 36.9)	0.09 (0.09, 0.09)*	45.4 (32.7, 83.6)*	82.8 (59.7, 114.9)***	98.3 (76.1, 132.9)***
15-30 min	38.9 (30.6, 45.3)	0.09 (0.09, 0.09)*	61.9 (39.2, 116.2)*	150.2 (116.3, 201.9)***	169.3 (149.1, 223.9)***
30-60 min	94.5 (62.3, 115.4)	0.09 (0.09, 0.09)*	147.1(115.1, 256.1)*	304.1 (224.1, 382.8)***	349.2 (334.9, 443.5)***
60-90 min	115.3(63.8, 138.9)	0.09 (0.09, 0.09)*	159.6(112.1, 243.2)*	236.0 (145.4, 286.1)***	273.1 (235.9, 328.3)***
90-120 min	108.8(65.3, 126.2)	0.09(0.09, 0.09)**	147.9(105.3, 227.7)*	131.3 (81.4, 193.3)	150.8 (87.8, 285.6)*
120-150 min	86.7 (65.9, 125.9)	0.09(0.09, 0.09)**	150.4 (98.6, 223.8)*	79.7 (29.5, 141.5)	140.9 (70.5, 208.9)
150-180 min	85.5 (60.0, 119.7)	0.09(0.09, 0.09)**	138.1(191.8, 172.1)*	49.7 (24.5, 87.8)	90.5 (56.3, 118.2)
Total AUC	383.0(199.8,557.3)	0.09(0.09, 0.09)*	839.5(609.8,1366.6)*	91.1 (547.1, 1260.5)**	1277.0 (1109.0, 1599.1)***
Total AUC first phase (0-15 min)	27.6(19.4, 36.9)	0.09(0.09, 0.09)*	45.4(32.7, 83.6)*	82.8(59.7, 114.9)***	98.3 (76.1, 132.9)***
TotalAUC second phase(15-180 min)	529.1(356.9,621.8)	0.09(0.09, 0.09)*	798.6(586.9,1282.9)*	931.4 (511.7, 1145.6)**	1176.5(988.2, 1522.9)***

MMTT: Mixed meal tolerance test, LD=Low-BMI Diabetes, T1D=Type 1 diabetes, T2D=Type 2 diabetes, DM=Diabetes Mellitus, AUC=area under the insulin secretion curve (total insulin secretion). Data are presented as median and interquartile range (25^{th}, 75^{th} percentile in parentheses). Asterisks indicate values that are significantly different to the Lean Diabetes group. (* $p<0.05$, ** $p<0.01$, *** $p<0.001$)

Table S1.B. Insulin secretion rate (ISR) during MMTT, for all time points across groups

Time points	LD (n=17)	T1D (n=5)	T2D (n=11)	Lean non-diabetics (n=13)	Overweight non-diabetics (n =7)
0 min	1.37 (0.7, 2.1)	0.09 (0.09, 0.09)**	2.3 (1.7, 3.6)*	1.5 (0.8, 2.5)	2.1 (1.8, 2.8)*
15 min	2.14 (1.4, 2.8)	0.09 (0.09, 0.09)	4.1 (2.6, 6.9)*	7.7 (6.3, 13.1)***	10.5 (6.0, 16.)***
30 min	2.8 (1.6, 3.3)	0.09 (0.09, 0.09)*	4.6 (3.7, 8.5)*	11.0 (8.1, 12.3)***	13.8 (11.4, 14.7)***
60 min	3.6 (2.2, 4.4)	0.09 (0.09, 0.09)*	5.2 (3.8, 8.5)*	8.9 (5.9, 11.7)***	10.9 (8.1, 14.9)***
90 min	3.8 (2.4, 4.3)	0.09 (0.09, 0.09)*	4.8 (3.6, 7.6)*	5.9 (2.7, 8.9)*	7.0 (4.6, 8.9)**
120 min	3.3 (2.1, 4.3)	0.09 (0.09, 0.09)**	5.1 (3.4, 7.5)*	3.6 (1.2, 5.1)	3.8 (1.4, 8.8)
150 min	2.8 (1.6, 4.1)	0.09 (0.09, 0.09)**	4.8 (3.2, 7.1)*	2.1 (0.6, 4.0)	4.0 (2.2, 5.2)
180 min	2.9 (1.3, 3.8)	0.09 (0.09, 0.09)***	4.7 (2.9, 5.8)*	1.1 (0.7, 3.5)	2.1 (1.5, 2.7)

MMTT: Mixed meal tolerance test, LD=Low-BMI Diabetes, T1D=Type 1 diabetes, T2D=Type 2 diabetes, DM=Diabetes Mellitus. Values are presented as median and interquartile range (25^{th}, 75^{th} percentile in parentheses). Asterisks indicate values that are significantly different to the Lean Diabetes group (* $p<0.05$, ** $p<0.01$, *** $p<0.001$).

Table S2. EGP and RD values on euglycemic- hyperinsulinemic pancreatic clamp procedure across groups

Variables	LD (n = 18)	T1D (n = 14)	T2D (n = 11)	Lean non-diabetics (n = 13)	Overweight non-diabetics (n = 9)
EGP (mg/kg. min) low insulin phase of the clamps	0.5 ± 0.1	0.6 ± 0.1	0.84 ± 0.1*	0.4 ± 0.1	0.7 ± 0.1
EGP (mg/kg. min)^{ß} low insulin phase of the clamps	0.01 ± 0.002	0.01 ± 0.002	0.02 ± 0.002	0.01 ± 0.003	0.01 ± 0.002
EGP (mg/kg. min) high insulin phase of the clamps$^{\#}$	0.082 (-0.04, 1.2)	-0.006 (-0.3, 1.4)	0.039 (-0.12, 0.7)	-0.3 (-0.7, 0.1)	0.12 (-0.26, 0.2)
RD (mg/kg. min) high insulin phase of the clamps	10.1 ± 0.7	8.5 ± 0.4	4.2 ± 0.5***	10.8 ± 0.7	7.6 ± 0.5
RD (mg/kg. min)^{ß} high insulin phase of the clamps	0.3 ± 0.02	0.2 ± 0.01**	0.1 ± 0.008***	0.3 ± 0.03	0.2 ± 0.01***

EGP=endogenous glucose production, RD =rate of glucose disposal. LD=Low-BMI Diabetes, T1D=Type 1 diabetes, T2D=Type 2 diabetes, DM=Diabetes Mellitus. Data are presented as Mean ± standard error of the mean or median and interquartile range (25^{th}, 75^{th} percentile in parentheses, indicated by #)). $^{\&}$ EGP assessed during the high insulin phase of the clamps; ^{ß}Adjusted for lean body mass. Asterisks indicate values that are significantly different to the Lean Diabetes group. (* $p<0.05$, ** $p<0.01$, *** $p<0.001$).

Table S3. Fasting and MMTT based surrogate indices of insulin resistance across groups.

Variables	LD (n = 20)	T2D (n =11)	Lean non-diabetics (n = 13)	Overweight non-diabetics (n = 7)
HOMA-IR	1.9 ± 0.4***	4.1 ± 0.32	0.8 ± 0.2	1.6 ± 0.46
FGIR	31.2 ± 5.6	20.7 ± 7.4	29.6 ± 6.1	18.8 ± 5.3
ISI	12.3 ± 2.2*	4.2 ± 0.3	20 ± 4.3	8.1 ± 2.1
Matsuda Index	13.2 ± 2.1*	3.9 ± 0.3	17.5 ± 3.9	6.9 ± 1.6
Insulinogenic index	0.04 ± 0.1***	0.2 ± 0.1***	0.9 ± 0.2***	0.9 ± 0.2***
Disposition index	1.7 ± 0.5***	0.7 ± 0.4	12.1 ± 1.9	5.8 ± 0.8

LD=Low-BMI Diabetes, T1D=Type 1 diabetes, T2D=Type 2 diabetes, DM=Diabetes Mellitus.
Data are presented as Mean ± standard error of the mean. Statistically significant. Asterisks indicate values that are significantly different to the Lean Diabetes group. (*p<0.05, **p<0.01, ***p<0.001).

Table S4. **Hormone and biochemical metabolite levels groups during clamp studies across groups**

Groups	Insulin (µU/ml)#	C-peptide (ng/ml)	Glucagon (pg/ml)	Lactate (mg/dL)	Free Fatty acid (µmol/L)
LD (n = 18)					
low phase	66.65(48.25, 124.5)	0.1(0.09, 0.2)	50.0(30.3, 65.4)	1.3(1.1, 1.5)	16.1(12.5, 16.1)
high phase	183.2(131.65, 378)	0.1(0.09, 0.14)	41.1(30.6, 69.7)	1.7(1.4, 1.9)	8.4(5.6, 20.7)
T1D (n = 14)					
low phase	94.9(52.5, 160.3)	0.09(0.09, 0.09)	49.9(38.5, 66.3)	1.1(0.9, 1.3)	66.45(40.0,91.8)
high phase	293.8(190.9, 420)	0.09(0.09, 0.09)	44.5(35.3, 44.5)	1.5(1.4, 1.7)	59.0(37.6, 65.5)*
T2D (n = 11)					
low phase	112.9(101.5, 126)	0.15(0.11, 0.4)	47.3(32.4, 78.8)	1.2(1.1, 1.3)	91.7(64.2, 142)***
high phase	288.8(249.3, 315)	0.15(0.09, 0.5)	55.5(35.5, 69.8)	1.3(1.1, 1.6)	57.3(42.0, 79.5)**
Overweight non-diabetics (n = 9)					
low phase	105.5(71.3, 122.8)	0.16(0.13, 0.4)	47.3(24.5, 67.3)	1.2(1.0, 1.4)	45.0(41, 102.8)
high phase	312.5(293.8, 346.25)	0.3(0.10, 0.9)	52.2(41.4, 66.1)	1.3(1.2, 1.7)	26.5(20.3, 53.8)
Lean non-diabetics (n = 13)					
low phase	91.5(54.1, 101.9)	0.18(0.11, 0.7)	46.6(42.5, 52.9)	1.3(1.0, 1.4)	25.0(12.9, 49)
high phase	255(185.6, 308.75)	0.5(0.12, 0.9)	51.2(45.9, 55.5)	1.5(1.2, 1.7)	14.3(9, 41.5)

LD=Low-BMI Diabetes, T1D= Type 1 diabetes, T2D=Type 2 diabetes, DM=Diabetes Mellitus. Data are presented as median and interquartile ranges (IQR). Asterisks indicate values that are significantly different when compared to the Lean Diabetes group. (*p<0.05, **p<0.01, ***p<0.001). #For calibrating the measurements of insulin values between those from Christian Medical College and Albert Einstein College of Medicine, we used two subjects that were measured at both sites. First, at each time point, we computed a ratio of sample means between the two sites. We then take the geometric mean of the ratios across the 7 time points to get a calibration factor of 2.5.

Table S5. Body composition profile (on DXA), abdominal adipose tissue depots, myocellular and hepatocellular lipids (on MRS) across groups.

Variables	LD (n = 20)	T1D (n = 15)	T2D (n = 13)	Lean non-diabetics (n = 16)	Overweight non-diabetics (n = 9)
Total fat mass (kg)	≠9.4 ± 0.6	≠9.2 ± 0.7	≠18.8 ± 1.2***	≠8.9 ± 1.1	≠17.0 ± 0.8***
Total lean mass (kg)	#39.8 (36.0, 42.5)	#45.8 (40.6, 49.5)**	#53.7 (49.8, 56.7)***	#43.0 (40.7, 51.1)**	#50.7 (49.3, 54.4)***
Truncal fat mass (kg)	#4.6 (3.1, 4.9)	#3.2 (2.4, 4.5)*	#9.7 (7.9, 11.1)***	#3.2 (2.5, 4.7)*	#7.8 (7.5, 9.0)**
Truncal lean mass (kg)	#19.0 ± 0.5	#22.3 ± 0.6**	#26.1 ± 0.9***	#22.0 ± 0.8*	#25.1 ± 0.7***
SAT (cm^3)	#489.9 (333.9, 759.5)	#645.5 (558.3, 910.7)	#1551.0 (1299.7, 2019.7)***	#525.1 (445.8, 111.8)	#1654.5 (1435.5, 1832.5)***
VAT/SAT ratio	#0.7 (0.4, 0.9)	#0.3 (0.2, 0.3)**	#1.1 (0.7, 1.4)	#0.3 (0.3, 0.3)**	#1.4 (0.8, 1.6)*
IMCL† Soleus	#1.2 (0.9, 2.8)	#1.2 (0.8, 1.5)	#2.6 (1.4, 4.2)*	#0.8 (0.6, 2.9)	#2.5 (1.2, 3.4)
EMCL† Soleus	#1.0 (0.7, 1.3)	#1.3 (0.8, 1.9)	#2.3 (1.7, 3.0)**	#1.5 (1.3, 1.9)	#0.7 (0.5, 2.4)
Tibialis Anterior IMCL†	#0.4 (0.2, 0.5)	#1.0 (0.2, 1.4)	#0.5 (0.2, 0.8)	#0.2 (0.1. 0.4)	#0.3 (0.2, 0.7)
Tibialis Anterior EMCL†	#1.0 ± 0.1	#1.3 ± 0.3	#2.1 ± 0.7*	#1.0 ± 0.2	#1.1 ± 0.2

LD=Low-BMI Diabetes, T1D=Type 1 diabetes, T2D=Type 2 diabetes, DM=Diabetes Mellitus, SAT=Subcutaneous adipose tissue, EMCL=Extramyocellular lipids, IMCL=Intra-myocellular lipids. Data are presented as mean ± standard error of the mean (mean values indicated by ≠) or median (indicated by #) and interquartile range (25^{th}, 75^{th} percentile in parentheses). Asterisks indicate values that are significantly different to the Lean Diabetes group. (* $p<0.05$, ** $p<0.01$, *** $p<0.001$). † % of water resonance peak intensity.

Table S6. Dietary intake of macro and micronutrients across groups.

Variables	RDA	LD	Lean normal	*P* value*	T1D	*P* value**
Proteins (gms/day)	60.0 ± 6.3	44.4 ± 15.6	54 ± 25	< 0.05	47.0 ± 7.1	0.31
Carbohydrates (gms/day)	225.4 ± 24.6	285.4 ± 63.4	298 ± 41.4	0.40	255.1 ± 58	< 0.05
Fats (gms/day)	46.3 ± 11.3	41.2 ± 4.3	55.1 ±17.4	0.62	46.5± 8.0	0.85
Fibre (gms)/day	25.0	9.4 ± 4.6	8.0 ± 4.0	0.33	53.5± 13.7	0.28
Calcium (mg/day)	600	658 ± 191	470 ± 171	< 0.01	14 ± 17.3	0.48
Carotene (µg/day)	4800	2500 ± 1968	1242 ± 957	< 0.05	726 ± 348	0.50
Thiamine (mg/day)	1.2 ± 0.8	1.5 ± 0.3	1.2 ± 0.4	< 0.05	1.4 ± 0.3	0.58
Riboflavin (mg/day)	1.4	0.91± 0.4	0.7 ± 0.3	0.25	1.3 ± 1.2	0.18
Niacin (mg/day)	1.6	12.1 ±	9.8 ± 3.1	0.11	10.8± 3.7	0.38
Folic acid (µg/day)	200	202.2 ± 73.4	214.3 ± 75.4	0.64	221 ± 74	0.48
Vitamin C (mg/day)	40.0	92.5 ± 38.6	88.4 ± 43.2	0.78	89.1 ±36	0.80
Iron intake (mg/day)	17.0	18.0 ± 10.7	10.5 ± 5.6	< 0.05	15.7 ± 7.5	0.48
Total energy intake (kcals/day)	1640 ± 201	1777 ± 250	1908 ± 338	0.37	1617 ± 191	0.57

* indicates significance for differences in mean values between the LD and the lean normal group.
** indicates significance differences in mean values between the LD and the T1D group.
P value: < 0.05; Statistically significant.
RDA: Recommended dietary allowance for Indians (Age and BMI specific)

Table S7. Dietary intake of macro and micronutrients between the T2D and the overweight-nondiabetic group.

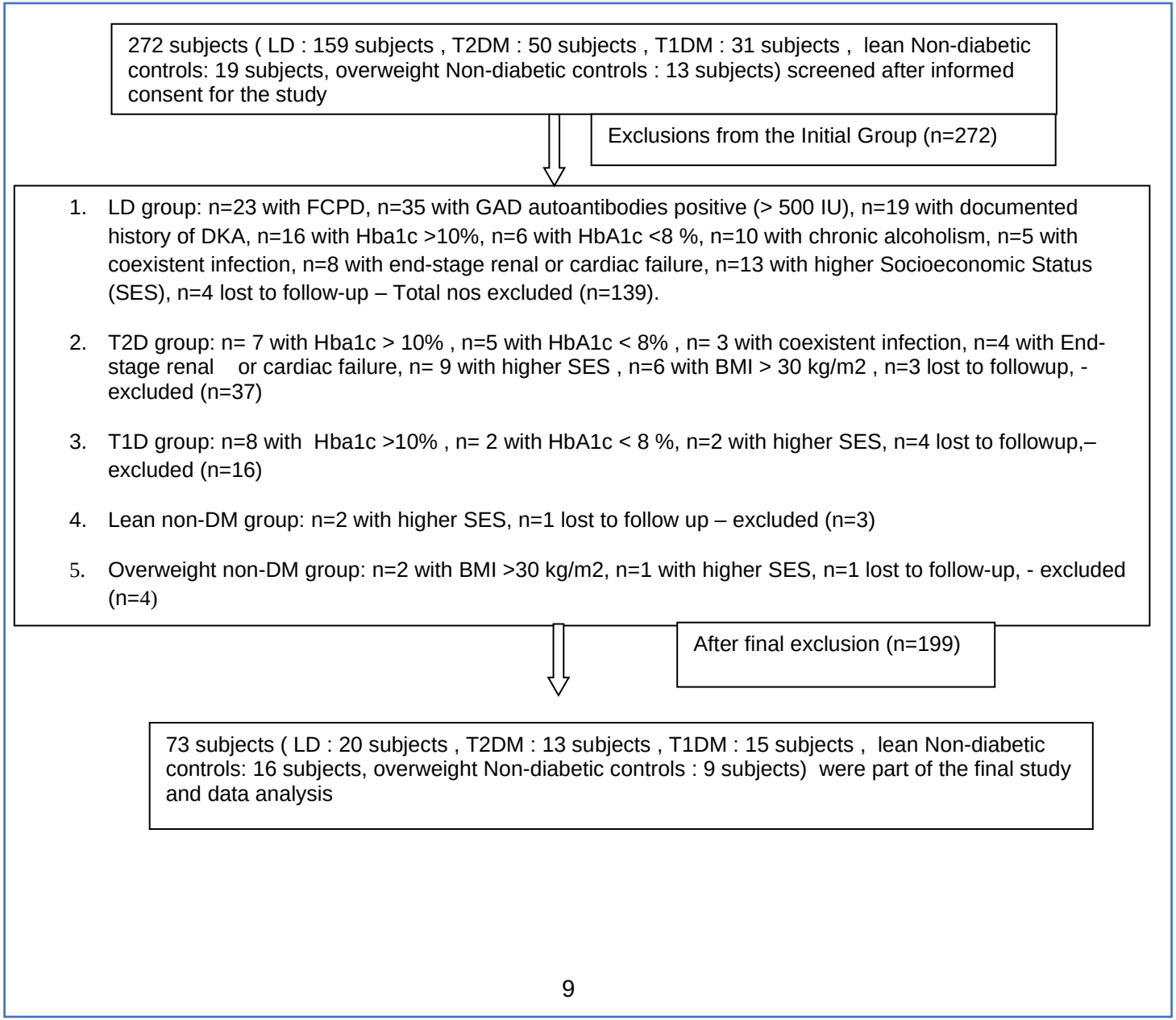
Variables	RDA	T2D	Overweight non-diabetic group	*P* value*
Proteins (gms/day)	82.6 ± 6.0	41.3 ± 12.3	51 ± 11	0.11
Carbohydrates (gms/day)	255 ± 18.5	272.3 ± 55	311 ± 60	0.15
Fats (gms/day)	48.2 ± 3.0	50 ± 15	62 ± 10	**< 0.05**
Fibre (gms)/day	25.0 ± 2.0	8.0 ± 3.5	9.2 ± 4.3	0.60
Calcium (mg/day)	600	482.0 ± 195	618 ± 207	0.14
Carotene (µg/day)	4800	1654 ± 894[#]	1927 ± 1047[#]	0.73
Thiamine (mg/day)	1.2	1.33 ± 0.5	1.4 ±0.3	0.76
Riboflavin (mg/day)	1.4	0.7 ± 0.3	0.8 ± 0.3	0.33
Niacin (mg/day)	1.6	7.2 ± 2.0	9.7 ± 3.7	0.48
Folic acid (µg/day)	200	188 ± 61.5	241 ± 96	0.13
Vitamin C (mg/day)	40	55.5 ± 28.5	94 ± 24	**< 0.05**
Iron intake (mg/day)	17.00	10.0 ± 3.0	13 ± 11	0.42
Total energy intake (kcals/day)	1705 ± 122.3	1712 ± 333	2004 ± 298	**< 0.05**

P value: < 0.05 : Statistically significant. RDA: Recommended dietary allowance for Indians (Age and BMI specific)

* indicates significance in differences of mean values between the T2D and the overweight non-diabetic group.

: indicates Median value.

Figure S1. Study design with exclusion criteria



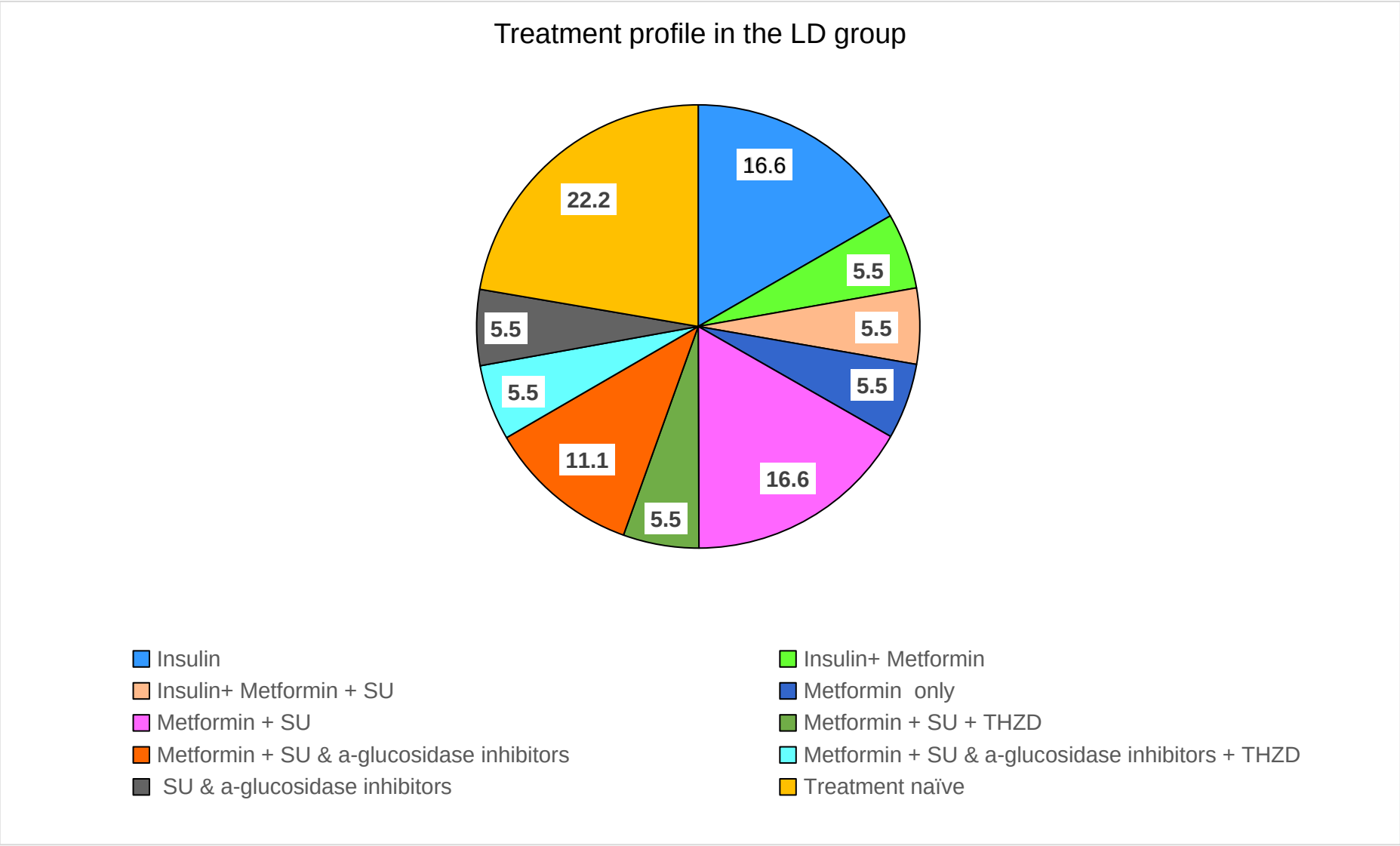


Figure S 2(a). Treatment profile in the Low BMI Diabetes (LD) group at recruitment.
(Data are shown as % values of actual numbers; THZD: Thiazolidinedione; SU: Sulphonlyureas)

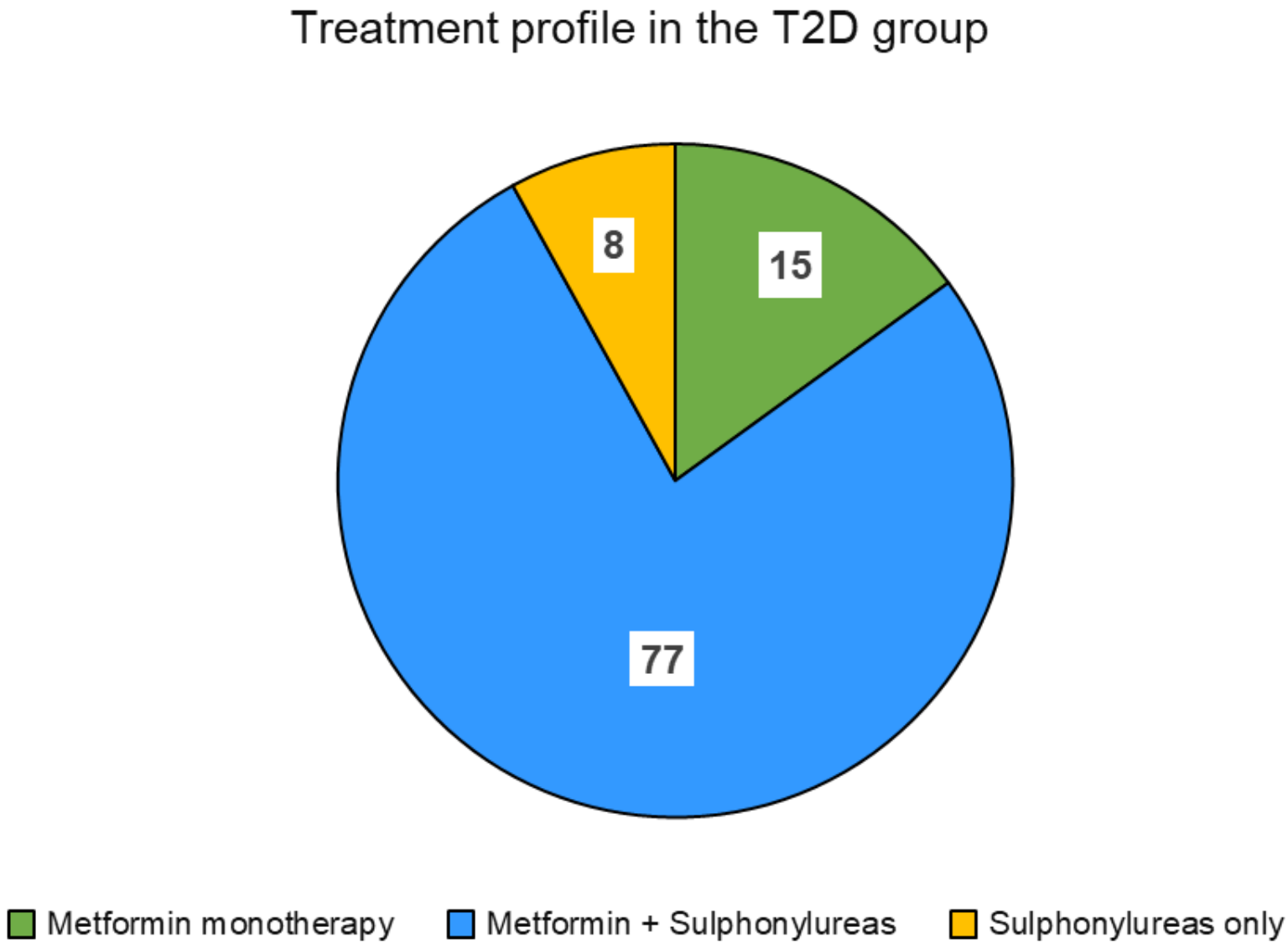


Figure S2(b). Treatment profile in the Type 2 diabetes (T2D) group (n =13) at recruitment (shown in % values of actual number)

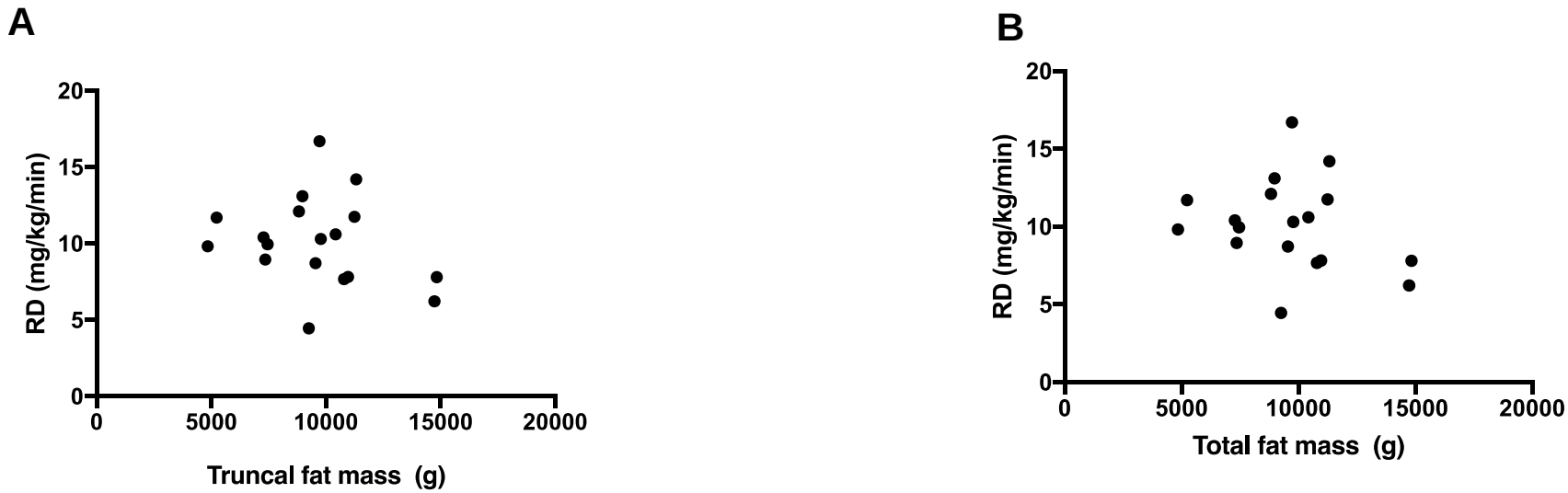


Figure S3. Correlation analysis across LD group. (A) Correlation between RD and truncal fat mass, (B) Correlation between RD and total fat mass. SAT=Subcutaneous adipose tissue, RD =rate of glucose disposal.

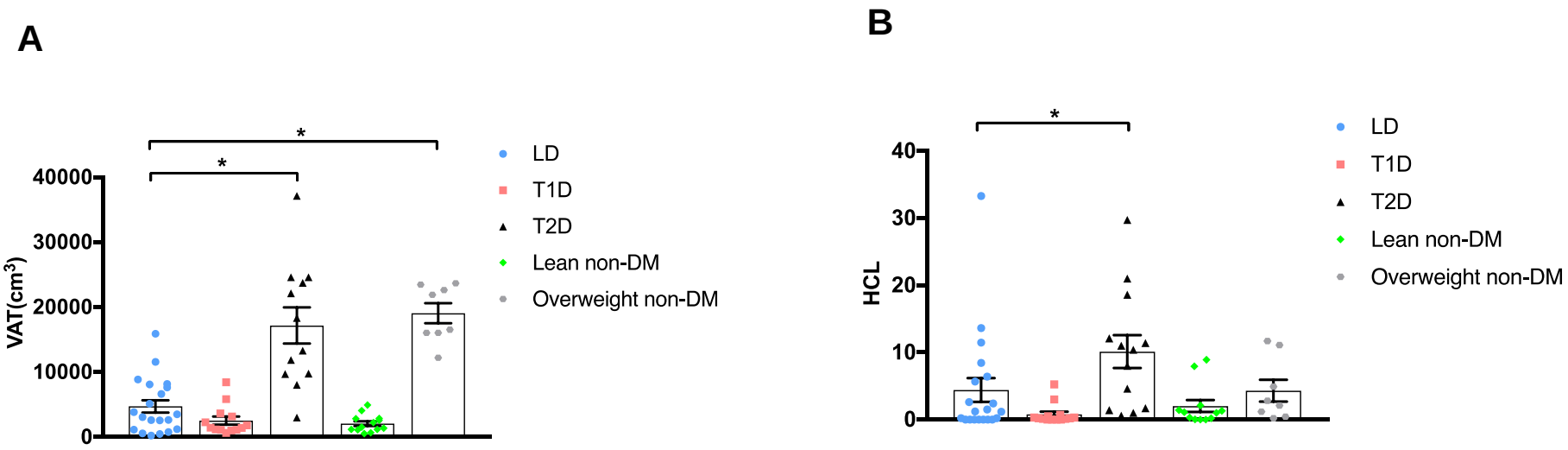


Figure S4. Visceral adipose Tissue: VAT (a), and Hepatocellular lipid: HCL (b) across groups. LD=Low BMI Diabetes, T1D= Type 1 diabetes, T2D=Type 2 diabetes. Data are presented as mean ± standard error of the mean (mean ± SEM). Asterisks indicate values that are significantly different when compared to the Lean Diabetes group versus T1D and T2D group. (* $p<0.05$).

Supplementary methodology

Inclusion and Exclusion criteria for lean participants with diabetes in the study.

Inclusion criteria : The study recruited lean (BMI </= 19.6 Kg/m^2) male subjects aged between 19 -45 years, with diabetes (HbA1C : 8 -10 %) in the LD group.

Exclusion criteria.

1. Signficant history of Alcoholism.
2. Documented history of diabetic ketoacidosis.
3. Seropositivity for Glutamic acid decarboxylase (GAD) and Islet tyrosine phosphatase 2 (IA 2) antibodies (for subjects in the LD group)
4. Medical history suggestive of acute pancreatitis, pancreatic diabetes or calcifications in pancreas as detected on imaging or ultrasonography.
5. History of significant liver dysfunction or chronic kidney disease.
6. History of cardiovascular disease, hypertension or diabetic neuropathy.
7. Family history suggestive of young onset diabetes (onset at < 35 years of age).

Anthropometric classification : Participants were classified as considered as Obese in accordance to the cut-offs for definition of obesity in South Asians as per the guidelines of the National Institute for Health and Care excellence 2013. (*weblink:https://www.nice.org.uk/guidance/cg189/ifp/chapter/obesity-and-being-overweight*) As per the cut-off values, the BMI

above 23.0-24.9 kg/m^2 was considered overweight and indicates increased risk and BMI > 27.5 kg/m^2 was considered as high-risk obesity.

Calibration of assays : Assay standards were calibrated against the WHO reference NIBSC (97/550) (20). The cut-off level was set to 5 U /ml for GAD 65 antibody titre and 7.5 U/ml for IA2 antibody titre (according to Juvenile Diabetes Federation standards), which are the lowest standard concentrations for detection of seropositivity, as recommended by the manufacturer for serum samples. Patients with GAD antibody titre 5U/ml and above were considered as T1D and included in the T1D arm, but not in the LD group.

Correction of glucose toxicity: Subjects with diabetes who were eligible for the clamp studies were provided with a glucose log book and a glucometer and instructed to maintain fasting, pre- and post-prandial glycemic profiles six times daily (fasting, premeal and 2 hours post meal with meals signifying breakfast, lunch and dinner respectively) for two weeks preceding the clamp procedure. The subjects would follow-up with the self-monitored glucose readings daily and consult the Diabetes Nurse educator and physician assigned to the study. Dietary counselling was provided to ensure all the subjects were consuming a standardized, balanced diet and taking precautions to avoid hypoglycemia, especially nocturnal. For subjects on subcutaneous insulin injections, either a twice daily premixed regimen or a basal-bolus regimen with four injections daily were used. Insulin doses were titrated to achieve optimal glycemic control as per the ADA targets (FPG or pre-meal: 80-130 mg/dl, PPPG < 180 mg/dl). For subjects on OADS, the dosage and drug regimen were optimized to meet the same targets of glycemic control without increasing the risk of hypoglycemia. Subjects were also provided with phone numbers which they could call for teleconsultation in cases of any acute rise or fall in blood glucose levels during this two-week period of correction of glucotoxicity.

We measured fructosamine levels as a measure of glycaemic control (10.2337/diacare.27.5.1028) for about 2 weeks, to also ensure that the groups were matched for glycaemic control by the time of the metabolic studies. Fructosamine levels measured prior to metabolic procedures has been reported in earlier studies[1-3].

Further, all biochemical measures including that of baseline glucose, C-peptide and insulin were taken after the intensive correction of glucotoxicity for two weeks and prior to the clamp procedure. Patients scheduled for the clamp procedure were admitted in the metabolic ward of the study centre and the glycemic profile was monitored for 8 hours prior to the clamp procedure, to avoid hyperglyemia/ hypoglycemia. (ADA: American Diabetes Association, FPG: Fasting Plasma Glucose, PPPG: Post-Prandial Plasma Glucose.)

Methodology of Stepped hyperinsulinemic- euglycaemic clamp (HEC) procedure.

Prior to the clamp study, the participants were admitted to the metabolic ward and the glycemic profile was monitored for atleast 8 hours. On the day of the HEC procedure, subjects presented to the study room in the morning after an 8 hour overnight fast. The vital physiological parameters and the overnight glucose profile was examined by the physician. Two intravenous cannulas were inserted on the right and left arms for infusions and blood sampling respectively. To obtain arterialized venous blood samples, the cannulated arm was maintained at 65°C in a heated blanket and the blood draw cannulas were checked frequently for patency. A bolus dose of (Deuteriated Glucose) (D2G) was infused at the rate of 200 mg/m^2 over the first 3 minutes initially, followed by a continuous infusion rate of 2 mg/min/m^2 for a total duration of 6 hours to quantify for plasma glucose turnover. In addition, the clamp procedure also

consisted of exogenous infusion of insulin/somatostatin (250 µg/hour) infusions with replacement of glucoregulatory hormones (glucagon 1 ng/kg/min; growth hormone 3 ng/kg/min). Throughout the entire 360 minutes, the plasma glucose concentration was maintained at euglycaemia (~90 mg/dl) with meticulously adjusted exogenous infusion of 20 % dextrose and calculated dose of insulin infusion in each phase. The entire study was divided into 3 inter-connected phases spanning a duration of 6 hours as detailed below

- Basal phase: From 0 min, the optimal insulin infusion rates were titrated in each individual by making frequent (~ every 20-25 minutes) adjustments to the insulin infusion rates in order to establish insulin infusion rates required to maintain euglycaemia (90 mg/dl) without the requirement for an exogenous glucose infusion.

- Low phase: Following establishment of basal insulin requirements during the basal phase, at T=0 the insulin infusion rate was increased by 20 mU/m^2/min, and it was maintained at this rate for 2 hours (T=120 -240 minutes). These rates are designed to optimally assess hepatic insulin sensitivity. Plasma glucose was maintained at euglycemic concentrations (~90mg/dl) by a variable infusion of 20% dextrose for the entire study.

- High phase: At the end of 240 minutes, the insulin infusion rate was increased by 80 mU/m^2/min above basal requirements, and was maintained at that rate for the final 2 hours of the study (T=240-360 min). These rates are designed to assess whole body insulin sensitivity.

Post-clamp observation phase*:* All infusions were stopped at t=360 minutes. The subjects were given a standard meal and plasma glucose levels were monitored at 15-30 minute intervals for the next one hour. Dextrose infusions were continued for approximately

45 minutes after the study in order to avoid hypoglycemia. Subjects were discharged in stable condition after observation for a further period of 3-4 hours.

Plasma samples obtained during the clamp study:

Throughout the 6 hour clamp studies, blood samples were obtained at hourly intervals to determine plasma glucose, insulin, glucagon, C-peptide, growth hormone, lactate and free fatty acids (FFA) and thereby to evaluate the inhibitory effects of somatostatin on hormone secretion, and uniformity of hormone replacement. Plasma samples were stored frozen at minus 80°C for subsequent assays. Additional samples for D2G glucose determinations were also obtained every 15 minutes during the steady state periods, ie during the final hour of each step. Plasma glucose levels were measured every 5 minutes to adjust the exogenous glucose infusion rate.

Assays for Glucose turnover: Samples for D2G determinations were obtained every 15 minutes. D2G determinations were performed at the Albert Einstein College of Medicine and were measured by gas chromatography mass spectrometry (GCMS), as previously described[4]. Rates of glucose appearance (Ra) and glucose disappearance (Rd, or glucose uptake) were calculated using Steele's steady-state equation[5]. Rates of endogenous glucose production (EGP) were determined by subtracting rates of glucose infusion from the tracer-determined Ra. Data for glucose turnover, plasma hormones, and substrate concentrations represent the mean values during the final 60 min of the euglycemic period (t = 180-240 min) and the final 60 min of the hyperglycemic period (t = 300-360 min).

Protocol for Mixed meal tolerance test

Mixed meal tolerance test: Insulin secretion rates in the study groups was assessed by a Mixed-Meal tolerance test (MMTT). Subjects were provided with a standard meal and snack to consume at home the night prior to the MMT and were fasting after 10 pm, in order to minimize metabolic variability between tests. Following an overnight fast, the fasting glucose levels were checked for iso-glycaemia. Subjects were administered the mixed meal of "Ensure"®, (Abbott Health care Pvt Ltd, India) – a nutritional supplement (composed of carbohydrate : 54%, fat: 32% and protein 14%). Six scoops of this mixture were dissolved in plain water (maximum of 360 ml) to be consumed as a liquid meal over 5-10 minutes. Blood samples were drawn through an indwelling intravenous catheter in the fasting state (0 minutes) and 15, 30, 45, 60-, 90-, 120- and 180-minutes following meal consumption, for measurements of glucose, insulin, glucagon and C-peptide levels[6]**.** Plasma triglycerides and FFA levels were measured at fasting and at 60, 120 and 180 minutes. Insulin secretion rate was calculated from the C-peptide deconvolution studies and glucagon secretion rates from the Area-under-curve (AUC) measurements using the trapezoidal method[7]**.**

Prior to the MMTT procedure, the fructosamine levels were measured in the LD and T2D groups to ensure similar glycemic status between groups. The dietary intake in all patients with diabetes was documented through a 24-hour dietary recall at three consecutive visits. As per medical advice, they were maintained on a diet containing 1800 kcals/ day inclusive of carbohydrates, fats and proteins. The subjects were monitored for glycaemic control with a dietary intake of 1800 kcals for at least three weeks prior to the MMTT to avoid calorie deficiency in the participants. As part of the clamp study protocol, patients were instructed to maintain a record of their dietary intake and the glycemic profiles, which were reviewed by the dietician and the clinician respectively. Any deviation in glycemic

profile was appropriately corrected through OADs or Insulin. On the day of the MMTT procedure, patients of the LD and the T2D groups were ceased- off their oral antidiabetic agents and insulin. This could not be applied in patients with T1D due to the risk of hyperglycaemia and ketosis, which may occur following withdrawal of insulin, and therefore the MMTT procedure was not done in such patients. Further, Insulinogenic index was calculated as a ratio of fasting insulin (µU/ ml)/ to fasting glucose (mg/dl) according to Uwaifo et al.[8].

Protocol for Genetic screening for markers of Lipodystrophy: Patients of the LD group were screened for Lipodystrophy using Next Generation Sequencing (NGS) technique as published in an earlier study[9]. using a six gene panel covering the Insulin resistance *INSR, and ZMPSTE24*) and lipodystrophy (*LMNA, AGPAT2*), *BSCL2, PPARG,* genes[10]**.** In short, the target enrichment was carried out utilizing a multiplex Polymerase Chain Reaction (PCR), followed by library preparation, and the amplicon sequencing was performed on the Ion torrent personal genome machine (PGM) using 316 chips and Ion PGM™ 200 Sequencing Kits (Ion Torrent, Life Technologies). Data analysis was performed on Ion torrent suit software v.5.10.1 and DNASTAR Lasergene 13 software.

Protocol for DXA imaging for body composition: All participants underwent whole body composition analysis in supine position for body fat %, fat mass, lean mass and truncal fat with light clothing on a Dual energy x ray absorptiometry (DXA) scanner (Hologic DEXA Discovery QDR 4500, CV 4%) which has a single Pass and sweep scanning system for better quality and precision. Bilateral sections and whole-body composition data were obtained by analysis of the regions of interest (ROI) using APEX software (Version 4.0.2)[11]**.** Values of lean mass, fat mass were expressed as kilograms and percentage values.

Protocol for Magnetic resonance spectroscopy (MRS) for myocellular lipids, hepatic and pancreatic fat.

For each participant who was included, the hepatic and pancreatic lipid content were assessed using ^{1}H- Magnetic resonance imaging and spectroscopy (3T Intera Achieva MR system (Philips Medical Systems, Eindhoven, the Netherlands) using single voxel stimulated echo acquisition mode (STEAM; TR/ TE/mixing time [TM] = 4000/10/16 ms; average = 32) with volumes of interest (VOI) of 3 × 3 × 2 cm for liver and 2 × 1 × 1 cm for pancreas. A point-resolved spectroscopy (PRESS) sequence with a TR/TE of 4000/36 ms, with 48 averages was acquired for a VOI of 1.5 x 1.5 x 1.5 cm for both soleus and tibialis anterior muscle. Water was used as an internal reference for all spectra. The detailed measurement techniques have been previously described[12,13].

MR Spectral analysis: The quantification of MR spectra from liver, pancreas, soleus and TA muscle were analyzed using an advanced magnetic resonance fitting algorithm with a Java-based magnetic resonance user interface software (jMRUI; Leuven, Belgium). The detailed quantification is discussed elsewhere[12]**.**

Protocol for Quantification of SAT and VAT

A T1w turbo spin echo (TSE) sequence with TR/TE = 400–510/ 38 ms with a turbo factor of 7 for a 5mm slice thickness was used to image the entire abdominal region in order to quantify subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) with similar protocol discussed by Kahl et al.[12]**.** The T1w MR images were processed using Image J software (NIH Bethesda, USA) version 1.52A for quantification of SAT and VAT[13]**.** The quantification involved extraction of SAT and VAT separately from the abdominal area covering T12 to L5 vertebral regions with the number of images ranging from 21 to 38 depending upon the size of the patient. The quantification was similar to the methods described in literature[13].

Protocol for Dietary intake assessment: We performed assessment of dietary intake of macro and micronutrients using a 24-hour dietary recall using a validated questionnaire. The dietary intake of macronutrients namely carbohydrates, fats and proteins were expressed in gms/ day. Micronutrient intake was expressed as (mg/day)/ or μg/day as applicable. This was compared the recommended dietary allowance (RDA) and the nutritive value of Indian foods stipulated by the National Institute of Nutrition, India (National Institute of Nutrition, India n.d. *https://www.nin.res.in/popular.html* and the Indian council of medical research, New Delhi, India.

LEGENDS FOR SUPPLEMENTARY TABLES

Table S1. Total Insulin secretion shown by area under curve (AUC) on MMCT across groups.

Table S2. EGP and RD values on euglycemic- hyperinsulinemic pancreatic clamp procedure across groups.

Table S3. Fasting and MMTT based glucose surrogate indices of insulin resistance across groups.

Table S4. Hormone and biochemical metabolite levels across groups during a HEC procedure.

Table S5. Body composition profile (on DXA), abdominal adipose tissue depots, myocellular, and hepatocellular lipids (on MRS) across groups.

LEGENDS FOR SUPPLEMENTARY FIGURES AND FILES

Figure S1. Study design with exclusion criteria

Figure S2(a). LD group: Treatment profile at recruitment

Figure S2(b). Treatment profile in the T2D group at recruitment

Figure S2(c). Treatment profile in the T1D group at recruitment

Figure S3. Correlation analysis across LD group. (A) Correlation between RD and truncal fat mass, (B) Correlation between RD and total fat mass.

Figure S4. Visceral adipose Tissue: VAT (a), and Hepatocellular lipid (b) across groups. For clarity of graphic representation, data in the figure S5.a and S5.b are presented as the means ± SEM. As data were not normally distributed, Kruskas Wallis tests were used to compare the levels of VAT and HCL in the five studies group. *$p<0.05$

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