Total Insulin Resistance Index to Risk-Stratify Dysglycemia and Define Pre-Prediabetes

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POSTER No. 0076

BACKGROUND

OGTT with insulin values can be used to evaluate insulin resistance (IR) and to risk-stratify dysglycemia.

HOMA-IR = (Fasting_Glucose x Fasting_Insulin)/405

HOMA-IR
- Widely used as surrogate of IR.
- Considers only fasting values i.e., Hepatic IR.
- Does not consider postprandial values i.e., Peripheral IR

Concept of Composite HOMA-IR
- Define PP_HOMA-IR using same formula but 2-hr post 75 gm glucose & insulin values
- Define Total Composite HOMA-IR by deriving average of Fasting_HOMA-IR & PP_HOMA-IR

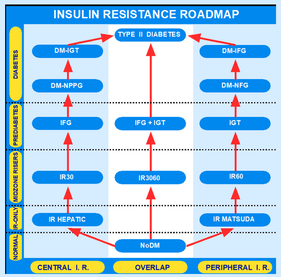
This study was aimed at finding the utility of simple OGTT-based 'Total IR index' to risk stratify the trajectory of dysmetabolism and dysglycemia.

METHODS

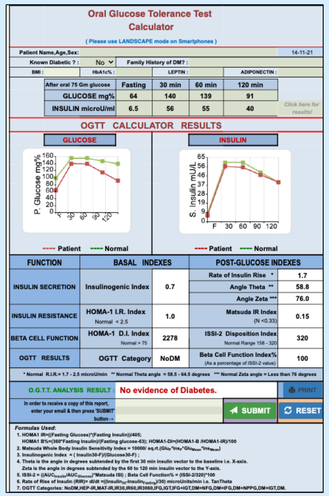
We analyzed OGTT glucose profiles of 1455 individuals, aged 15 to 80 years, who were not previously diagnosed as having T2D.
They were administered 'standard two hour 75-gram Oral Glucose Tolerance Test' with insulin levels (OGTT_PLUS) with 0, 30, 60 and 120 minute time points.

1	DM	Diabetes (FG Level >125 & 2 hour Post Glucose I>199)
2	DM-IGT	Diabetes with Impaired Glucose Tolerance (F>125 & PG>139,<200)
3	DM-IFG	Diabetes with Impaired FG (F>99<126, PG>199)
4	DM-NFG	Diabetes with Normal FG (F<100, PG>199)
5	DM-NPPG	Diabetes with Normal PG (F>125, PG<140)
6	IFG	Impaired FG (F>99 <126, PG<140)
7	IGT	Impaired Glucose Tolerance (F<100, PG>139 <200)
8	IFG+IGT	Impaired FG + Impaired Glucose Tolerance (F >99 <126, PG >139 <200)
9	IR30	IIR with 30 min Glucose > 155 with Normal F & PG.
10	IR60	IIR with 60 min Glucose > 155 with Normal F & PG.
11	IR3060	IIR with both 30 & 60 min Glucose > 155 with Normal F & PG.
12	IRMatsuda	IIR with F<100,30 min<155, 60 min<155, 120 min<140, & Matsuda Index <3.0
13	IRHepatic	IIR with F<100,30 min<155, 60 min<155, 120 min<140, & HOMA1 IR >2.7 & Matsuda Index >3.0
14	NoDM	Normal Glucose Tolerance with Normal Insulin Sensitivity (No IR).

OGTT data were grouped into 14 categories according to glucose, HOMA1-IR and Matsuda Index values. IR_Hepatic & IR_Matsuda were added into a single category named, 'IR-only'.



Insulin roadmap was proposed considering the genetic IR in either liver, muscle or adipose tissue or their combination.



Individual OGTT_PLUS data was entered into a web-calculator, which gives results of important indexes of insulin resistance, insulin secretion and disposition index values. This calculator is developed by us and is released in public domain at www.ogtt.in for free use by physicians.

RESULTS

Data was analyzed with excel pivot tables and a graph was generated.

Category	Patients N=1455	Total I.R.	TIR Index
No Diabetes	100	6.58	1
Euglycemic Hyperinsulinemia	156	15.13	2.3
MID-ZONE risers	228	23.53	3.6
Pre-Diabetes	561	40.35	6.13
Diabetes	410	48.73	7.4

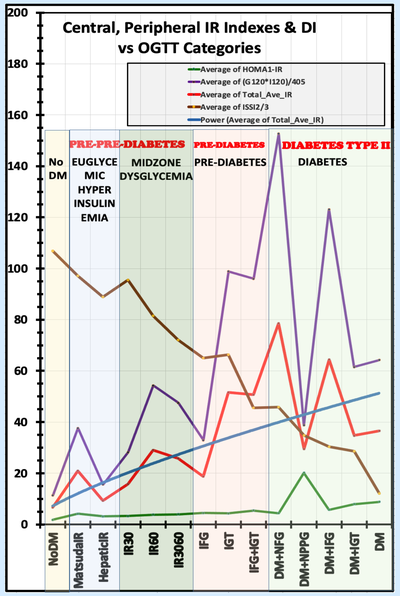
The 'X' axis of this graph has all the categories arranged with increasing stages of dysmetabolism / dysglycemia & has five zones as shown in the table below,

Zone	Categories
No Diabetes	NoDM
Euglycemic Hyperinsulinemia	IR_Hepatic, IR_Matsuda (IR_only)
Midzone Dysglycemia	IR30, IR60, IR3060
PreDiabetes	IFG, IGT, IFG+IGT
Diabetes	DM+NPPG, DM+IGT, DM+NFG, DM+IFG, DM

The 'Y' axis has four series & one trendline as shown in the table below,

Series Name	Particulars
ISSI-2	Disposition Index
Fasting_HOMA-IR	Hepatic (Central) IR
PP_HOMA-IR	Muscle, Adipose, Pancreas, Brain (Peripheral) IR
TOTAL_COMPOSITE_HOMA-IR	Two Time-Point IR index
TIR_Trendline (TRDL)	Linearized TIR Trendline

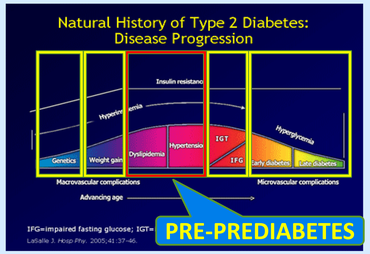
Using ISSI-2 index as a measure of beta cell function (BCF), these categories were arranged in descending order from NoDM to DM. Average values of Fasting_HOMA-IR, PP_HOMA-IR, COMPOSITE_HOMA-IR & ISSI-2 of these 14 categories were plotted. A 'COMPOSITE_HOMA-IR trendline' (TRDL) was drawn & its cut-off values were determined.



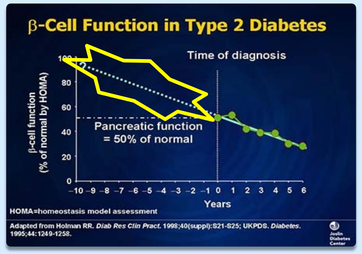
DISCUSSION

The graph revealed a negative linear relationship between 14 categories & ISSI-2 index. The Fasting_HOMA-IR & PP_HOMA-IR curves showed an upward trend as T2D evolved, although these curves were zigzag. This variability, which is most marked in PP_HOMA-IR curve, enabled us to regroup these categories into three groups, namely, dominant Fasting_HOMA-IR or PP_HOMA-IR and a combination of both.

This can be explained by the presence of genetic mutations causing IR in liver or peripherally in muscle &/or adipose tissue, in addition to acquired IR due to ectopic fat accumulation. **HOMA-IR is based only on Central IR & omits peripheral IR, which is an important contributor of TIR.** As ISSI-2 decreases, the TRDL value increases linearly until DM category is reached, where-after TRDL declines.
BCF trajectory is conventionally divided into three subgroups, namely, normoglycemia, prediabetes & diabetes. We subdivided normoglycemia group using TIR-index.



A large part of normoglycemia group was seen to be occupied by two zones, i.e., Euglycemic Hyperinsulinemia and Midzone Dysglycemia. ('IR-only, G-30, G-60 & G-3060' categories) Since this part occupies the area between NoDM & IFG (i.e., prediabetes), we propose to name this group as '**Pre-Prediabetes**', an eponym first used by Prof. Ralph A. DeFronzo. TRDL cut-off points can be used to differentiate various transition points between these groups.



CONCLUSIONS

- **"Pre-PreDiabetes"** as a new subset of Dysmetabolism comprising of 'Sole IR and Midzone Dysglycemia' is defined.
- New concept of **Total Composite HOMA-IR (TIR Index)** is introduced to evaluate insulin resistance.
- Only two values of fasting & 120 min glucose as well as insulin are required for calculation of the TIR index.
- TIR Index is very simple tool to assess dysmetabolism in clinical practice.
- TIR index will prove helpful in defining and populating the proximal half of dysglycemia trajectory, which has not been explored and indexed so far.
- TIR Index is useful in prevention and intervention of dyslipidemia, hypertension and macrovascular morbidity.
- TIR Index is useful in clinical evaluation & follow-up of obesity, MAFLD, PCOS and GDM.
- TIR Index will be useful for primary prevention, intervention, to monitor evolution, progression as well as reversal of T2D in clinical practice.
- TIR Index will help in making a rational choice of antidiabetic therapy.

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