

**Summary of the 4th international congress on the insulin resistance syndrome
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Once again this international conference on the insulin resistance syndrome (IRS) featured a Pediatrics symposium in the initial meeting day. While three days of detailed discussion of all aspects of the insulin resistance syndrome in adults followed, this summary focuses solely on the full day pediatric session that was filled with state of the art information.

After opening comments from Yehuda Handelsman, co chair of the Congress, Alan Sinaiko and Sonia Caprio, co chairs of this days symposium welcomed the attendees and set out the plan of the presentations.

Stephen Cook led off by addressing the question, “is there a metabolic syndrome in children and adolescents?”. He answered this question with a resounding yes. (We shall here refer to the IRS rather than the metabolic syndrome throughout this discussion.)

After demonstrating the now well know tripling of the prevalence of obesity in childhood and adolescence in the US over the last few decades, he showed that the change in central adiposity as reflected by the waist circumference between 1998-1994 with NHANES-III to 1999-2000 increased by 1.6 –4.9 cm for males and 2.6 – 5.2 cm for females in the US, with other countries showing the same or greater increase. The prevalence of children

with WC \geq 90th %tile from NHANES III to 1999-2000 increased by 65.4% for boys and increased 69.4% for girls.

In the US, the percentage of adults with the metabolic syndrome increases with age; in adults there is an overall prevalence of 23.7% across all ages and genders. In adolescence, there is a 4.2% overall prevalence of the metabolic syndrome; of those teenagers <1 % had normal weight, of those with BMI values between the 85% and <_95%, 6.8% while in those with BMI >95th% for age and gender, 27.9% had the metabolic syndrome. Boys had a greater than two fold greater prevalence than girls and Mexican American girls a greater prevalence than Caucasian girls while Mexican American and Caucasian boys both had a prevalence of approximately twice that of girls, about 7%, but African American children were far less likely to have the metabolic syndrome than the other ethnic groups. The criteria for the metabolic syndrome originated in adults and had to be adjusted to age appropriate values.

Using these guidelines, the prevalence of the metabolic syndrome in the population of 5-11 year old children is 4.3% while when considering overweight children, the prevalence rises to 20.2%. Data from Canada and Finland show that clustering of the features of the syndrome in children persist for 6-12 years of follow-up. The longitudinal Bogalusa heart study demonstrated that the risk ratio for clustering of 4 variables was 9.8 in white and 7.4 for black individuals over several decades. On the positive side, low risk tracks as well as high risk; the Bogalusa study demonstrated that the children in the bottom quartiles of risk factors retained a low risk for metabolic syndrome into adulthood. The

metabolic syndrome also crosses generations as in Minnesota and Bogalusa, children of parents with the IRS had higher BMI, waist circumference, serum insulin levels and were more insulin resistant, demonstrating genetic factors found in the syndrome.

Unfortunately, children who survive ALL in Finland later demonstrated features of the metabolic syndrome; after 13 years, 62% had 1 CVD risk factor and 30% had 2 CVD risk factors, while 31% of the survivors were obese. These trends are well described in the US as well.

In the US NHANES and in Canada, children with the metabolic syndrome had greater mean values of serum CRP than controls; e.g. higher mean CRP (3.8 vs 1.4 mg/L).

Focusing upon teenagers with metabolic syndrome, 38.4% had CRP > 3.0 mg/L compared to the 10.3% of teenagers without the metabolic syndrome had CRP > 3.0 mg/L. Further, those with top quartile CRP values had an odds ratio of 2.5 for a cluster of adverse risk factors (high blood pressure, triglyceride/hDL cholesterol and small dense LDL particles). Of those children with BMI >85th, 7% have the small dense LDL phenotype and of those with the metabolic syndrome, 10% have the phenotype, in contrast to those who were thinner or lacked the metabolic syndrome. Further, smoke exposure increases the risk for the metabolic syndrome in children and adolescents.

There are several definitions of the metabolic syndrome in adults and prevalence changes with the definition criteria, 4.2% of children and adolescents met the NCEP criteria while 8.4% met the WHO criteria. Of girls in the national girls health study, 0.2 % of girls 9-10

yrs had ≥ 3 criteria for the IRS and after 10 years, 3.5% of Black and 2.3 % of White girls developed IRS by adult criteria. Higher baseline triglycerides (OR = 1.12) and waist circumference (OR = 1.16) were predictors of IRS at 10 years but BMI, HOMA, SBP/DBP and glucose were *not* predictive. This brings up the important concept that the IRS can occur without obesity; further, serum insulin values or simple equations incorporating baseline insulin values, such as HOMA, are not predictive. Further, insulin is not included in any definition of the IRS by any criteria. Using one definition of the IRS, the US and Iran have the greatest prevalence with Brazilian teenagers following and Korean teenagers bringing up a more distant third of several countries studied. Just as there is a variation in prevalence of the metabolic syndrome in the adult depending upon the definition, in children, the three published definitions suffer from a similar dissonance with an overall prevalence from 9.4-2.0% in the entire population.

Dr Cook summarized his presentation with these points: 1. Clustering of the IRS around obesity, exists; 2. Obesity and clustered cardiovascular risk factors track from Childhood to Adulthood, and cluster within families 3. Lifestyle factors are important in developing the metabolic syndrome as, factors listed in order of importance in the development of the metabolic syndrome: Sedentary activity is more significant than the next factors including lack of exercise, excess caloric intake and smoking 4. Cut-off points exist in the definition of the metabolic syndrome, although all factors are truly continuous variables 5. Above all, prevention is key in addressing this syndrome. Achieving appropriate gestation weight gain, avoiding tobacco, promoting physical activity and dietary

moderation in homes, schools, childcare settings and worksites could considerably cut down on the prevalence of the metabolic syndrome in all age groups.

Dr. Sherin Devasakar next addressed the fetal origin of adult disease with respect to the insulin resistance syndrome. She started by speaking of the outcome of babies born to obese mothers noting the prevalence of stillborn, of macrosomia (>90%) and of IUGR (<10%). These add to the customary outcomes of birth injuries during delivery, respiratory distress, hypoglycemia, hypocalcemia, hyperbilirubinemia, congenital defects as well as neurological impairment. The long term outcome including hyperinsulinism and hyperleptinemia significant factors.

She pointed out how childhood obesity later leads to gestational diabetes, leading later to adult onset obesity and eventual type 2 diabetes demonstrating the transgenerational propagation of the syndrome. The “secondary hit” of increased energy intake along with inactivity in addition to these factors all lead to the epidemic of obesity and type 2 diabetes along with the complications of hypertension, cardiovascular disease, stroke and dyslipidemia. She reviewed the data demonstrating that breast feeding leads to more appropriate weight gain in infants even years after breast feeding ceases. After a review of the hypothalamic factors associated with appetite and satiety, she described her experimental design for in vivo animal studies, which aim to explain human epidemiological data. She reviewed the several long-term studies of outcome of abnormalities of gestational nutrition and abnormal birth weight such as historical

episodes of famine. All studies showed an increase of insulin resistance and type 2 diabetes later in life being inversely related to birth weight. This, evidence describes the “U” shaped curve relating birth weight to later insulin resistance: babies with either low or high birth weight have a higher prevalence of insulin resistance compared to those of normal birth weight. She presented her experimental data from in vivo animal studies showing that catch up growth after IUGR leads to visceral adiposity, hyperinsulinism and hyperleptinemia, type 2 diabetes and transgenerational propagation of these problem. She emphasized the importance of self regulated caloric intake, prevention strategies and the message that the effects of dysregulation of fetal growth may appear two generations later in an epigenetic process.

Dr. Dana Dabalea next explored the ethnic differences in the insulin resistance syndrome in youth. She pointed out the higher fasting insulin levels in African American and Hispanic American and American Indian children compared to Non Hispanic white children by the early teenage years. In response to a glucose load, African American children secrete greater than expected insulin, as do Mexican American children, due to reduced hepatic insulin extraction. These patterns appear due to genetic factors. While visceral fat is more related to insulin resistance in Non-Hispanic White children, African American children have a weaker relationship of visceral fat to insulin resistance but increased relationship of subcutaneous fat to insulin resistance than in Non Hispanic Whites. In summary she suggested that African American, Mexican American and American Indian children were more likely to develop type 2 diabetes due to obesity

independent IR, while African American children may be less likely to develop obesity related clustering of IRS components than the other ethnic groups.

Due to the multiple definitions of the IRS in youth and lack of sufficient data in certain ethnic groups, it is difficult to determine what should be considered the true prevalence of the IRS. It is apparent that the IRS is lower in African American than non Hispanic White children and Mexican American children but the prevalence is increasing in all groups. However there are specific trends of particular factors; there is increased abdominal obesity in African American only, increased dyslipidemia (LDL-c) in African American and Hispanic Americans but increased hypertension in all groups. Type 2 diabetes mellitus is rare in children <10 years, is more frequent in minority ethnic groups compared to Non-Hispanic White adolescents. The highest rates are found in American Indians and African American youth. (most of this data comes from SEARCH for diabetes in youth study). In addition SEARCH demonstrated the components of the IRS are far more common in youth with type 2 diabetes compared to type 1 diabetes but the IRS is more common in Hispanic and American Indian youth with diabetes regardless of type of diabetes. The prevalence of micro-albuminuria is more common in youth with type 2 diabetes and, in sequence, in African American, Hispanic, Asian and Pacific Islanders and American Indians compared to non Hispanic White Youth. Her conclusion was that there are important ethnic differences in IRS. Compensatory insulin secretion, and obesity related clusters of IRS in youth might account for different chronic disease patterns later in life in different ethnic groups. Future challenges are to study different

ethnic groups in greater detail, to use reliable indices of insulin resistance/secretion rather than the controversial measures utilizing fasting insulin values.

Dr. Andra Dunaif next spoke of polycystic ovarian syndrome (PCOS). There is a 7% prevalence of anovulatory PCOS making it the leading cause hormone-related infertility. Affected women progress from insulin resistance to Type 2 Diabetes Mellitus with a 7 fold increased risk over a woman without PCOS. Of adolescents and young adult women with PCOS, only 60% have normal GTT, 40 % have IGT and 10 % have type 2 DM. About 80-90% of oligomenorrheic women have PCOS. The diagnosis is based upon 2 of 3 of the new Rotterdam criteria: hyperandrogenism, chronic anovulation, exclusion of other disorders or the demonstration of polycystic ovaries (all but the last are part of the criteria developed by a consensus conference at the NIH in 1990). The heaviest individuals with PCOS have more insulin resistance and type 2 diabetes but even thin individuals with PCOS can have type 2 DM. There is an increased prevalence of the metabolic syndrome using age appropriate criteria in PCOS with a greater prevalence in those with increased BMI: of those with BMI>30, 45% of the young adult population surveyed by NHANES III had the IRS while 68% of women with PCOS have the metabolic syndrome; with respect to adolescents, the comparable numbers are 32% and 63%, respectively. Teenagers with PCOS have increased prevalence of all features of the IRS compared to peers. Further the IRS starts at a lower range of BMI in PCOS than in the general population. Insulin sensitizing agents successfully decrease androgen levels and increase ovulation in PCOS. Testosterone and free testosterone are increased in PCOS but blocking testosterone with agents such as flutamide, added to insulin

sensitizing agents, decreases the metabolically active visceral fat, decreases the BMI but has less effect on subcutaneous fat. Sisters of adolescents or adults with PCOS also have increased androgen values and increased risk of anovulation and, as well, increased risk of PCOS themselves, as well as risk of IRS. Likewise brothers of women with PCOS similarly have decreased insulin sensitivity and increased adrenal androgen production. Dr. Dunaif is studying genetic linkages to PCOS and finds the D19S884 of the Intron 55 of the Fibrillin 3 Gene of significance.

The prenatally virilized female rhesus monkey serves as a good model for PCOS in human beings. She posed the question as to the etiology of PCOS, is it genetic or is it environmental, or both? Lastly she humorously suggested that this disease of women that presents so many features of the metabolic syndrome might be called "Syndrome XX"!

Dr. Jeffery Schwimmer spoke of factors in the various conditions associated with fatty liver. NAFLD is the abbreviation of nonalcoholic fatty liver disease while NASH represents nonalcoholic steatohepatitis. Steatosis can progress to NASH, to fibrosis and in some to cirrhosis. The prevalence of fatty liver increases with age, with increasing BMI. Detection of these conditions becomes increasingly more accurate with measurement of liver enzymes, ultrasound and, the gold standard, to liver biopsy. Fatty liver is most prevalent in Hispanic American children, Asian American, Non Hispanic White and finally a distant fourth African American children. While there is no proven treatment for these hepatic conditions, Dr. Schwimmer described the ongoing trial of 1000 mg of metformin daily which initially shows a decrease in liver enzymes and liver

fat with treatment. Larger and longer term studies must be completed before a recommendation for therapy can be made. He finished by pointing out that fatty liver is not just a benign variant as has been stated in the past.

Dr. Sonia Caprio, co chair of the symposium, spoke next on spectrum of insulin resistance in childhood obesity: from benign to type 2 diabetes. The prevalence of type 2 diabetes in the world is predicted to increase 46% from 1995 to 2010. Presently there are 97 million known cases of T2DM, 97 million undiagnosed cases and 314 million with IGT. She and her colleagues at Yale have shown the presence of ectopic fat as a feature of insulin resistance and is associated with increased hepatic glucose production and decreased insulin mediated glucose disposal in muscle. The group uses ^1H NMR spectroscopy of the Soleus muscle (intra myocellular lipid (IML)) or liver. She uses the method to examine whether altered partitioning of myocellular and abdominal fat relates to changes in insulin sensitivity in obese adolescents with IGT using the hyperinsulinemic euglycemic clamp to assess insulin sensitivity, the hyperglycemic clamp to assess insulin secretion and Dexa to evaluate body composition. She found an inverse linear relationship between IML and insulin sensitivity, an increase in visceral fat as well as an increased visceral to subcutaneous fat ratio.

Dr Alan Sinaiko, the originator of the pediatric section of the World conference, ended the day's discussion with a presentation on his decades of longitudinal studies in the

Minneapolis study. He pointed out that the normal physiological decrease in insulin sensitivity with increasing pubertal status was a prelude to the changes brought about by obesity and genetic tendencies toward insulin resistance even in thinner adolescence. Blood Pressure and hDL cholesterol increase with age during normal pubertal development although triglycerides decrease in girls compared with boys. He showed the tracking of BMI between 10 to 20 years of age as well as systolic blood pressure, hDL and total cholesterol, increase in fasting insulin and “m”, a reflection of insulin resistance. All of the adverse factors of insulin resistance are increased in those with increased BMI compared to thin individuals, including systolic blood pressure, triglycerides, hDL and fasting insulin. Looking from the other point of view, of those who are insulin sensitive compared to insulin resistance teenagers, adverse tendencies are increased in those with higher BMI. Further dividing the groups into high and low BMI and high and low insulin sensitivity, the most adverse predictors are the highest BMI and lowest insulin sensitivity and the best situation occurs with low BMI and highest insulin sensitivity. A stepwise trend is found from high BMI, low insulin sensitivity to low BMI, high insulin sensitivity. Risk factors progress in the same direction. Lastly, tracking of all risk factors between 13 and 19 years shows that lean body mass is associated with a decrease in the risk factors while increase in BMI predicts an increase in risk factors. Visceral fat was higher in insulin resistant thin subjects than thin insulin sensitive subjects. Thin insulin resistant children experience increased risk factors with the passage of time while thin insulin sensitive children remained stable. These data showed that increase in BMI led to significant decreased insulin sensitivity and increased risk factors over the teenage years but imply that good control of weight can improve risk factor, showing that the problems

of the IRS are not inevitable. There is a genetic tendency toward insulin resistance without regard to weight changes.

These remarkable presentations shed considerable light on the IRS and suggested factors that bear watching in the children we treat. Genetic factors provide a substrate that increased weight plays upon to further the development of the IRS. It is also clear that an individual does not have to have an increased BMI to manifest the IRS. The 5th Annual World Congress of the Insulin Resistance Syndrome will be held October 11-13, 2007, Boston Marriott Newton. Once again there will be a Pre-Congress Symposia on Insulin Resistance in Pediatrics Wednesday, October 10, 2007 (as well as Insulin Resistance & the Liver).