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RESEARCH ARTICLE

Insulin sensitivity index (ISI_{0-120}) from oral glucose tolerance test in healthy young adults

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ABSTRACT

Background: Insulin sensitivity (IS) is the body's systemic responsiveness to glucose and it is the measure of the ability of endogenous insulin to reduce the glucose in extracellular fluids by inhibition of gluconeogenesis and increase peripheral glucose uptake. IS reflects on the efficiency of insulin in response to glucose intake in the body. In diabetics, IS subjects are interpreted to require smaller amounts of insulin to lower blood glucose levels than someone who has low sensitivity. There is a need to detect insulin resistance (IR) in the pre-disease state, i.e., before the onset of impaired glucose tolerance (IGT). Early detection of IR or decreased IS in healthy subjects before the onset of IGT is of importance as it facilitates implementation of preventive measures in subject with such high risk. **Aims and Objectives:** The objective of the study is detect early occurrence of low Insulin Sensitivity in healthy young adults, using Insulin Sensitivity Index derived from OGTT. **Materials and Methods:** A total of 80 healthy volunteers in the age group of 18-25 years were recruited for the study, 40 subjects were siblings of diabetics and 40 subjects were siblings of non-diabetics (SND) a standard (75 g) OGTT was performed for the study. Blood samples for determination of plasma glucose and insulin levels drawn at 0 (fasting), 30, 120 min after glucose solution ingestion. Assays of fasting (basal), 30, 120 min venous plasma glucose during OGTT was performed with glucose oxidase method on site using glucose auto analyzer. The serum plasma was stored at −20°C until assayed. Corresponding specific insulin concentration was determined using radioimmunoassay (RIA) with human specific antibody RIA kit IS was calculated using physiological OGTT based mathematical models. QUICKI was derived for fasting insulin and fasting glucose values. ISI 0-120: Uses OGTT values, using only 0 and 120 min post-glucose challenge insulin and glucose concentrations. The reference values for various IR and IS indexes for our urban population with normal OGTT (n = 79) are QUICKI = 0.31 (0.20-0.52) sibling of diabetics (SD) - 0.07, ISI 0-120 = 63.62 (27.37-134.79) SD - 22.71. We observed that SD had significantly lower IS indices ISI 0-120 (56.27, $P < 0.002$) and a trend toward significance for QUICKI (0.29578, $P < 0.056$). **Results:** We observed that the mathematical models ISI 0-120 to be a fairly reliable tool for assessment of IS in normoglycemic young adults, compared to QUICKI. ISI 0-120 take into consideration the all the parameters of the 2 h OGTT glucose and also includes insulin into consideration for evaluation. Simple OGTT based mathematical models can be used as a reasonable alternative to measure IS or IR instead of the cumbersome glucose clamp or other expensive techniques in epidemiological or general clinical settings. **Conclusion:** Detection of IR in pre-disease condition in healthy individuals, allows the physician to initiate preventive measures, such as lifestyle modification, diet and exercise, thereby preventing the high-risk subjects from progressing to disease state.

KEY WORDS: Insulin Sensitivity Index; Insulin Sensitivity; Oral Glucose Tolerance Test; Insulin Sensitivity Index (ISI_{0-120}); Quantitative Insulin Sensitivity Check Index; Insulin Resistance

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INTRODUCTION

Insulin sensitivity (IS) is the body's systemic responsiveness to glucose and it is the measure of the ability of endogenous insulin to reduce the glucose in extracellular fluids by inhibition of gluconeogenesis and increase peripheral glucose uptake. IS reflects on the efficiency of insulin in response to glucose intake in the body. In diabetics, IS subjects are interpreted to require smaller amounts of insulin to lower blood glucose levels than someone who has low sensitivity. Therefore, insulin resistance (IR) is interpreted to exists when the physiological normal concentration of insulin produces a less than normal biological response. IR is a patho-physiological condition in which cells fail to respond normally to the hormone insulin. The ability to measure IR or its sensitivity before the onset of impaired glucose tolerance (IGT) is important to understand the aetio-pathology of Type 2 diabetes, to perform epidemiological studies and to assess the impact of intervention in a population.[1,2]

In subjects with low IS, it is observed that there is a compensatory increase in insulin production (hyperinsulinemia). High level of circulating insulin is associated with damage to blood vessels, high blood pressure, heart disease and heart failure, obesity, osteoporosis and even cancer.[2-4] The ability to easily assess IS would, therefore, be useful for investigating pathophysiology of IR and its impact in these diseases.

Euglycemic hyperinsulinemic clamp or glucose clamp is generally recognized as a method of reference for assessing IS; it directly measures and evaluates the effects of insulin in the promotion of glucose utilization under steady state conditions, wherein hepatic glucose production is completely shut off by insulin infusion. However, this method being laborious, expensive, inconvenient to patients or study subjects and is not routinely available for every physician. A simple oral glucose tolerance test (OGTT) is the simplest and most commonly used method for evaluating whole body glucose tolerance. Since OGTT is simple and cheap, a number of mathematical models formulas for IS index (ISI) or IR have been developed using OGTT parameter to evaluate IR and IS.[5,6]

IS/IR indices based on fasting glucose and insulin concentrations reflect primarily hepatic IS/resistance. In most conditions, hepatic and skeletal muscle IS/IR are proportional to each other. In the diabetic state, fasting hyperglycemias with low insulin levels are insufficient to maintain euglycemia. Here, indexes like homeostasis model assessment-IR (HOMA-IR) is based on fasting glucose and insulin levels is also widely used to express IR across diverse populations. Though HOMA-IR is practical. IR in obesity is primarily due to impaired stimulated insulin concentrations to increase peripheral glucose uptake.[1,7-10]

Two other ISIs have been demonstrated in adults to have a high degree of correlation with the euglycemic-hyperinsulinemic clamp-derived M-values for stimulated IS. Both indexes use parameters obtained from a standard OGTT.[10-12]

Quantitative IS check index (QUICKI) is derived for fasting insulin and fasting glucose values. It is applicable to both diabetic and nondiabetic subjects. QUICKI uses a log transform of the insulin-glucose product. Arie Katz et al. evaluated the correlation between glucose clamp studies and found that substantial correlation existed between QUICKI and SI clamp ($r = 0.78$).[6,9,13] ISI 0-120: A simple method of assessing IS using OGTT values, using only 0 and 120 min post glucose challenge insulin and glucose concentrations. ISI 0-120 is adapted from sensitivity index developed by Cederholm and Wibell. This simplified formula is used to calculate the glucose uptake rate in peripheral tissues, designated as m (mg/min) from the 0 and 120 min glucose values (mg/l) obtained from OGTT, where the term $0.19 \times BW$ denotes glucose space (l) and BW is body weight in kg.[14-23] ISI 0-120 the index is also known to correlate well with direct estimates of IS obtained from the glucose clamp study ($r = 0.63$).[9]

Type 2 diabetes mellitus (T2DM) is known to have genetic predisposition, the pathophysiology of diabetes progress through the stage of IR and hyperinsulinemia, to beta cell failure with IGT and overt clinical diabetes. Both IR and impaired insulin secretion are necessary for the onset of IGT. About 40-50% of people with IGT will develop type 2 diabetes within 10 years. Subjects with IR are therefore considered to be at increased risk for developing type 2 diabetes and cardiovascular diseases and their complications. It is well recognized that even during the period of undiagnosed disease, risk factors for diabetic micro, and macrovascular complications are markedly elevated and diabetic complications are developing. Given the extreme increase in pre-diabetes (IGT), type 2 diabetes, and the potential for metabolic syndrome in obese youth, Identifying simplified indexes for assessing IR/IS is critical.[7-9,24] Rationale for the study: There is a need to detect IR in the pre-disease state, i.e., much before the onset of IGT. Detection of IR or decreased IS in normoglycemic young subjects before the onset of IGT is of importance as it affords implementation of preventive measures in such high-risk subject.[1,6-13] We hypothesized that normoglycemic young adult who are siblings of diabetics (SD) (test subjects) or obese subjects are genetically predisposed, and they are known to have a higher substantial heritable component of IR than the siblings of non-diabetics (SND) (control subjects).[16,17] To eliminate the effect of puberty on IR, the study subjects were in the age range of 18-25 years.

The objective of the study is detect early occurrence of low IS in healthy young adults, using ISI (QUICKI, ISI 0-120) derived from OGTT.

MATERIALS AND METHODS

The study was conducted as per good clinical practice guidelines and it was approved by the Institute Scientific and Ethics committee (IEC). With informed consent, 80 healthy young adult volunteers were recruited for the study, 40 subjects had family history of diabetes (sibling of diabetics [SD]) and 40 subjects had no family history of diabetes (SND) and they were in the age range of 18-25 years. The study subject's demographic and clinical data were collected. A standardized questionnaire was used to collect age, sex, physical activity at work, at leisure, socioeconomic status, previous diseases, and any medication consumption. Complete clinical evaluation included weight and height measured while the subjects were fasting overnight and wore light clothes without shoes. Waist and hip circumferences (to the nearest 0.5 cm) were measured using a plastic tape meter at the umbilicus level and at the greater trochanters, respectively, and waist-to-hip ratio was calculated. Blood pressure was measured using a standard mercury sphygmomanometer on the left arm after at least 10 min of rest; Mean BP was determined from two independent measurements.

Laboratory Evaluation

At baseline, in the morning after an overnight fast, venous blood was sampled for the measurement of level of total and high-density lipoprotein cholesterol, triglycerides, and insulin. A standard (75 g) OGTT was performed on all the study subjects. After an overnight fast the study subjects ingested the OGTT solution within 2 min. Blood samples for determination of plasma glucose; insulin levels were drawn using disposable scalp vein set at 0 (fasting), 30, 120 min after solution ingestion. Assays: Fasting (basal), 30, 120 min venous plasma glucose during OGTT was determined by glucose oxidase method on site using glucose auto analyzer. The serum plasma was stored at −20°C until assayed. Corresponding specific insulin concentration was determined by radioimmunoassay (RIA) using a human specific antibody RIA kit, which does not cross-react with human proinsulin. This immunoassay uses the principle where there is competition between a radioactive and non-radioactive antigen for a fixed number of antibody site. The WHO diabetes criteria for labeling the subjects as normoglycemic: A fasting venous plasma glucose concentration of less than <6.1 mmol/l (<110 mg/dl) and a 2 h post glucose load <7.8 (<140 mg/dl) was used. The data were systematically collected in the case record form designed for the study and a coded master chart prepared for data analysis. Assessment of IS calculated using physiological mathematical models and their formulas derived from OGTT (Table 1).

Statistical Analyses

The Student's *t*-test and Mann–Whitney *U*-test was used to find if there was any significant difference between various OGTT parameters and indices between SD and SND. Chi-square and Fisher exact test have been used to find the significant difference of frequencies between SD and SND. Statistical diagnostic values (namely sensitivity, specificity, and predictive value) have been computed at various cutoff values of indices obtained from literatures. The odds ratio has been computed to find relationship of indices for the various cutoff between SD and SND. The Pearson correlation coefficient between HOMA-IR and ISI 0-120 and clinical and lab parameters have been computed.

RESULTS

In this prospective study, the mean age of the study population was 19.01 (18-25 years); all the study subjects were from Bangalore urban (north). The sex distribution was male: 33 (41.3%) and female: 47 (58.8%). Of the 80 normal young adult volunteers who were enrolled for the study, 79 were considered evaluable, the overall clinical and laboratory characteristics of the study subjects is seen in (Table 2). 40 subjects were SD and 39 were SND (1 subject in the SND group with 2 h glucose >140 mg/dl was excluded from the analysis). The clinical parameters SD and SND is seen in Table 2, SD were obese compared to SND. The in SD, subjects with 1st degree association were 19 (47.5%) and 2nd degree association (grandparents) 34 (85%) and 13 (32.5%) of the subjects had both 1st and 2nd degree relationship. The SD were compared with siblings of nondiabetics, both the groups were matched physically, clinically and by routine laboratory parameters and were found to be similar with no statistically significant difference between the two groups.

SD are known to be more prone to develop T2DM; they had significantly higher body mass index (BMI). The reference values of IS (IS and IR) indexes for our Bangalore urban population are shown in Table 3. The IS indexes by QUICKI = 0.31 ± 0.07 and with ISI 0-120 = 63.62 ± 22.71. It was observed that subjects with higher fasting Insulin had significantly lower ISIs (Table 3). It was observed that SD had significantly lower IS indices ISI 0-120 (56.27, $P < 0.002$) and a trend toward significance was seen with QUICKI (0.29578, $P < 0.056$) (Table 4).

In the subset analysis, it was observed that in subjects who had first degree and second degree relatives with T2DM had significantly lower IS values and higher IR values. It was observed that ISI 0-120 indices showed a significantly better correlation with compared to HOMA IR in SD (Table 5). Evaluation of sensitivity and specificity of the IS/IR index demonstrates ISI 0-120 is a better indicator of IS in normoglycemics with a positive predictive value of 90% and negative predictive value of 75% (Table 6).

Table 1: Physiological mathematical models ISI 0-120 and QUIKI and their formulas derived from OGTT

Mathematical models	The equations	Units
QUICKI	QUICKI=1/[log (FPI)+log (FPG)]=1/[log (FPI×FPG)]	Where FPI is the fasting plasma insulin (micro units per ml) and FPG is fasting plasma glucose level (milligram per dL)
ISI 0-120	m=(7500 mg+(0 min glucose 120 min glucose) ×0.19×BW)/120 min	MPG, the mean of the 0 min and 120 min glucose values from OGTT is used the obtain the MCR which is corrects for the potential influence of variable blood glucose concentration on glucose uptake rate
	MCR=m/MPG	To correct the skewness of distribution, the mean serum insulin (MSI, mIU/l) was calculated as the mean of the 0 min and 120 min insulin values, which is logarithmically transformed
	ISI 0-120=MCR/log MSI=*m*/MPG/log MSI	

MCR: Metabolic clearance rate, ISI: Insulin sensitivity index, QUICKI: Quantative insulin sensitivity check index, MPG: Mean plasma glucose, OGTT: Oral glucose tolerance test

Table 2: Overall clinical and lab parameters

Parameters	Mean values	Range
Clinical parameters		
Height (cm)	163.43	146.90-190.50
Weight (kg)	59.69	37.00-107.00
BMI	22.37	14.17-39.48
Hip circumference (cm)	92.66	74.00-124.00
Waist-hip ratio	0.81	0.66-0.98
Lab parameters		
Cholesterol mg/dl	157.08	86.00-208.00
Triglycirides mg/dl	96.24	56.00-198.00
HDL mg/dl	40.66	32.00-49.00
LDL	97.48	34.00-154.00
OGTT parameters		
Glucose fasting mg/dl	81.68	64.00-108.00
Glucose-30 mi	111.03	66.00-169.00
Glucose-120 min	91.69	61.00-166.00
Insulin-fasting IU/L	8.33	1.60-40.00
Insulin-30 min	68.84	2.00-300.00
Insulin-120 min	37.31	5.20-142.00
Indices of IR/IS		
HOMA-IR	1.69	0.30-6.91
% BETA	245.94	21.00-2400.00
Insulino Genic Index	0.75	−139.05-27.00
QUICKI	0.31	0.20-0.52
ISI 0-120	63.62	27.37-134.79
I_0/G_0 ratio	0.10	0.02-0.57

BMI: Body mass index, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, OGTT: Oral glucose tolerance test, IR: Insulin resistance, IS: Insulin sensitivity, HOMA: Homeostasis model assessment, QUICKI: Quantative insulin sensitivity check index,

ISI 0-120 values were significantly lower in subjects (SD) with higher BMI, longer Waist circumference. Significant correlation with clinical measures like BMI and waist circumference can be considered as markers in larger population size.

DISCUSSION

It is interesting to study whether decreased IS exists at a much younger age before the onset of IGT in the normoglycemic subjects and to study the feasibility of detection of lowering of IS from mathematical models like ISI 0-120, QUICKI derived from OGTT. The concept of IR is relatively easy to understand, but determining precisely who is insulin resistant is more complicated. It is known that the relationship between glucose and insulin is quite complex and involves the interaction of many metabolic and regulatory factors. Normal IS varies widely it is influenced by age, ethnicity, and obesity.[15-18]

Even though hyperinsulinemic-euglycemic clamp technique is believed to be the most scientifically sound technique for measuring IS and similarly "clamp" techniques which have been developed are also known to be expensive, time-consuming, and labor intensive, these complex techniques are not very practical in an office setting. To overcome these obstacles, alternative tests have been developed, including the frequently sampled IV glucose tolerance test, insulin tolerance test, IS test, and continuous infusion of glucose with model assessment. Unfortunately, all of these methods require intravenous (IV) access and multiple venipunctures, making them relatively impractical for routine outpatient assessment.[1,6,9-12]

The OGTT does not require IV access but does involve several venipunctures and 2-4 h of patient and technician time. OGTT has been shown to correlate reasonably well with dynamic clamp techniques.[6,12,17-23] In our study, we observed a similar relationship between hyperinsuliniemia and IS, correlation of fasting insulin levels and fasting glucose level demonstrated that, not significant, subject with higher fasting insulin (>14.0) had comparatively higher fasting glucose levels 84.3 ± 12.71, compared to insulin levels <14.0 with lower fasting glucose of 81.52 ± 9.49.

Warram et al. in their study on the SD parents found that in truly normoglycemic subjects the presence of IR was the

Table 3: Correlation of fasting insulin levels with insulin sensitivity: Subjects with higher fasting insulin had significantly lower insulin sensitivity indexes

ISI	Baseline (fasting insulin)	*N*	Mean±Standard deviation	*t*	Sig. (2-tailed)
QUICKI	≥14.0	10	0.22228±0.016626	−4.803	0.000
	<14.0	69	0.32355±0.066023	−10.626	0.000
ISI 0-120	≥14.0	10	46.43734±14.278375	−2.683	0.009
	<14.0	69	66.34204±22.746214	−3.769	0.002

QUICKI: Quantative insulin sensitivity check index, ISI: Insulin sensitivity index

Table 4: Siblings of diabetics are known to be more prone to develop T2DM, they had significantly higher body mass index and their insulin sensitivity values were significantly lower are demonstrated

Insulin sensitivity	Mean±Standard deviation		*t*-test for equality of means	
	Siblings of non-diabetics (*n*=39)	Siblings of diabetics (*n*=40)	*t*	*P* value
QUICKI	0.32606±0.06817	0.29578±0.7049	1.940	0.056*
ISI 0-120	71.56±26.219	56.27±15.80	−3.147	0.002**

P values are obtained by Mann–Whiteny *U*-test. *Significance at 5% **Significance at 1%. T2DM: Type 2 diabetes mellitus, QUICKI: Quantative insulin sensitivity check index, ISI: Insulin sensitivity index

Table 5: Comparison of mathematical model of IR using fasting glucose and fasting insulin and models of IS using both fasting and 2 h glucose and insulin data from OGTT

Parameter	Effect of 1st degree of relationship in the family			Effect of 2nd degree of relationship in the family			
Family history 1st degree	Number	HOMA-IR	ISI 0-120	Family history 2nd degree	Number	HOMA-IR	ISI 0-120
No family history	40	1.37±0.96	70.96±26.16	Nil	40	1.39±1.07	70.96±26.16
2nd degree family history only	21	1.67±0.97	60.73±15.78	2nd degree family history only	21	1.67±0.97	60.73±15.78
1st degree family history only	19	2.40±1.91	51.35±14.68	2nd degree family history	34	2.03±1.49	57.95±16.11
Father	14	2.55±2.11	53.29±16.39	Paternal grand parents	15	1.82±0.81	62.56±14.37
Mother	4	1.60±1.12	48.13±5.25	Maternal grand parents	11	2.06±1.67	52.63±17.47
Both	1	3.59	53.61	Both	8	2.58±1.97	56.63±16.77
Significance between no F/H and 1st degree F/H	-	*F*=4.390 *P*=0.016*	*F*=5.624 *P*=0.005**	Significance No F/H versus.2nd F/H	-	*F*=2.570 *P*=0.083	*F*=5.325 *P*=0.007**

*Significance at 5%, **Significance at 1%. IR: Insulin resistance, ISI: Insulin sensitivity index, HOMA: Homeostasis model assessment, OGTT: Oral glucose tolerance test

Table 6: Evaluation of sensitivity and specificity of the IS/IR index demonstrates ISI 0-120 is a better indicator of is in normoglycemics, significantly

Values with various cut-off	Association IS/IR Parameters in subjects with and without family history of T2DM							
	Siblings of diabetics *N* (%)	Siblings of non-diabetics *N* (%)	*P* value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	OR
HOMA>1.0	29 (72.5)	24 (60.0)	0.237	73.0	40.0	58.0	59.0	1.76
QUICKI<0.35	33 (82.5)	27 (67.5)	0.121	82.5	32.5	55.0	65.0	2.23
ISI 0-120<80	36 (90.0)	28 (70.0)	0.025	90.0	30.0	56.3	75.0	3.86

IS: Insulin sensitivity, IR: Insulin resistance, ISI: Insulin sensitivity index, HOMA: Homeostasis model assessment, QUICKI: Quantative insulin sensitivity check index, PPV: Positive predictive value, NPV: Negative predictive value, OR: Odds ratio, T2DM: Type 2 diabetes mellitus

best predictor of the development of T2DM. In our study, normoglycemic SD had a significantly lower IS values than the control sibling of non-diabetics, demonstrating the feasibility of mathematical models such as ISI and QUICKI derived from OGTT in evaluating IR/IS in normoglycemic young adults.[14] In our study, SD had higher basal insulin value of 9.94 versus 6.71 (*P* - 0.059) and baseline glucose of 82.98 versus 80.38, respectively. The basal, 30 min, 120 min insulin and 30 min glucose was significantly higher in SD, but the insulinogenic index was not different - 0.2623.09

(SD) versus 1.763. Depicting similar 30 min insulin, lesser response to oral glucose load in SD.[1,6-9,11,12,16,25]

ISI 0-120 is calculated from 0 min and 120 min values of OGTT, using the dynamic continuum of insulin and glucose ratios from fasting and stimulated glucose giving it gives a superior correlation with sensitivity index than other indexes.[16,6,25] Better correlation of ISI 0-120 with clinical parameters and the other predictors of T2DM like family history of diabetes were observed in our study (Table 5).

Warram et al. showed that the fractional glucose removal rate was reduced in nondiabetic offspring of diabetic parents, suggesting IR in such offspring. In addition, second, although not first, phase insulin secretion was higher in the offspring; a finding that is compatible with compensatory hypersecretion of insulin in response to IR.[14] Our results are similar to those of several cross-sectional studies performed in both nondiabetic and diabetic subjects. Furthermore, our results are in concurrence with the few longitudinal studies exploring the association of IR with cardiovascular disease.

There is substantial evidence that IR, typically defined as decreased sensitivity or responsiveness to the metabolic actions of insulin, is a precursor of the metabolic syndrome and type 2 diabetes. Alvar Loria et al., in their study to establish a cutoff point for hyperinsulinemia demonstrated that subjects with BMI <25 kg/m^2 the subjects fasting plasma glucose <100 mg/L has a mean insulin of 13.7.[25] The fasting plasma insulin is often used in clinical medicine to classify subjects in a binary categorization of normal versus hyperinsulinemic patients. In our study, we observed that the relationship between fasting glucose level and insulin levels, though not significant subject with higher Fasting Insulin had comparatively higher fasting glucose levels (Table 3). It was interesting to observe that on the correlation of fasting insulin levels with IS: Subjects with higher fasting Insulin had significantly lower ISIs (Table 4).

ISI 0-120 correlates well with the family history of T2DM, clinical and lab parameters which are considered as predictors of T2DM. Evaluation of sensitivity and specificity of the IS/IR index demonstrates ISI 0-120 is a better indicator of IS in normoglycemics young adults. OGTT derived ISI 0-120 IS index is evolving to be noticed as an important tool evaluate IS in normoglycemic young adults. Long-term follow-up of the study subjects is contemplated. It is important detect IS earlier as it helps in planning preventive strategies for the subjects being evaluated and the population at large.

CONCLUSION

Simple IS/IR modes derived from OGTT can be used for assessment of IS in normoglycemic subjects. Mathematical models of ISI 0-120 is a reliable tool in assessment of IS compared to HOMA IR, QUICKI as it takes into consideration the all the parameters of the 2 h OGTT glucose and also includes insulin into consideration for evaluation. Simple OGTT based IS models can be used as a reasonable alternative to measure IS index in a population instead of the cumbersome glucose clamp or other sophisticated techniques in epidemiological studies or general clinical settings. Healthy SD had comparatively lower IS levels. A physiological model like ISI 0-120 is a simple and cost effective method, which can be used for screening IR or sensitivity. Detection of IR in pre-disease condition in healthy individuals, allows the physician to initiate preventive measures, such as lifestyle modification, diet and exercise, thereby preventing the high-risk subjects from progressing to disease state.

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