Author's response to reviews

Title: Insulin resistance in adolescents with Down syndrome: a cross-sectional study Cristina T da Fonseca (1S), Daniela M Amaral (1*), Marcia G Ribeiro (2*), Izabel CR Beserra (3*), Marilia M Guimaraes (3,4*) 1. Post-Graduate Program of Endocrinology, Medicine School, Hospital Universitario Clementino Fraga Filho (HUCFF), Federal University of Rio de Janeiro (UFRJ) - Av. Brigadeiro Trompowski, s/n, Ilha do Fundao, Rio de Janeiro, Brazil 2. Genetics Department, Instituto de Puericultura e Pediatria Martagao Gesteira (IPPMG), UFRJ - Av. Brigadeiro Trompowski, s/n, Ilha do Fundao, Rio de Janeiro, Brazil 3. Pediatrics Department, IPPMG, UFRJ - Av. Brigadeiro Trompowski, s/n, Ilha do Fundao, Rio de Janeiro, Brazil 4. Endocrinology Department - HUCFF, UFRJ - Av. Brigadeiro Trompowski, s/n, Ilha do Fundao, Rio de Janeiro, Brazil * These authors contributed equally to this work; S Corresponding author

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Author’s response to reviews: see over
Covering Letter – comments on the revision of the manuscript

Title: INSULIN RESISTANCE IN ADOLESCENTS WITH DOWN SYNDROME: A CROSS-SECTIONAL STUDY
Cristina T da Fonseca (1S), Daniela M Amaral (1*), Marcia G Ribeiro (2*), Izabel CR Beserra (3*), Marilia M Guimaraes (3,4*)
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Version: 1 Date: 7 April 2005
Reviewer: Phyllis Speiser

Answers to the reviewer's report:

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Methods, p5, p6: The normal range of fasting blood glucose should not exceed 100 mg/dl according to the American Diabetes Association. Please correct this in the text.
   Information corrected now (p.7). Sorry for the mistake.

2. The authors should acknowledge that none of their study subjects had insulin resistance. Obese children with normal glucose tolerance measured by either clamp or OGTT have HOMA values of ~7.0 +/- 0.5, whereas those with impaired glucose tolerance had levels 10.4-11.7 +/- 1 (JCEM 89:1096, 2004). The highest HOMA reported in the present manuscript os 3.8. Since there was no longitudinal follow-up, one has no idea of the clinical significance of higher versus lower normal HOMA values in this study population.

   We agree that if we consider such article from JCEM to be compared to our results, none of our patients had insulin resistance, and now, we mentioned this fact in the revised manuscript as you have suggested. Nevertheless, we also mentioned that such study (JCEM) involved exclusively moderate to severe obese children and adolescents whose body mass index was much higher than the mean BMI of our just 2 obese patients, and this fact may have contributed to the highest HOMA values showed by them. As there is no consensus for ideal HOMA values for children and adolescents we chose to use a Brazilian study that involved only normal-weighed pediatric patients as a reference to be compared to our results, especially because most of our patients had normal weight and not obesity, and as Brazilian people, ethnically more similar to the patients of the mentioned study. We also added a new reference (Allard et al) that showed lower HOMA values for a representative sample of young patients (it involved 2244 children and adolescents). Moreover, we can not forget that we are comparing studies that involved children and adolescents without Down syndrome to patients with this syndrome; we did not find previous studies about insulin resistance indexes in patients with this genetic syndrome.

   We included your suggestion for the need of longitudinal follow-up studies in the section “conclusions”.

   Please, read the text that follows; it is part of the main manuscript just revised (p. 10, p. 11), or if you prefer, just read the main revised manuscript that was submitted again:
“In the present study, the highest values of HOMA were found in the obese and overweight patients, but we cannot affirm if such patients really have insulin resistance, as there is no consensus for ideal HOMA values for children and adolescents and much less for patients with DS. No references about insulin resistance indexes in DS were found in literature. Nevertheless, comparing our results to those showed in some studies involving youth without DS, such as the study of Yeckel et al (25), we could say that none of our patients had IR because such authors found mean values of HOMA of about 7.00 for normal glucose tolerant children and adolescents without DS, based on clamp and OGTT studies, while our highest HOMA value was 3.8. Nevertheless, such study involved exclusively moderate to severe obese patients whose BMI was much higher than that of our obese patients (38.1 x 27.8 respectively), fact that may have contributed to the highest values of HOMA presented by them, confirming the direct relation between obesity and HOMA values, which is in accordance with our results. Moreover, our sample involved just 2 obese patients; most of them had normal weight. On the other hand, Allard et al showed lower mean values of HOMA, ranging from 0.83 to 1.62 in a representative sample of 2244 children and adolescents without DS (26). A study performed in Rio de Janeiro, Brazil, with normal-weighted healthy students, also without DS, suggested a mean value of HOMA of 2.36 for girls and 2.66 for boys, using the same method of insulin dosage as the one used in our study (27). Based on such reference values of Brazilian children and adolescents, we found 4 (26.7%) patients (3 females and 1 male) in our study with insulin resistance when assessed through the HOMA method. Among them, 2 had obesity, 1 overweight and the other, normal weight, that is, 100% (2/2) of the obese, 25% (1/4) of the overweight and 11.1% (1/9) of the normal weight groups had insulin resistance. Unfortunately, our small sample did not permit us to confirm these data with statistical analysis as referred in previous reports that correlated obesity and insulin resistance, in obese patients, without DS (28, 29).”

3. The authors should further acknowledge that HOMA is not as sensitive or as reproducible a measure of insulin sensitivity as clamp studies.

We recognize that the clamp study is the gold-standard method, but we describe the need to find alternative methods that may be more practical and less invasive than the clamp. We already know that HOMA is not as sensitive and reproducible as the clamp, but now, we wrote that on the manuscript. On the other hand, we also mentioned some references that have validated HOMA, showing good correlation between HOMA and clamp studies, not only in adults, but also in pediatric and adolescent patients. Moreover, it would be very difficult to perform an OGTT in patients with Down syndrome because of their behaviour; they would probably need sedative medication and it would be very invasive. Please, read the text that follows; it is part of the main manuscript just revised (p. 9), or if you prefer, just read the main revised manuscript that was submitted again:

“The hyperinsulinemic euglycemic clamp has been regarded as the standard method to evaluate insulin resistance. Considering that it is a difficult and relatively invasive technique that requires a specialized team and, in general, it is not available to the clinical practice (14), researchers have been studying other more practical methods that would be
able to measure insulin resistance. One of these studied methods is the HOMA method, a mathematic model based on measurement of fasting plasma glucose and insulin levels, which is especially useful for DS patients in whom the use of other methods based on the results of an oral glucose tolerance test (OGTT), for example, would be extremely difficult to perform. Although it is not as sensitive or reproducible a measure of IR as the clamp technique, it has been validated both in adults (10, 14) and in children and adolescents without DS (15, 16) and, for this reason, it has been extensively used, not only in epidemiological studies, but also in clinical practice (10)’”.

We hope that we also have corrected such minor mistakes. If not, we would be very grateful for your suggestions.
We are waiting forward for your new revision and thank you for this one.
Best wishes,
Cristina Fonseca