Alternative Methods of Insulin Sensitivity Assessment in Obese Children and Adolescents

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Running Title: Validation study of fasting indices

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ABSTRACT

Objective: To validate fasting indices against minimal model analysis of the frequently sampled intravenous glucose tolerance test (FSIVGTT-MMOD) in an obese pediatric population.

Research Design and Methods: FSIVGTT-MMOD results were compared to HOMA-IR and fasting insulin with sample stratified by sex, puberty and \( S_i \) median in 191 children (82 males; 13.9±2.9y, BMI 36.9±6.2 kg/m\(^2\), BMI-SDS 6.1±1.6).

Results: Across pubertal groups correlation coefficients between \( S_i \) and HOMA-IR ranged from -0.43 to -0.78 in males, and from -0.53 to -0.57 in females (age and BMI adjusted, \( p<0.05 \) in all instances). Similar results were seen for fasting insulin. In females the relationship was significantly weaker in more insulin resistant subjects.

Conclusions: The validity of fasting indices in explaining \( S_i \) was sex dependent, varied with pubertal stage, and in females influenced by degree of insulin sensitivity. In obese pediatric populations we generally discourage the use of fasting indices, although the validity varies within subgroups.
Obesity in children and adolescents (1-6) with the complication of insulin resistance requires accurate methods for insulin sensitivity assessment. Minimal model analysis of the frequently sampled intravenous glucose tolerance test (FSIVGTT-MMOD) (7) is a well validated method. However, alternative methods for routine clinical use have been developed using fasting plasma glucose and insulin concentrations, such as HOMA-IR (8) and QUICKI (9).

In obese children and adolescents, the use of fasting indices has been promoted (10; 11) as well as discouraged (12). We performed FSIVGTT-MMOD among obese participants ranging from children to young adults and compared results with fasting indices, aiming to evaluate these as surrogate measures of insulin sensitivity in an obese pediatric population.

RESEARCH DESIGN AND METHODS

The study included 191 overweight or obese Swedish participants, ranging from children to young adults. Patients with mental, endocrine or metabolic disorders (except mild dyslipidemia), were excluded. Anthropometric and pubertal assessments were performed (13; 14), BMI-SDS calculated (15) and DEXA scan performed (16). The study protocol was approved by the local Ethics Committee, and written informed consent obtained.

FSIVGTT was performed according to standard protocol (7; 16; 17) with sensitivity index ($S_i$) calculated by computer program MINMOD version 3.0 (Richard Bergman, 1994). Fasting insulin and glucose were analysed using standard laboratory techniques, and HOMA-IR and QUICKI calculated as previously described (8; 9).

Results are reported as mean ± SD. Fasting indices and $S_i$ were transformed logarithmically. Analyses were sex stratified and the sample divided into groups of pre-pubertal (Tanner 1), pubertal (Tanner 2-3) and post-pubertal (Tanner 4-5)(13; 14). Partial correlation coefficients were calculated with adjustment for BMI and age. To explore the effect of insulin resistance on the relationship between $S_i$ and fasting indices, a variable denoting high/low $S_i$ was tested in regression models (determined as above/below median). An interaction term between indices and the high/low variable was included to investigate potential effect modification. When testing for interaction, adjustment was made for main effects. P-values of <0.05 were considered statistically significant.

As QUICKI and HOMA-IR showed consistently highly similar results, only HOMA-IR results will be reported.

RESULTS

The study included 191 overweight or obese participants (82 males, age 13.9±2.9 years (14.0; 5.5-22.8 years [median; range]), BMI 36.9±6.2 kg/m$^2$ (35.8; 24.2-60.3 kg/m$^2$), BMI-SDS 6.1±1.6 (6.0; 2.7-14.0), DEXA 45.7±5.2% (45.6%; 27.2-58.8%). Tanner stage (I/II/III/IV/V) for males was 37.8/14.6/12.2/14.6/20.7% and for females 8.3/9.2/2.8/16.5/46.8%, respectively. Males were heavier (3.1 kg; p=0.001), taller (2.9 cm; p<0.001), had higher fasting glucose (0.1 mmol/l; p=0.022) and were less adipose (2.6 %; p=0.001). Statistically significant differences in Tanner stage were found (p=0.001). DEXA results showed that 99% were above the 98th percentile in body fat percentage (age and sex adjusted) (18).

The relationships between HOMA-IR, fasting insulin and $S_i$ are presented in Table 1, stratified by sex and pubertal status. The female prepubertal group was too small to provide any reliable results (n=6). In both sexes, the pubertal group had the highest correlation coefficients. When including the high/low $S_i$ variable in regression analysis, in females the relationship appeared to vary with degree of insulin sensitivity; while variations in HOMA-IR explained 33.7% of the variation in $S_i$ for subjects with high $S_i$ (p<0.001), the corresponding number for subjects with low $S_i$ was only 3.2% (p=0.197). Fasting insulin explained 14.1%
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of the variation in \( S_i \) in female subjects with high \( S_i \) (p<0.004), with corresponding number for subjects with low \( S_i \) being 0.3% (p=0.715). In males, no such interactions were detected either graphically (parallel lines) or in regression analysis.

Pearson correlation coefficient of HOMA-IR to fasting insulin was 0.81 (males 0.87, females 0.78, p<0.001 in all instances).

**CONCLUSIONS**

We found sex dependent differences in the explanatory power of fasting indices, with consistently better ability to explain the variation in \( S_i \) among males. In both sexes the explanatory power varied with pubertal status, surprisingly showing highest correlations in the pubertal groups, where insulin sensitivity is known to be low (19). When stratifying for high/low \( S_i \) the relationship was significantly weaker in the more insulin resistant females, in which fasting indices exhibited virtually no explanatory value at all. HOMA-IR yielded little additional explanatory value compared to fasting insulin alone.

The validity of fasting indices in children and adolescents has been investigated with correlations of HOMA-IR and clamp or FSIVGTT ranging from 0.4-0.9 (10; 20-23). Conwell et al found fasting indices to correlate strongly with \( S_i \) of the FSIVGTT-MMOD, concluding that these are valid tools in obese children and adolescents (10). The high correlation seen in the Conwell study of 18 individuals in three repeated tests (r=-0.9 for HOMA-IR and \( S_i \), p<0.001) is not found in our larger study although the correlation in pubertal males is reasonably high. The results in most of our sub-groups are in better agreement with the study by Cutfield et al, in which fasting indices exhibited only weak correlation with the \( S_i \) of the FSIGVT-MMOD (r=-0.4, p<0.001 for HOMA-IR and \( S_i \) (24). Brandou et al, who examined fasting indices in obese and lean children at varying stages of puberty, found no correlation between HOMA-IR or QUICKI and \( S_i \) (12). Also, in the present study for each given value of the fasting indices there was a wide spread in \( S_i \), which warrants careful interpretation.

In summary, we have shown the validity of HOMA-IR and fasting insulin in explaining \( S_i \) as determined by the FSIVGTT in obese children and adolescents to be sex dependent as well as influenced by pubertal stage and in females by level of insulin sensitivity. In pubertal males, HOMA-IR and fasting insulin correlated reasonably well with FSIVGTT-MMOD, whereas in pre- and postpubertal subgroups the correlation was low. In females the strength of the association was generally weaker, especially among the most insulin resistant participants. Thus, in obese pediatric populations, especially those at risk of altered glucose homeostasis, we discourage the use of these measures.

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REFERENCES

TABLE 1. Partial correlation coefficients of ln S_i to ln HOMA-IR and ln fasting insulin respectively, adjusted for age and BMI.

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