

Background (I)

- The benefits of HAART are potentially offset by newly emerging toxicities
- Metabolic abnormalities and changes in body shape, known collectively as the Lipodystrophy syndrome(s), lead to alterations in body fat, dyslipidemia, insulin resistance, decreased bone mineral density, and possibly other related abnormalities¹
- Sequelae include decreased QOL, and possibly accelerated atherosclerosis and complications of osteoporosis
- Early recognition of these metabolic changes and related risk factors is being strongly advocated

Background (II)

- Although both Type I and Type II diabetes contribute to cardiovascular risk, insulin resistance alone as a comorbid factor remains controversial^{2,3,4}
- While measurement of lipid profiles and bone mineral density is readily and reliably available, appropriate screening tools for insulin resistance remain uncertain⁵
- Various tests are available to diagnose insulin resistance but none is routinely accepted as being easily acceptable to the patient and sufficiently reliable compared to the more complicated and time consuming “gold standards”
- The American Diabetes Association and the World Health Organization differ in their recommendations as to how glucose intolerance and type 2 diabetes should be diagnosed^{6,7,8,9,10}

Abbreviations

OGTT	Oral Glucose Tolerance Test
FBG	Fasting Blood Glucose
NGT	Normal Glucose Tolerance
IGT	Impaired Glucose Tolerance
IFG	Impaired Fasting Glucose
HOMA	Homeostasis Model Assessment
QUICKI	Quantitative Insulin Sensitivity Check Index
IVITT	Intravenous Insulin Tolerance Test

Insulin Resistance Measurements

- Hyperinsulinemic euglycemic clamp
 - gold standard, time consuming, costly
- Minimal model
 - reliable index of insulin sensitivity, correlating with “clamp”, requires frequent blood draws
- Insulin tolerance test
 - insulin sensitivity correlating with “clamp”, requires frequent blood draws
- Insulin suppression test
 - continuous IV infusion and frequent blood draws
- Fasting plasma insulin and C-peptide
 - traditional insulin resistance surrogate markers do not correlate well with “clamp” results
- HOMA¹¹
 - population-based computer model predicting beta cell function with insulin resistance, highly correlated with insulin sensitivity by “clamp” on a population basis, requires single blood draw
- QUICKI¹²
 - new test, requires single blood draw, index of insulin sensitivity useful for clinical research

Prevalence of Insulin Resistance/ Glucose Intolerance in Cohort Studies

Author	Number	Test Used	Insulin Resistance
Walli ¹³	67 on PI	OGTT in 24	13 (54%)
		IVITT	41 (61%)
	13 ART naïve	IVITT	0 (0%)
Carr et al ¹⁴	113	OGTT	16%
Behrens ¹⁵	38 on PI	OGTT	18/32 (46%)
	17 PI naïve		4/17 (24%)
Tsiodras ¹⁶	221	random glucose	11 (5%) with hyperglycemia (> 7.8 x 2)
Dabis ¹⁷	581	HOMA > 4.0	76 (13%)
Batterham ¹⁸	100	HOMA	prevalence not reported
Viard ¹⁹	51	FBG	0 (0%)

Purpose

To compare the reliability of different readily available blood tests and derived indices consistent with insulin resistance to results obtained from a standard glucose tolerance test.

Methods

- Adult HIV+ subjects underwent a standard 75gm oral glucose tolerance test (OGTT)
- Diagnosis of normal glucose tolerance, insulin resistance, and type 2 diabetes mellitus was done as per WHO guidelines
- Results of the following parameters were obtained within 1 month of the OGTT: T cell subsets, HIV RNA quantification, fasting insulin, C-peptide, uric acid, lipid profile
- Body Mass Index (BMI) was calculated ($Wt[kg]/Ht[m]^2$)
- Clinic recorded BP readings at 3 time intervals over a 6 month period were averaged
- Results were analyzed for non-diabetic patients only (as per OGTT results)

Methods (cont'd)

- The homeostasis model assessment method was used to calculate the HOMA: $\frac{\text{fasting insulin} \times \text{glucose}}{22.5}$
- The quantitative insulin-sensitivity check index (QUICKI) was calculated: $\frac{1}{[\log(\text{fasting insulin}) + \log(\text{fasting glucose})]}$
- Means, standard deviations (S.D.), ranges, and 95% confidence intervals were calculated for continuous variables
- Mean values of markers were compared between groups by the Wilcoxon non-parametric test
- Proportions were compared across groups using the Chi-square test
- Sensitivity and specificity of different measures of insulin resistance using the OGTT as the reference standard were calculated

Results (entire group)

Total number of non-diabetic subjects (M:F)	53 (49:4)
Age (mean \pm S.D. [range])	44 \pm 9.6 (24-70)
BMI	24 \pm 3.5 (18.5-32.7)
Systolic BP	130 \pm 10 (105-150)
Diastolic BP	80 \pm 8.0 (65-102)
CD4 (number/ml ³)	450 \pm 250 (16-1175)
Viral Load (log ¹⁰ number/ml)	2.5 \pm 1.2 (1.7-5.3)
HAART duration (m.)	50 \pm 18 (3-80)
Cholesterol (mmol/L: normal <5.19)	5.0 \pm 1.2 (2.6-9.1)
Triglycerides (mmol/L: normal 0.4 - 2.29)	2.5 \pm 1.5 (0.8-7.4)
HDL (mmol/L: normal >1.1)	1.0 \pm 0.3 (0.6-2.1)
LDL (mmol/L: normal < 3.37)	2.9 \pm 1.0 (0.9-6.1)
Cholesterol/HDL	5.1 \pm 1.3 (2.1-7.8)
Insulin (pmol/L: normal 0-160)	121 \pm 190 (19-1280)
C-peptide (umol/L: normal 0.3-1.30)	1.7 \pm 1.0 (0.4 -7.0)
Fasting blood glucose (FBG [mmol/L]: normal 3.3 -6.4)	4.9 \pm 0.9 (3.7-8.8)
HOMA	4.4 \pm 9.9 (0.5-70.0)
QUICKI	0.34 \pm 0.04 (0.225-0.438)
Uric acid (umol/L: normal 150-510)	364 \pm 89 (186-740)

Total - 53 (non-diabetic)

IGT-12 (25%)

IFG- 1

BMI (mean) 25 ± 3.7

BMI > 30 -1/12 (8.3%)

Increased FBG-3 (23%)

Increased insulin-5 (38%)

Increased C-peptide -6/10 (60%)

HOMA > 4.0 -5 (38%)

QUICKI < median -10/13 (77%)

NGT- 40 (75%)

BMI (mean) 23.5 ± 3.4

BMI > 30 -2/32 (6.3%)

Increased FBG -1 (2.5%)

Increased insulin -2 (5%)

Increased C-peptide -16/39 (41%)

HOMA > 4.0 -3 (8%)

QUICKI < median -15/40 (38%)

Results

<u>Test</u>	<u>Abnormal</u>
Abnormal GTT	13/53 (25%)
Elevated FBG	4/53 (7.5%)
Increased insulin	8/53 (15%)
Increased C-peptide	24/49 (51%)
HOMA > 4.0	9/53 (17%)
Decreased QUICKI	25/53 (47%)

Results

GTT (IGT=7.8-11.1 on 2 hr PC)	HOMA (>4.0)	QUICKI (<0.34 [median])	N	%
+	+	+	6	11
+	+	-	0	0
+	-	+	5	9
+	-	-	2	4
-	+	+	3	6
-	+	-	14	26
-	-	+	10	19
-	-	-	13	25

Results

GTT (IGT)	FBG (6.1-7.00)	Insulin (>160)	N	%
+	+	+	2	4
+	+	-	1	2
+	-	+	3	6
+	-	-	7	13
-	+	+	1	2
-	+	-	0	0
-	-	+	2	4
-	-	-	37	70

Test Characteristics:

Compared to reference standard - OGTT

Variable	Sensitivity	Specificity	PPV*	NPV ⁺
	(%)	(%)	(%)	(%)
FBG	23	98	75	80
Insulin	39	93	63	82
HOMA	46	93	67	84
C-peptide	63	54	28	84
QUICKI	85	63	42	93

*PPV - Positive Predictive Value

⁺NPV - Negative Predictive Value

Summary

- The QUICKI may be the simplest and most accurate derived value to diagnose insulin resistance
- FBG did not diagnose as many patients with glucose intolerance as did the OGTT
- Less than 1/3 of subjects with increased C-peptide levels had IGT, increased fasting insulin or elevated HOMA suggestive of insulin resistance
- BMI was similar in subjects with NGT and IGT (including obese subjects)
- Not all subjects with IGT are insulin resistant and some subjects with NGT may be insulin resistant

Conclusions

- The diagnosis of IGT and insulin resistance is a function of the specific test used
- C-peptide is not a useful determination to use to diagnose insulin resistance
- FBG alone is not helpful in diagnosing insulin resistance
- The simplest, most reliable parameter to use to screen HIV patients for insulin resistance remains to be established

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