Metabolon

Quantose® IR

Disease Summary

Insulin Resistance

Insulin Resistance is a characteristic feature for the development of prediabetes, type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, stroke and polycystic ovarian syndrome.[1,2]

Insulin Resistance is evident when glucose builds up in the blood stream instead of being absorbed by the body's cells. It is a result of a diminished response to the hormone insulin at the whole body, organ, or cellular level (see Figure 1).[3] An outcomes study that followed 208 healthy, non-obese individuals for an average of 6 years proved that Insulin Resistant patients had a statistically significant increase in the incidence of type 2 diabetes, hypertension, coronary heart disease, stroke and cancer in patients and that there was a lack of these outcomes in insulin sensitive patients.[4] Additionally, Insulin Resistance can be present >10 years prior to changes in glycemic measures or the development of diabetes.[5]

Test Summary

Quantose®IR

Quantose®IR identifies Insulin Resistance with a single fasted blood draw.

The Quantose®IR test measures Insulin Resistance based on a panel of biomarkers comprised of a small organic acid (α-hydroxybutyric acid (AHB)), 2 lipids (oleic acid and linoleoylglycerophosphocholine (LGPC)) and insulin. The test Score was developed to estimate the value obtained from the hyperinsulinemic euglycemic clamp, the gold standard for determining insulin sensitivity, within a prospective, observational cohort study of 1277 clinically healthy, non- diabetic people recruited from 13 European countries.[6] It is the first and only test to be clinically developed and validated using the clamp.

The Insulin Resistance cut-off of 63 was defined by the top tertile of scores from the European study.[6] Concentrations of the panel biomarkers are measured by clinical chemistry (insulin) and mass spectrometric (UHPLC-MS/MS) based quantitation and then combined to generate the Quantose®IR Score.

The Quantose®IR Score is based on a linear regression algorithm utilizing the quantitative measures (natural log transformed) of AHB, oleate, LGPC, and insulin and was designed to estimate the natural log of the Mwbm (insulin-induced glucose infusion rate normalized by whole body mass) from the hyperinsulinemic euglycemic clamp procedure.[6] Fasting plasma levels of AHB, LGPC, oleate, and insulin individually correlate significantly with Mwbm.[6,7] The algorithm score is then converted to the Quantose®IR score within a range of 1-120 by an arithmetic calculation where higher scores denote greater Insulin Resistance

Monitoring Treatment with Quantose®IR

In the ACT NOW study, patients with impaired glucose tolerance were randomized to pioglitazone (45mg/day) or placebo and followed for an average of 2.4 years. Researchers conducted a retrospective study using samples from 210 subjects treated with pioglitazone to assess the clinical validity of Quantose®IR for monitoring changes in insulin sensitivity. Quantose®IR tracked insulin sensitivity and glucose tolerance, with a significant 29 percent improvement in Quantose®IR score in pioglitazone-treated patients. In contrast, A1C scores worsened slightly in the same subjects.[8]

Clinical Use

- Identification of patients with Insulin Resistance
- Guide treatment strategy for patients with Insulin Resistance

This Guide provides information relating to the selection, utilization, and interpretation of the Quantose®IR test. Information provided is based on peer-reviewed publications and clinical practice guidelines.

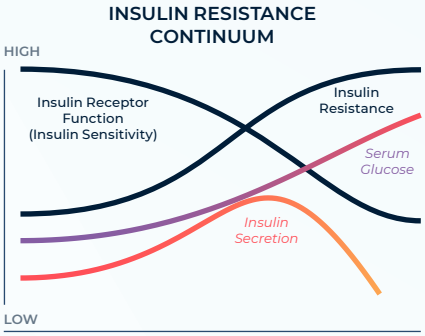


Figure 1

Individuals Suitable for Quantose®IR Testing

Adults who are overweight (BMI ≥25kg/m2 or ≥23kg/m2 in Asian Americans) and have one or more of the following risk factors:

- Physical inactivity
- Hypertension (≥140/90 mmHg or on therapy for hypertension)
- HDL cholesterol level < 35mg/dL (0.90 mmol/L) and/or a triglyceride level > 250 mg/dL (2.82 mmol/L)
- High risk ethnic background (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- First-degree relative with diabetes
- Delivered a baby weighing > 9 lb. or diagnosed with gestational diabetes mellitus
- Polycystic ovary syndrome
- History of cardiovascular disease (CVD)
- Other clinical conditions associated with Insulin Resistance (e.g., severe obesity, acanthosis nigricans)

Fasted 8-10 hours.

Method

Liquid chromatography, tandem mass spectrometry (LC-MS/MS) using the stable isotope dilution technique to quantify AHB, LGPC and oleate (µg/mL).

- EDTA plasma samples are extracted with methanol and spiked with stable isotope labeled standards of of AHB, LGPC and oleate
- Separation via ultra-high-performance liquid chromatography (UHPLC)
- Detection and quantitation via tandem mass spectrometry

Plasma insulin is quantified (µU/mL) using the Abbott chemiluminescent micro particle immunoassay on the Architect platform.

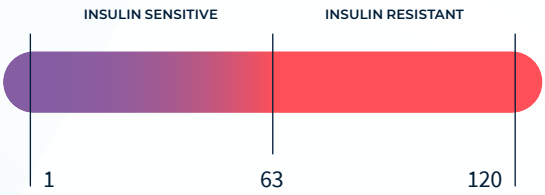
Analyte concentrations used in conjunction with an algorithm to calculate level of Insulin Resistance.

Report includes concentrations of AHB, LGPC, oleate, and insulin along with the Quantose®IR score.

Interpretive Information

It is recommended that the Quantose®IR test be administered to patients with relatively stable weight (+/- 3 lbs. over one month) and before and after diet and exercise programs.

In a 12-week, 70 subject study, the Quantose®IR measurement demonstrated fluctuations in individual analytes in subjects experiencing active weight loss. Further studies are required to more fully understand potential correlations between active weight loss, Insulin Resistance and the Quantose®IR measurement. In a situation when a patient is experiencing active weight loss, clinicians should interpret the Quantose®IR test results with caution.[9]



Test Scores

REFERENCE INTERVALS

AHB	1.92 - 7.37 µg/mL	**Oleate**	25.9 - 114 µg/mL
LGPC	7.60 - 25.4 µg/mL	**Insulin**	3.13 - 21.3 µU/mL

Patients with a Quantose®IR Score of 63 or higher are defined as insulin resistant. This cut-off is defined by the top tertile of scores from a study of 1277 hyperinsulinemic glycemic clamp values of clinically healthy, non-diabetic people recruited from 13 European countries.[6] Quantose®IR test score reference intervals were established using 456 non-diabetic subjects at risk for diabetes (IFG, IGT, and/or FINDRISC score > 12).

Performance

Quantose®IR scores have an AUC of 0.84 for the ROC curve for the identification of people with Insulin Resistance using the lowest tertile definition of the condition. Using this same criterion, the test has a sensitivity of 65% and a specificity of 85%. These data were generated in the 1277 subjects.[6]

Specimen Requirements and Shipping/Handling

- 0.5 mL refrigerated or frozen plasma (EDTA (K2)/lavender top tube).
- Patient must be fasted for 8 to 10 hours prior to sample collection
- Refrigerated samples should be sent overnight with cold packs to maintain 4°C
  Frozen samples should be sent on dry ice and remain frozen at -20°C to -80°C

Caution: It is critical that plasma is separated from whole blood within 1 hour of collection to ensure integrity of results.

REFERENCE INTERVALS

STORAGE TEMP.	SPECIMEN TYPE	COLLECTION VIAL	TRANSPORT VIAL	MINIMUM VOLUME	SHIPMENT CONDITION	STABILITY
Refrigerated 4°C	Plasma	EDTA (K2) / Lavender Top	Thermo Scientific™ Nalgene™ Cryogenic Tube P/N 5000 0050	0.5 mL	Cold Pack / Overnight	96 hours
Frozen -20°C-80°C	Plasma	EDTA (K2) / Lavender Top	Thermo Scientific™ Nalgene™ Cryogenic Tube P/N 5000 0050	0.5 mL	Dry Ice / Overnight	5 months

Note: Detailed shipping and handling information guidance available upon request.

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9. Data on file, Metabolon 2014

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info@metabolon.com

+1 (919) 572-1711
info@metabolon.com
www.metabolon.com

617 Davis Drive, Suite 100, Morrisville, NC, 27560

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