Published in final edited form as:
Metabolism. 2009 February ; 58(2): 220–225. doi:10.1016/j.metabol.2008.09.017.

Validity of the Reduced-Sample-Insulin-Modified-Frequently Sampled Intravenous Glucose Tolerance Test Using the Nonlinear Regression Approach

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Abstract

The Disposition Index, the product of the insulin sensitivity index (S_I) and the acute insulin response to glucose, is linked in African-Americans to chromosome 11q. This link was determined with S_I calculated with the nonlinear regression approach to the minimal model and data from the Reduced-Sampled-Insulin-Modified-Frequently-Sampled-Intravenous-Glucose-Tolerance-Test (Reduced-Sample-IM-FSIGT). However, the application of the nonlinear regression approach to calculate S_I using data from the Reduced-Sample-IM-FSIGT has been challenged as being not only inaccurate but also having a high failure rate in insulin-resistant subjects. Our goal was to determine the accuracy and failure rate of the Reduced-Sample-IM-FSIGT using the nonlinear regression approach to the minimal model. With S_I from the Full-Sample-IM-FISGT considered the standard and using the nonlinear regression approach to the minimal model, we compared the agreement between S_I from the Full and Reduced-Sample-IM-FSIGT protocols. One hundred African-Americans, (BMI 31.3 ±7.6 kg/m^2 (mean±SD), range 19.0-56.9 kg/m^2) had FSIGTs. Glucose (0.3g/kg) was given at baseline. Insulin was infused from 20 to 25 minutes (total insulin dose 0.02U/kg). For the Full-Sample-IM-FSIGT, S_I was calculated based on the glucose and insulin samples taken at ***-1***, 1, ***2***, 3, ***4***, 5, 6, 7, ***8***,10, 12, 14, 16, ***19***, ***22***, 23, 24, 25, 27, ***30***, ***40***, ***50***, 60, ***70***, 80, 90, ***100***, 120, 150, ***180***. For the Reduced-Sample-FSIGT, S_I was calculated based on the timepoints which appear in bold. Agreement was determined by Spearman correlation, concordance and the Bland-Altman method. In addition, for both protocols, the population was divided into tertiles of S_I. Insulin resistance was defined by the lowest tertile of S_I from the Full-Sample-IM-FSIGT. The distribution of subjects across tertiles was compared by rank order and kappa statistic. We found that the rate of failure of resolution of S_I by the Reduced-Sample-IM-FSIGT was 3%(3/100). For the remaining 97 subjects, S_I for the Full and Reduced-Sample-IM-FSIGT were: 3.76±2.41 L.mU^{-1}.min^{-1}, range 0.58-14.50 and 4.29±2.89 L.mU^{-1}.min^{-1}, range 0.52-14.42, relative error 21±18%, Spearman r=0.97, concordance 0.94, (both P<0.001). After log transformation the Bland Altman limits of agreement were: -0.29 and 0.53. The exact agreement for distribution of the population in the insulin-resistant tertile versus the insulin-sensitive tertiles was 92%, kappa 0.82±0.06. Using the nonlinear regression approach and data from the Reduced-Sample-IM-FSIGT in subjects with a wide range of insulin

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sensitivity, failure to resolve S_I occurred in only 3% of subjects. The agreement and maintenance of rank order of S_I between protocols supports the use of the nonlinear regression approach to the minimal model and the Reduced-Sample-IM-FSIGT in clinical studies.

Introduction

The combination of insulin resistance and beta-cell failure is the most widely accepted construct of the etiology of type 2 diabetes. This concept was reinforced by the discovery that the Disposition Index (DI) predicts type 2 diabetes[1]. DI represents the ability of beta-cells to overcome insulin resistance [2]. Importantly, a genome scan for glucose homeostasis traits in the Insulin Resistance Atherosclerosis (IRAS) Family Study found in African-Americans that DI is linked to chromosome 11q[3].

DI, a hyperbolic function, is calculated as the product of the insulin sensitivity index (S_I) and the acute insulin response to glucose (AIRg)[2]. S_I is determined by a mathematical model, the minimal model[4]. The input for the minimal model is data obtained from the frequently sampled intravenous glucose tolerance test (FSIGT). There are several FSIGT protocols and more than one mathematical approach to the minimal model[5-8]. The calculated value of S_I differs depending on the FSIGT protocol and the mathematical approach. In contrast, the determination of AIRg is the straightforward analysis of an area under a curve.

Consequently the strength of DI is dependent on the validity of S_I. The link between DI and chromosome 11q was determined with S_I calculated with the nonlinear regression approach to the minimal model and data from the Reduced-Sample-Insulin-Modified-Frequently-Sampled-Intravenous-Glucose-Tolerance-Test (Reduced-Sample-IM-FSIGT). However, the application of the nonlinear regression approach to Reduced-Sample-IM-FSIGT has been challenged as being not only inaccurate but also having a high failure rate in insulin-resistant subjects[6, 7]. Yet, the IRAS Family Study as well as other important epidemiological studies are using the nonlinear regression approach to the minimal model with data from the Reduced-Sample-IM-FSIGT. Therefore we believe it is important to review the history of the development of Reduced-Sample-IM-FSIGT and systematically test the validity of S_I calculated from the minimal model using the nonlinear regression approach with data from the Reduced-Sample-IM-FSIGT.

For background, the minimal model is based on two differential equations[4]. The final result for S_I depends not only on these equations but also on the specific FSIGT protocol used to collect the data that is entered into the minimal model. The first FSIGT protocol used was the glucose-only FSIGT[9]. In a glucose-only-FSIGT, a glucose bolus (0.3 g/kg) is given at baseline. Glucose and insulin concentrations are measured at 30 timepoints over three hours. However, in the presence of beta-cell failure, a glucose-only-FSIGT cannot be used to calculate insulin resistance. This is because with a standard glucose bolus, the absence of a robust beta-cell response makes it impossible to model the influence of insulin on glucose disappearance. To address this challenge, additional FSIGT protocols were developed: specifically the tolbutamide-boosted-FSIGT, the insulin-modified-FSIGT and the high-glucose-dose-FSIGT[6, 8, 10]. In the tolbutamide-boosted-FSIGT an intravenous bolus of glucose is administered at baseline and then at 20 minutes intravenous tolbutamide, an insulin secretagogue, is given. In an insulin-modified-FSIGT, an intravenous bolus of glucose is given at time 0 and intravenous insulin is administered at 20 minutes. In the high-glucose-dose-FSIGT the dose of glucose given at baseline is 0.5g/kg. This is higher than the standard glucose dose of 0.3g/kg and thereby provides extra stimulus for endogenous beta-cell secretion of insulin[6]. No exogenous insulin is given in the high-glucose-dose-FSIGT.

The insulin-modified-FSIGT is now the FSIGT protocol most commonly used. Originally the insulin-modified-FSIGT was performed over 3 hours with glucose and insulin sampled at 30 time points. However the cost and labor of this insulin-modified-FSIGT precluded its widespread application. To address this problem, a less frequently sampled FSIGT was developed using only 12 time points [11]. Steil et. al. designed the reduced sample protocol empirically with the first 4 time points selected to capture acute insulin secretion (0, 2, 4, 8 minutes), the next 2 time points selected to be immediately before and after the exogenous insulin injection (10 and 22 minutes) and the remaining 6 time points chosen to minimize parameter variance and reduce error in reconstructing the insulin profile (30, 50, 90 and 180 minutes)[11]. Since the publication of the reduced sample protocol the reduced sample time points have been widely accepted. Consequently a debate in the literature has risen as to the proper mathematical protocol to apply to the minimal model equations when the reduced sample protocol is used[6, 7]. In this investigation we refer to the insulin-modified-FSIGT which uses 30 time points as the Full-Sample-IM-FSIGT. The FSIGT protocol which uses only 12 time points is known as the Reduced-Sample-IM-FSIGT.

Initially, data from the Reduced-Sample-IM-FSIGT was entered into the minimal model using individual estimates and nonlinear regression[11]. Some investigators have suggested that when data from a Reduced-Sampled-FSIGT protocol is entered into the minimal model using a nonlinear regression approach, S_I cannot be resolved in many insulin resistant subjects[7]. Therefore, alternative approaches to the minimal model have been proposed using much more computationally complex population based methods such as Bayesian hierarchal analyses[5-7]. However, the analyses which linked DI to chromosome 11q in African-Americans calculated S_I based on data from a Reduced-Sampled-IM-FSIGT and a nonlinear regression approach to the minimal model[3].

Our goal was to determine the rate of resolution and accuracy of the Reduced-Sample-IM-FSIGT, using the nonlinear regression approach to the minimal model. Accuracy was determined by comparing S_I calculated from the Full and Reduced-Sample-IM-FSIGT.

Research Design and Methods

One hundred African-Americans (46M, 54W, age 35±7, mean±SD, range 22-50y, BMI 31.3 ±7.6, range 19.0-56.9kg/m^2) participating in Triglyceride and Cardiovascular Risk in African-Americans (TARA), a cross-sectional study at NIH, Bethesda, Maryland were evaluated. Basic demographics for these subjects are provided in Table 1. Results from these subjects have previously been reported[12]. Forty-eight percent of the subjects were obese and 24% glucose intolerant. Recruitment was by newsletters, flyers and websites. The Institutional Review Board of NIDDK approved the study. Subjects gave informed consent.

As described [12], subjects had a Full-Sample-IM-FSIGT in the morning after a 12h overnight fast. Glucose (0.3g/kg) was injected at baseline and insulin was infused from 20 to 25 min (4 mU.kg^{-1}.min^{-1}). The total dose of insulin administered over 5 minutes was 0.02U/kg. Glucose and insulin levels were determined at -10, -5, **-1**, 1, **2**, 3, **4**, 5, 6, 7, **8**,10, 12, 14, 16, **19**, **22**, 23, 24, 25, 27, **30**, **40**, **50**, 60, **70**, 80, 90, **100**, 120, 150, **180** minutes. The Reduced-Sample-IM-FSIGT timepoints are in bold. We note that in the original design of the reduced sample protocol, the 90 minute time point was used[11]. We chose to report our results using the 100 minute time point because the IRAS Family Investigators chose this time point[3]. However, all analyses were performed with S_I calculated using the 90 minute time point and again with S_I calculated using the 100 minute point. S_I calculated with the 90 minute time point was 4.31 ±2.89 mU.L^{-1}.min, range 0.58-14.26. When the 100 minute time point was substituted for the 90 minute timepoint, S_I was essentially unchanged. Specifically, S_I using the 100 minute time point was 4.29±2.89 mU.L^{-1}.min, range 0.52-14.42.

S_I was calculated for the Full and Reduced-Sample-IM-FSIGT using MinMOD Millenium v. 6.02[13]. The minimal model equations are:

- $G`(t) = -(X+Sg)G(t)+Sg.Gb$ Eqn 1

- $X`(t) = -p2.X(t)+p3\,(I(t) - Ib)$ Eqn 2

- $S_I = p3/p2.$

Equation 1 is the net rate of change of glucose concentration. Equation 2 is net rate of change of insulin action over time at an insulin concentration above basal. X represents insulin action in the remote compartment. Sg is glucose effectiveness. *P*2 stands for the loss of insulin from the remote site. *P*3 describes circulating insulin crossing the capillary endothelium into the remote site to promote glucose disposal.

Failure of resolution of S_I was defined as parameter coefficient of variation (PCV)>100%[6]. S_I calculated with nonlinear regression approach and the Full-Sample-IM-FSIGT is the accepted standard used to compare methodologies[5]. Initially 101 subjects were analyzed. However using the Full-Sample-IM-FSIGT for one of the subjects the PCV for S_I was 177%. As S_I from this subject could not be calculated with the accepted standard method, this subject was excluded.

Statistical Analyses

With the Full-Sample-IM-FSIGT considered the standard, percent relative error of S_I [7] was calculated as: ((absolute value of Full minus Reduced)/Full)*100. Spearman correlation coefficient was used to compare S_I obtained from the Full and Reduced-Sample-IM-FSIGT.

The agreement of S_I between FSIGT protocols was assessed by the Lin concordance correlation coefficient[14]. This coefficient determines whether the observed data from each method significantly deviates from the line of perfect concordance (that is, a line at 45 degrees when both measurements are plotted against each other)[14, 15].

In addition, the agreement of S_I by the two FSIGT protocols was assessed by the Bland Altman method. In this method the mean of the values obtained from each protocol is plotted against their difference[16]. With good agreement the mean difference in the measurements is close to zero and there is limited and uniform variation around a zero difference line along the full range of the average values. The limits of agreement demonstrate the range of differences that might be expected from both methods. Due to the variability in measurements, limits of agreement are usually based on log transformed data[17].

To assess the ability of these methods to maintain rank order, subjects were grouped into tertiles using values obtained from the Full and Reduced-Sample-IM-FSIGT. Then rank order agreement for both methods was assessed using percent agreement and the kappa statistic. In this investigation, insulin resistance was defined *a priori* by the lowest tertile of S_I determined by data from the Full-Sample-IM-FSIGT.

All results are presented as mean±SD unless specified otherwise. Analyses were performed with STATA, version 10.0 (College Station, TX).

Results

Using the nonlinear regression method with the Reduced-Sample-IM-FSIGT, S_I was successfully resolved in 97% (97/100) of participants. Therefore the rate of failure of resolution with the Reduced-Sample-IM-FSIGT was 3% (3/100).

The three subjects for whom S_I could not be calculated with the Reduced-Sample-IM-FSIGT had S_I values from the Full-Sample-IM-FSIGT of: 2.23, 2.76 and 10.1 $L.mU^{-1}.min^{-1}$. As insulin resistance was defined by the lowest S_I tertile (S_I of $\leq$2.37 $L.mU^{-1}.min^{-1}$), for the three subjects for whom S_I could not be resolved by the Reduced-Sample-IM-FSIGT, two were relatively insulin-resistant and one was insulin-sensitive.

All subsequent analyses are based on the 97 subjects who achieved successful resolution of S_I by both FSIGT protocols. The frequency distributions of S_I for the two protocols are provided in Figure 1. S_I for the Full and Reduced-Sample-IM-FSIGT were: 3.76±2.41 and 4.29±2.89; relative error 21±18%, Spearman correlation 0.97, $P<0.001$ (Figure 2) and concordance 0.92, $P<0.001$. For log transformed data, the Bland Altman limits of agreement were: -0.29 and 0.53 and the mean difference was 0.12 (Figure 3).

When the tertile distribution of S_I for each of the two FSIGT protocols is compared, the exact agreement by tertile category is 86% with kappa 0.78±0.07 (SE). However insulin resistance was defined by S_I calculated from the lowest tertile. Those in the middle and upper S_I were classified as insulin-sensitive. The exact agreement for the distribution of the population in the lowest tertile versus the combination of the middle and upper tertiles is 92% with kappa 0.82 ±0.06 (SE). Therefore, predicting insulin-resistant subjects with tertiles led to a misclassification error by the Reduced-Sample-IM-FSIGT of only 8%.

Discussion

There is controversy as to whether S_I can be accurately and successfully resolved in insulin-resistant subjects using the nonlinear regression approach to the minimal model[6, 7]. We enter the debate by presenting results from subjects with a wide range of insulin sensitivity and a prevalence of glucose intolerance of 24%. We found a failure rate in the resolution of S_I of only 3% with the Reduced-Sample-IM-FSIGT. Therefore when data from the Reduced-Sample-IM-FSIGT are entered into the minimal model with a nonlinear regression approach a high rate of success in resolving S_I can be expected. Furthermore we suggest that insulin resistance does not preclude the use of the nonlinear regression approach to the minimal model. In this investigation of the three subjects for whom S_I could not be resolved with the Reduced-Sample-IM-FSIGT, two were relatively insulin-resistant (2.23 and 2.76 $L.mU^{-1}.min^{-1}$) and one was insulin-sensitive (10.1 $L.mU^{-1}.min^{-1}$).

Yet, other investigators have reported high failure rates using the nonlinear regression approach to the minimal model. Using only a Reduced-Sample-FSIGT and the nonlinear regression approach, Godsland et. al. reported a failure rate of 7%[6]. Krudys et. al. found a failure rate in the resolution of S_I of 17% [7]. With glucose intolerant subjects Krudys et. al. reported a failure rate of 31%[7].

The higher failure rate in the resolution of S_I reported by both Godsland et. al. and Krudys et. al. may be due, at least in part, to differences in the FSIGT protocol rather than to the mathematical approach used. The FSIGT protocol that we used was insulin-modified. Godsland et. al. used a high-glucose-dose-FSIGT protocol[6]. Even though Godsland et. al. administered a higher dose of intravenous glucose than we did (0.5g/kg vs. 0.3g/kg), the absence of an intravenous bolus of insulin may account for their higher failure rate. The high failure rate by Krudys et. al. may also be protocol dependent[7]. First they provided an

intravenous glucose bolus based on body surface area (BSA) (11.4g/m^2) rather than weight (0.3g/kg). In obese subjects a dose of glucose based on BSA is generally lower than a dose of glucose based on weight. For example, using the DuBois formula for BSA in a person with a BMI of 35.7 kg/m^2 and a weight of 106.1 kg, the dose of glucose administered would be 24.9g. However, if the glucose dose is based on weight, the glucose dose at 0.3g/kg would be 31.8g or 28% higher than the dose based on BSA. A smaller glucose dose will provoke a lower endogenous insulin response and consequently poorer resolution of S_I. Further, they infused intravenous tolbutamide rather than insulin at 20 minutes. Differences in S_I determined from the tolbutamide-boosted versus the insulin-modified FSIGTs are well recognized[18].

S_I calculated with the nonlinear regression approach to the minimal model has been validated against glucose clamp measures of insulin resistance[19]. Further the agreement of S_I calculated from the Full and Reduced-Sample-IM-FSIGT is highly significant[11]. Yet, in any modeling endeavor, when the number of samples is decreased, there is a loss of accuracy. Comparing S_I from the Full and Reduced-Sample-IM-FSIGT, we found a relative error of 21%. This relative error is consistent with the work of Steil et.al. as they report an error rate of 20% with the Reduced-Sample-tolbutamide-boosted-FSIGT [11]. In interpreting this error, we found that the mean difference in S_I between protocols was positive. Thus, the error between the two determinations may be accounted for by an overestimation of S_I with the Reduced-Sample-IM-FSIGT protocol. Krudys et. al. also found that S_I calculated with data from the Reduced-Sample-tolbutamide-FSIGT consistently overestimated S_I[7]. Despite the overestimation of S_I when the reduced sample protocol is used, rank order of S_I is maintained. In fact, our tertile analyses of S_I demonstrated that subjects identified as insulin-resistant with the Full-Sample-IM-FSIGT had a misclassification error by the Reduced-Sample-IM-FSIGT of only 8%. However, due to the persistent and consistent overestimation of S_I with the reduced sample protocol, in any single study results from the reduced and the full sample FSIGT cannot be combined.

In this investigation using the nonlinear regression approach to the minimal model, we tested the validity of S_I obtained from the Reduced-Sample-IM-FSIGT. Even in the presence of insulin resistance, the Reduced-Sampled-IM-FSIGT was very successful in resolving S_I. Further, the agreement and maintenance of rank order of S_I between the Full and Reduced-Sample-IM-FSIGT provides support for the value of the Reduced-Sample-IM-FSIGT. Consequently we suggest that it is not necessary to switch from nonlinear regression analyses to more complicated mathematical techniques such as Bayesian hierarchal analyses to calculate S_I. Indeed the IRAS Family Study linking DI to Chromosome 11 is an example of how the application of the Reduced-Sample-IM-FSIGT can be utilized to obtain important information about glucose homeostasis[3]. Therefore, we encourage the use of the Reduced-Sample-IM-FSIGT with the nonlinear regression approach for epidemiological studies to better understand the role of insulin resistance in human disease.

Acknowledgements

This work was supported by the intramural research program at NIDDK.

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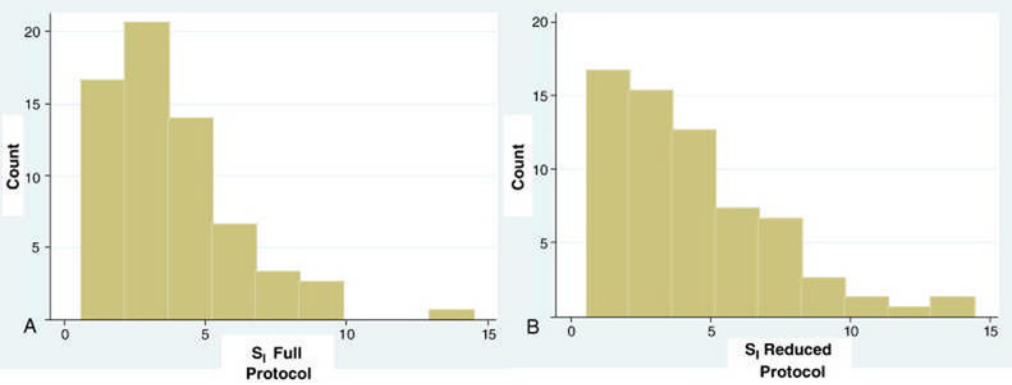

Figure 1.
Histograms of the Frequency of S_I according to FSIGT protocol.
(A) Full-Sample-IM-FSIGT. (B) Reduced-Sample-IM-FSIGT.

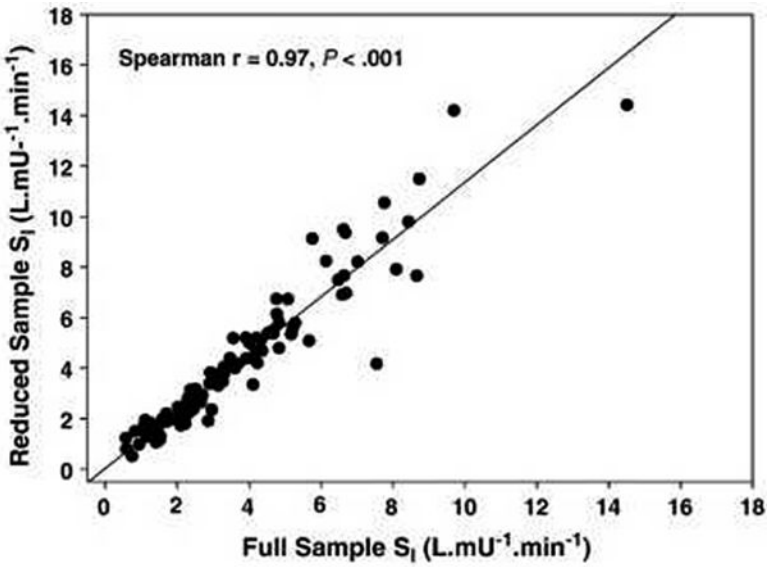

Figure 2.
S_I from the Full-Sample-IM-FSIGT versus S_I from the Reduced Sample-IM-FSIGT. Spearman correlation is 0.97, $P<0.001$.

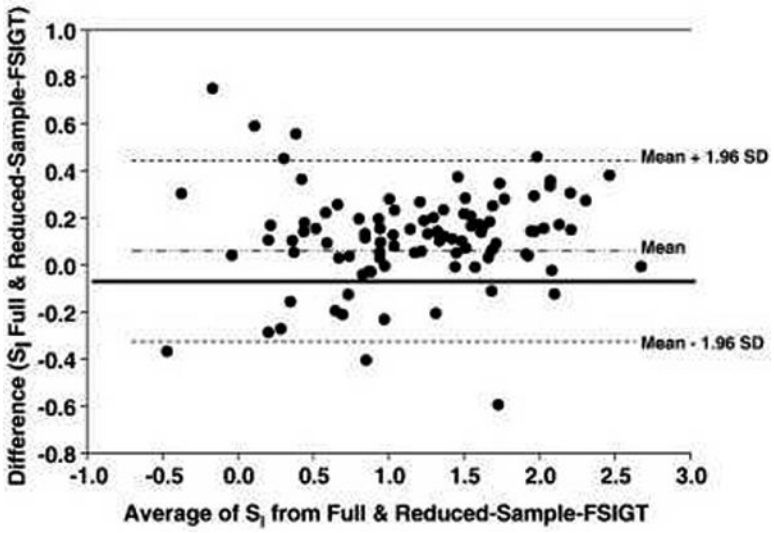

Figure 3.

Bland Altman Plot for agreement between S_I calculated from Full and Reduced-Sample-IM-FSIGT. Data is log transformed. X-axis presents the mean of the two determinations of S_I. Y-axis presents the difference. With back transformation, the limits of agreement were 0.75 and 1.69 and the geometric mean difference was 1.12. The mean difference of 1.12 suggests that S_I is overestimated when data from the Reduced-Sample-IM-FSIGT protocol is used.

Table

Characteristics of the Participants

Variable (n=101)	Mean±SD	Range
Age (y)	35±7	22 - 50
Percent Male	46	
BMI (kg/m^2)	31.4±7.6	19.0-56.9
Waist Circumference (cm)	99±16	67-142
Systolic Blood Pressure (mmHg)	117±14	92-153
Diastolic Blood Pressure (mmHg)	70±9	48-92
Fasting Glucose (mg/dL)	84±9	66-112
Fasting Insulin (mU/mL)	8.3±4.5	1.9-25.0
Percent Glucose Intolerant	31	