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.

WELCOME: After opening comments from overall Congress co-chair Yehuda Handelsman, Alan Sinaiko and Sonia Caprio, co-chairs of the Pediatric symposium, welcomed the attendees and set out the plan of the presentations.

METABOLIC SYNDROME IN CHILDREN AND ADOLESCENTS: 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 refer to the "metabolic syndrome" as "IRS" throughout this discussion for consistency.) After demonstrating the now well known 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 $\geq 90^{th}$ percentile 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 IRS 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 IRS; but of these affected teenagers, <1 % had normal weight. Considering those with BMI values between the 85% and <95%, 6.8% had the IRS while those with BMI >95^{th} percentile for age and gender, 27.9% had the IRS. 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%. African American children were far less likely to have the IRS than the other ethnic groups. Of course, the criteria for the IRS originated in adults and had to be adjusted to age appropriate values to develop these prevalences.

Using these guidelines, the prevalence of the IRS in the population of 5-11 year old children is 4.3% but when considering children with BMI >95^{th} percentile, 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 IRS into adulthood. The IRS also crosses generations as found in Minnesota and Bogalusa, where 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 IRS; 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 Canadian surveys, children with the IRS 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 the IRS, 38.4% had CRP > 3.0 mg/L compared to the 10.3% of teenagers without the IRS who 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 percentile, 7% have the small dense LDL phenotype and of those with the IRS, 10% have the phenotype, in contrast to those who were thinner or lacked the IRS. Further, smoke exposure increases the risk for the IRS in children and adolescents.

There are several definitions of the IRS 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 $\geq$ 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, fasting insulin is not included in the definition of the IRS by most 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 IRS in the adult depending upon the definition, in children, the three published definitions suffer from a similar dissonance with an overall prevalence from 2.0 - 9.4% in the entire population.

Dr. Cook summarized his presentation with these points: 1. Clustering of the IRS around obesity does exist; 2. Obesity and clustered cardiovascular risk factors track from childhood to adulthood, and cluster within families; 3. Lifestyle factors are important in developing the IRS with factors listed in order of importance in the development of the IRS as: sedentary activity, lack of exercise, excess caloric intake and smoking; 4. Cut-off points exist in the definition of the IRS, although all factors are truly continuous variables; 5. Above all, prevention is key in addressing this syndrome. Achieving appropriate gestational 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 IRS in all age groups.

FETAL ORIGIN OF ADULT DISEASE WITH RESPECT TO THE INSULIN RESISTANCE SYNDROME: Dr. Sherin Devasakar 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 factors add to the customary outcomes of birth injuries during delivery, respiratory distress, hypoglycemia, hypocalcemia, hyperbili, rubinemia, congenital defects as well as neurological impairment. The long term outcomes include hyperinsulinism and hyperleptinemia as 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 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.

ETHNIC DIFFERENCES IN THE INSULIN RESISTANCE SYNDROME IN YOUTH:

Dr. Dana Dabalea explored the ethnic differences in the insulin resistance syndrome in youth. She pointed out the higher fasting insulin levels in African American, 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 and Mexican American children also secrete greater than expected insulin, 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 an 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 of 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; increased abdominal obesity in African Americans only; increased dyslipidemia (LDL-c) in African American and Hispanic Americans; and increased hypertension in all groups. While Type 2 diabetes mellitus is rare in children <10 years, it is more frequent in minority ethnic groups compared to Non-Hispanic White adolescents, with the highest rates 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, sequentially, in African American, Hispanic, Asian and Pacific Islander and American Indian youth 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 and to use reliable indices of insulin resistance/secretion rather than the controversial measures utilizing fasting insulin values.

POLYCYSTIC OVARIAN SYNDROME: Dr. Andra Dunaif 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 oligomennorrheic 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 than thin affected women but even thin individuals with PCOS can have type 2 DM. There is an increased prevalence of the IRS using age appropriate criteria in PCOS with a greater prevalence in those having 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 IRS. 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 and 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 along with 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. Providers of families who might want to join in the genetics studies should contact PCOS Studies Northwestern University 1-800-847-6060 pcos@northwestern.edu; http://www.endocrine.northwestern.edu/pcos/index.asp

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, is it environmental, or both? Lastly she humorously suggested that this disease of women that presents so many features of the IRS might be called "Syndrome XX"!

NON ALCOHOLIC FATTY LIVER DISEASE (NAFLD): 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 and with increasing BMI. Detection of these conditions becomes increasingly more accurate with measurement of liver enzymes, ultrasound and the gold standard measure, liver biopsy. Fatty liver is most prevalent in Hispanic American, Asian American and Non-Hispanic White children and finally, in a distant fourth, African American children. His study of unselected liver specimen in San Diego County showed an approximately 10% prevalence of NAFLD in children autopsied.

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.

SPECTRUM OF INSULIN RESISTANCE IN CHILDHOOD OBESITY FROM BENIGN TO TYPE 2 DIABETES: Dr. Sonia Caprio spoke on spectrum of insulin resistance in childhood obesity: from subtle 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 Yale colleagues 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 ^{1}H NMR spectroscopy of the Soleus muscle to determine intramyocellular lipid (IML) and lipid in the 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, and a direct relationship to an increase in visceral fat as well as an increased visceral to subcutaneous fat ratio. She emphasized how rapidly a subset of adolescents with IGT can progress to type 2 Diabetes Mellitus in contrast to the usually slower rate in adults.

LONGITUDINAL STUDIES OF HYPERTENSION IN MINNEAPOLIS: 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 that there are genetic tendencies toward insulin resistance even in thin~~ner~~ 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 teenagers 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 reminded 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. However, there is a genetic tendency toward insulin resistance without regard to weight changes.

CONCLUDING REMARKS: 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.

NEXT CONFERENCE DATES: 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).