Quantification of adipose tissue insulin sensitivity

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ABSTRACT

In metabolically healthy humans, adipose tissue is exquisitely sensitive to insulin. Lipolysis is almost completely suppressed at insulin concentration as low as 50–100 pmol/L. Similar to muscle and liver, adipose tissue lipolysis is insulin resistant in adults with central obesity and type 2 diabetes. Perhaps uniquely, however, insulin resistance in adipose tissue may directly contribute to development of insulin resistance in muscle and liver because of the increased delivery of free fatty acids to those tissues. It has been hypothesized that insulin adipose tissue resistance may precede other metabolic defects in obesity and type 2 diabetes. Therefore, precise and reproducible quantification of adipose tissue insulin sensitivity, in vivo, in humans, is an important measure. Unfortunately, no consensus exists on how to determine adipose tissue insulin sensitivity. We review the methods available to quantify adipose tissue insulin sensitivity and will discuss their strengths and weaknesses.

In addition, glycerol tracers have been used to measure lipolysis. In theory, glycerol tracers better reflect total lipolysis because it has been argued that fatty acids may be re-esterified within adipocytes; this remains to be shown in vivo. However, glycerol is also released from the hydrolysis of circulating triglycerides. Under insulin suppressed conditions, this can be a significant confounder. Furthermore, we argue that the FFA released from adipose tissue into circulation is the physiological relevant measure as FFA, not glycerol, contributes to the metabolic effects of adipose tissue. The microdialysis technique can measure regional adipose tissue lipolysis, but the nuances of the using approach lies outside the scope of this brief review.

MULTISTEP INSULIN CLAMP

The multistep insulin clamp in combination with a FFA tracer has been used for decades to determine the dose–response relationship between plasma insulin concentration and lipolysis rates. It can be performed using the pancreatic clamp approach using somatostatin to obtain insulin concentrations ranging from near zero to those achieving complete suppression of lipolysis. However, the low-dose insulin infusion rate has to be carefully selected to obtain suppression in the mid-portion of the suppression range. The very steep relationship between FFA release and plasma insulin concentrations is such that it is easier to linearize the function by logarithmic transformation of both x (insulin) and y (FFA flux) axes. This allows for easier calculation of the ‘true’ IC50 (insulin concentration required for a 50% suppression of lipolysis). A multistep clamp performed without somatostatin can also be used to calculate an IC50 from basal insulin concentrations, which might be referred to as a ‘basal’ FFA-IC50. The FFA-IC50 is well correlated with other indices of metabolic health, including whole body insulin sensitivity, with regard to glucose disposal and triglyceride concentrations. The drawback is that the method is cumbersome and time consuming. A single study requires 6–8 h to obtain a steady state in FFA turnover at each insulin step, limiting the number of subjects that can be studied.

SINGLE STEP HYPERINSULINAEMIC EUGLYCEMIC CLAMP

A simpler approach for measuring adipose tissue insulin sensitivity is to use a single step,
provide similar estimates of ED50 as the multistep clamp and insulin suppressed) obtained using this method can
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of insulin concentrations and
insulin concentration.

a similar level as for insulin sensitive individuals, but at a higher
resistant to the effect of insulin on lipolysis. Lipolysis suppress to
clamp method and that this approach may be able to detect
measure the dynamic response of FFA concentrations to a
which itself can markedly alter lipolysis.13 These methods
above the euglycemic range, with a glucose infusion to
hyperinsulinemic, euglycemic clamp with isotopic tracer
measures of lipolysis under basal and hyperinsulinemic
conditions. This approach is considered the gold standard
for quantifying whole body insulin sensitivity for glucose
and is less time consuming than the multistep clamp. The
single step insulin clamp can provide reasonable estimates
of adipose tissue (and glucose) insulin sensitivity, again
because the relationship between insulin concentration and
FFA flux can be linearized using logarithmic transformation
of insulin concentrations and flux. The two points (basal
and insulin suppressed) obtained using this method can
provide similar estimates of ED50 as the multistep clamp
method.9 However, as can be observed in figure 1, because
the curve is very steep in insulin sensitive individuals,
if the insulin dose selected is even slightly above that
needed for maximal suppression, the IC50 can be grossly
overestimated.9

MODELLING THE EFFECT OF INSULIN ON LIPOLYSIS
Analog to the minimal model for quantification of the effect
of insulin on glucose disposal,10 modelling approaches are
available for the suppressive effect of insulin on FFA
concentrations.11 Here, the effect of insulin on lipolysis is modelled
during an insulin-modified frequently sampled intravenous
glucose tolerance test (IM-FSIVGTT)11 or an oral glucose
tolerance test12 without using an FFA tracer. For the
IM-FSIVGTT, glucose concentration is maintained in at or
above the euglycemic range, with a glucose infusion to
avoid a hypoglycemia-induced counter-regulatory response,
which itself can markedly alter lipolysis.13 These methods
measure the dynamic response of FFA concentrations to a
glucose bolus that stimulates endogenous insulin secretion.
It has been argued that the dynamic insulin response to a
glucose bolus is a more physiological challenge than the
clamp method and that this approach may be able to detect
differences in the adipose tissue response to insulin not
revealed during constant insulin infusions.11 Our concern,
however, is that these mathematical models rely on number
assumptions regarding compartments and the kinetics of
FFA clearance that have not been fully validated against
models lacking such assumptions. Furthermore, high baseline
FFA levels may negatively affect β-cell function and
reduce the insulin response to the glucose bolus.14 Another
limitation with model-based methods is their complexity.
Researchers not trained in or lacking collaborators in math-
ematical modelling may have insufficient appreciation of
the limitations and assumptions. This can lead to over-
interpreting the results. In contrast, the clamp methods
provide straightforward dose–response curves that are more
easily interpreted.

SIMPLE INDICES TO MEASURE ADIPOSE TISSUE
INSULIN SENSITIVITY
A simpler approach to measure adipose tissue insulin sensi-
tivity is to measure postabsorptive plasma insulin and FFA
concentrations (the Adipo-IR). This index is similar to the
HOMA-IR,15 16 and is calculated by multiplying postab-
sorptive concentrations of insulin and FFA. However, valid-
ation of the Adipo-IR against other measures of adipose
tissue insulin sensitivity is lacking. Our concerns are that
the relationship between insulin and FFA concentrations is
affected by factors other than adipose tissue insulin sensi-
tivity, such as age, sex, body composition, ethnicity or
physical fitness. Furthermore, the index is based on a single
measurement of insulin and FFA concentration, and is
therefore more prone to analytical and day-to-day vari-
ation. The day-to-day variability of palmitate flux is sub-
stantial, as much as 31% in subjects consuming their usual
diet.8 This can be reduced to half by providing subjects
with a weight maintaining diet;3 however, that will often
not be applicable for larger studies where the Adipo-IR is
applied. Whether the day-to-day variation in FFA concentra-
tion is independent of or follows the variation in insulin
centration remains unknown. The major advantage of
this index is that it is easy to measure and calculate for
large numbers of subjects. Therefore, it can be applied for
studies with substantially larger sample size compared with
that of the clamp method.

Another index of adipose tissue insulin sensitivity has
been suggested, but has not yet been applied for any add-
tional studies. The Adipose Tissue Insulin Resistance Index
(ATIRI) multiplies postabsorptive palmitate flux rates deter-
mined by a palmitate tracer relative to postabsorptive
insulin concentrations.17 This has been validated with a
reasonable predictive value to suppression of lipolysis
during a hyperinsulinemic euglycemic clamp (R2=0.73) in
obese individuals.17

CONCLUSION
Adipose tissue insulin sensitivity has attracted less attention
than has insulin sensitivity in muscle and liver. However,
the key role of adipose tissue in delivering FFA for other
insulin sensitive tissues necessitates a better understanding
of the regulation of lipolysis. Several methods are available
to estimate adipose tissue insulin sensitivity. We argue that
the most pharmacologically pure approach is the ‘true’
FFA-IC50 that we described above, using somatostatin to

Figure 1 Relationship between insulin concentration and palmitate flux. Individual with obesity and type 2 diabetes are
resistant to the effect of insulin on lipolysis. Lipolysis suppress to
similar level as for insulin sensitive individuals, but at a higher
insulin concentration.
obtain near zero insulin concentrations. How the other methods compare to this approach, and whether any of the methods is superior in term of predicting clinical outcomes, is unknown.

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