Low Birth Weight and the Risk of Type II Diabetes

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**Background:** In 1967 Barker first established the concept that a harmful intrauterine environment can have lifelong effects and contribute to adult onset disease. This Barker hypothesis, as it is now referred to, has since been cited in numerous disease associations including the well established correlation between low birth weight and adult onset type 2 diabetes. Studies have shown that full term, low birth weight (< 2.5 kg) individuals have increased prevalence of type 2 diabetes in adulthood. While this association has been clearly established in numerous human cohort studies and experimental animal studies, the underlying etiology remains unknown. As has been previously established, type 2 diabetes is a combination of both insulin resistance and deficiency of insulin secretion. Some researchers have focused on insulin secretion as the possible link between low birth weight and type 2 diabetes but have not been able to prove a causal relationship. Genome wide research has identified novel type 2 diabetes susceptibility variants and in a theory referred to as the fetal insulin hypothesis researchers have proposed that low birth weight and type 2 diabetes may be phenotypes of the same genotype. While these recent studies on the fetal insulin hypothesis may have theoretical implications for future research, most of the current literature has focused on the link between insulin resistance and low birth weight. Numerous studies have shown that low birth weight predisposes adults to insulin resistance and eventual adult onset type 2 diabetes. While these associations have been well established the underlying etiology remains to be fully elucidated. Current research has focused on three potential hypotheses’ including acquired skeletal/hepatic insulin resistance, altered adipose tissue composition and fetal stress induced disruption of the hypothalamic-pituitary-adrenal (HPA) axis.

**Specific Aim:** In order to review the current status of evidence on this topic, we compiled a comprehensive literature review of studies focusing on these three main hypotheses.

**Methods:** We conducted a MEDLINE search of articles from 1993 to present using keywords: low birth weight, type 2 diabetes, insulin resistance and insulin clamp studies. We used limits of English and human subjects. We completed a selective cross reference of articles cited and focused on articles that address one of the 3 above outline hypotheses. These methods produced 18 current articles across diverse study populations. We reviewed these in-depth in an effort to compile a consensus of the current evidence.

**Results:** Much of the current literature on this topic has centered around insulin clamp techniques and have been able to show various alterations in glucose tolerance as well as adipose tissue composition in subjects previously identified as low birth weight. However, these have only been able to show risk association and not causative pathophysiology. Animal studies clearly indicate HPA axis abnormalities associated with fetal stress and low birth weight. These in turn have been directly linked with insulin resistance. However at this time human studies have only been able to show a theoretical link to insulin resistance via the metabolic syndrome.

**Conclusion:** Our review of the current literature found no cohesive body of evidence as studies have focused on a multitude of various etiologies. We believe that the strongest evidence at this time lies in the association with HPA axis dysregulation established in the animal literature and believe that further testing of this hypothesis in human study populations remains necessary.