Annals of Diabetes, Metabolic Disorders & Control

SCIENTIFIC LITERATURE

CASE REPORT

Childhood Obesity, Diabetes Mellitus and Cardiovascular Consequences

***Larry H. Bernstein**

Department of Diabetes, England

ARTICLE INFO

Received Date: October 28, 2017

Accepted Date: November 03, 2017

Published Date: November 07, 2017

Citation this article: Bernstein LH. Childhood Obesity, Diabetes Mellitus and Cardiovascular Consequences. Ann Diabetes Metab Disord Contr. 2017; 1(1):114.

Corresponding Author :

Larry H. Bernstein, Department of Diabetes, 54 Firethorne Lane, Northampton, MA 01060, England,

Email: larry.bernstein@gmail.com

EDITORIAL

Diabetes Mellitus (DM) is an epidemic of worldwide proportion, and especially in developed countries. DM has many adverse consequences from related diseases that include hypertension, macrovascular and microvascular disease, pancreatic islet cell loss and hyperglycemia, renal impairment leading to end stage renal disease. While Type 1 diabetes has long been known as a disease of childhood with an autoimmune mechanism, Type 2 diabetes has been largely considered an adult acquired disease with a progressive loss of pancreatic islet cells associated with islet cell deposition of amyloid fibrils. The metabolic consequencesaffects the heart, vasculature, liver and kidneys.

In recent decades the incidence of T2DM has increased in childhood, and as T2DM is associated with obesity, so also is the rising incidence of childhood DM. T2DM is now the predominant DM in children, primarily over age 10 years. This has led to a shortened population survival due to its associated complications, including stroke, is a situation that exists beside a current opiod crisis. Owing to the increasing rates of childhood obesity, the life expectancy decline in the US the American Heart Association (AHA) has classified obesity as a 'major, modifiable risk factor' for Coronary Heart Disease (CHD). This elevated cardiovascular morbidity and mortality includes stroke, congestive heart failure, myocardial infarction and cardiovascular death, and affects individuals with a visceral deposition of adipose tissue [1].The obesity may develop in late childhood, but the associated conditions are accelerated.

Insulin resistance plays an important role in the development of T2DM [2], as demonstrated by cross-sectional and longitudinal studies demonstrating that insulin resistance occurs 10–20 years before the onset of the disease and that it is the best predictor of whether or not an individual will later become diabetic. The alterations in glucose metabolism results from the gradual fall in b-cell function occurring within a background of insulin resistance, the b-cell function loss being related to the beta amyloid deposition. Insulin resistance in the muscle and liver concordant with islet b-cell failure [3].

The association between obesity and dyslipidemia observed in adults has been documented also in children and adolescents. Obese adolescents were reported to have an abnormal "atherogenic" lipid profile consisting of elevated LDL cholesterol and triglycerides and low HDL cholesterol in the Lipid Research Clinics Population Studies Data Book. Adolescents with type 2 diabetes mellitus are usually obese, and they have a mean body mass index ranging from 26 to 38 kg/m2 [4]. As elevated blood pressure is associated with insulin resistance, there is increases renal sodium retention with increased water clearance, and also increased sympathetic nervous system activity, stimulation of vascular smooth muscle growth, and essential hypertension. In a study of 122 adolescents, obese individuals were significantly more insulin resistant and had an abnormal lipid profile when compared with lean subjects, and the insulin resistance was significantly related to an abnormal lipid profile and correlated with the degree of adiposity.

Obesity has become a major health problem in American Indians in the recent generations and is likely to be associated with the availability of high-fat foods and the rapid change from active to sedentary lifestyles [5]. A recent study of 115 children undergoing evaluation for hypertension found an overall prevalence of LVH of 38%.This shows young individuals develop LVH early in the course of hypertension. Those with LVH had greater BMI than those without LVH [6]. The Bogalusa Heart Study reported that resting heart rate was positively correlated with blood pressure and subcapsular skinfold thickness in children, and obesity was correlated with a hyperdynamic cardiovascular state. Similarly, a school-based screening for obesity and hypertension found that obese hypertensive adolescents had the highest resting heart rate and nonobese normotensive adolescents had the lowest heart rate. Irrespective of race, gender, or age, the risk of elevated blood pressure was significantly higher for children in the upper compared with the lower decile of BMI, with an odds ratio of systolic hypertension ranging from 2.5 to 3.7 [6].

In a study of adult coronary heart disease risk factors, 30% of obese adults reported that their obesity began in childhood, and pediatric obesity rates have tripled in the United States in just 30 years [7]. 40% of obese children have evidence of steatohepatitis, now the leading cause of cryptogenic

cirrhosis. In addition, National Health and Nutrition Examination Survey (NHANES) data shows that children of all ages are at risk from obesity, but the greatest burden falls on those from minority groups.43% of boys and 40% of girls among Hispanic adolescents are overweight, and further, the obesity rates for Mexican-American adolescents are 46% for boys and 42% for girls. In addition, the rates for non-Hispanic black Americans are 33% for adolescent boys and 46% for girls [7]. Children born in the year 2000 in the United States have a 33% chance of developing diabetes, and the rate increases for people of color and is as high as 50% among Hispanic children.

The ADA recommendations endorse screening children who are overweight (BMI > 85th percentile for age and gender), those who have a body weight greater than 120% of the ideal for height, and anyone who meets at least 2 high risk criteria [8]. AUK Prospective Diabetes Study showed that each 10 mmHg decrease in mean systolic blood pressure was associated with 12% reduction in the risk for any complication related to diabetes [9]. Finally, are port of the (NHBPEP) Working Group on Children and Adolescents [10] evaluates the evidence of early target-organ damage in children and adolescents with hypertension; provides the rationale for early identification and treatment; and provides revised recommendations, based on recent studies, for the use of antihypertensive drug therapy. Abdominal obesity, T2DM and hypertension are related as follows: abdominal obesity is related to the high prevalence of hypertension and type 2 diabetes regardless of ethnicity, while insulin resistance is a major mechanism linking the onset and development of hypertension and type 2 diabetes, and finally, weight loss with diet and exercise is an important aspect in treating hypertension in type 2 diabetes and aids in increasing the efficacy of antihypertensive medications [10]. Finally, two major studies deal with the pathophysiology of diabetes in this population [11]: SEARCH for Diabetes in Youth (SEARCH) and Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) [12].

How does the cardiomyopathy associated with obesity develop? It has been proposed that an important abnormality in hypertrophic cardiomyopathy is reduced contractile stress (the force per unit area).The contractile force is that generated by myocardial tissue. The reduced contractile stress is secondary to abnormalities in the cardiomyocyte, whichin turn, leads to a progressive deterioration in contractile stress. The increased end-diastolic wall thickness augments the thickening and maintenance of the ejection fraction [13]. It has been proposed that Left Ventricular (LV) remodeling occurs in hypertension and cardiomyopathy, and as a result we conjecture that it results in elevated high sensitivity troponin T (or I) hs-TnT levels [14,15]. The authors report that hs-TnT level gradually increased in hypertensive subjects with LV normal geometry, concentric remodeling, concentric hypertrophy and eccentric hypertrophy. What has been described as cardiac remodeling is molecular, cellular and interstitial changes manifested clinically as changes in size, shape and function of the heart. The remodeling results from cardiac load or injury and it is influenced by hemodynamic load, neurohormonal activation and other undetermined factors [15].

Is there still more to consider? Cells are able to maintain proteostasis and to limit the accumulation of damaged proteins by using different degradation, repair and refolding systems. Any impairment in these systems leads to the increased accumulation of damaged proteins which results in a dysregulation of cell behavior. This has to be considered in both diabetes mellitus and cardiomyopathy [16]. The increased amounts of damaged proteins produced during diabetes mellitus may be explained either by the increased intensity of nonenzymatic modifications, or as a consequence of a progressive loss of the ability of cells to degrade or repair altered proteins. A large proportion of intracellular proteins (about 80%) are removed by the ubiquitin–proteasome system, which is responsible for the degradation of short-lived proteins or misfolded newly synthesized proteins as well as of damaged proteins. A decline in proteasome activity would have a great impact on cell homeostasis [17]. Diabetes mellitus promotes the accumulation of damaged proteins and limits their degradation by inhibiting autophagosome formation, and by lowering the efficiency of lysosomal enzymes. In addition, there is decreased expression or impaired activity of molecular chaperones, also called Heat Shock Proteins (HSPs), in mediating correct protein folding and prevent protein aggregation associated with diabetes complications. In addition, insulin signaling regulates protein synthesis and degradation as well as posttranslational modifications. Insulin plays a crucial role on amino acid flux in skeletal muscle and splanchnic tissues, has a role in regulating protein quality control, and has a role in turnover of mitochondrial protein pools [18]. Theevidence indicates that insulin and insulin-like growth factor 1 receptors are important for the mechanistic control of proteostasis. The catabolic state of insulin deficiency causes mitochondrial function impairment, and this is associated with production of reactive oxygen species. The result is oxidative damage of proteins and alterations in the regulation of proteostasis. Decreased insulin signaling, as occurs with fasting or in diabetes, increases Foxo isoform translocation and transcription of critical mediators of ubiquitin-proteasome and autophagy lysosome systems, leading to a marked increase in protein degradation that outweighs protein synthesis, leading to muscle atrophy and a high protein-turnover state [18].The b-cell is one of the most susceptible cells for ER stress, and ER stress mediated apoptosis in b-cells can be a cause of DM [19,20]. ER stress is associated with inhibition of protein glycosylation, reduction of formation of disulfide bonds, calcium depletion from the ER lumen, impairment of protein transport from the ER to the Golgi, expression of malfolded proteins, etc. The translational attenuation reduces the load of new protein synthesis and prevents accumulation of unfolded proteins. This process eliminates misfolded proteins by the UPS, but apoptosis is induced to destroy the cell when functions of the ER are severely impaired. The importance of mitochondriais concerned both with high energy dependence on mitochondrial electrontransport, and a role in the signaling between the mitochondria and the ER [21] under stress. The left ventricular wall thickening iscorrelated with phosphorylated eIF2/eIF2 ratio and apoptosis.

REFERENCES

1. Chaudhary N. Impact of Diet & Lifestyle on Reversal of Cardiovascular Disease Markers-Diet & Lifestyle Change Primary Influencing Factor Compared to Genetic Predisposition.
2. Ebe D'Adamo, Sonia Caprio. (2011). Type 2 Diabetes in Youth: Epidemiology and Pathophysiology. 34: 161-165.
3. D'adamo E, Caprio S. (2011). Diabetes Care May. 34: 161-165.
4. Steinberger J, Daniels SR. (2003). Obesity, Insulin Resistance, Diabetes, and Cardiovascular Risk in Children. Circulation. 107: 1448-1453.
5. Story M, Evans M, Fabsitz RR, Clay TE, Rock BH, et al. (1999). The epidemic of obesity in American Indian communities and the need for childhood obesity-prevention programs. Am J ClinNutr. 69: 747S–754S.
6. Sorof J, Daniels S. (2002). Obesity Hypertension in Children - A Problem of Epidemic Proportions. Hypertension. 40: 441-447.
7. Shubrook Jr JH. (2011). Childhood obesity and the risk of diabetes in minority populations. AOA Health Watch.
8. Lago RM, Premranjan Singh P, Nesto RW. (2007). Diabetes and hypertension. NCP Endocrinology & Metabolism. 3: 667.
9. Pediatrics. (1996). Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. (NHBPEP) Working Group on Children and Adolescents. Chair: Bonita Falkner. 98: 649-58.
10. Masuo K, Tuck ML, Lambert GW. (2011). Hypertension and Dia-

betes in Obesity. SAGE-Hindawi Access to Research. Intern J Hypertension.

11. Chiang J. (2015). Hypertension and Diabetic Kidney Disease in Children and Adolescents. Spectrum DiabJ. 28: 220-224.

12. Today Study Group. (2013). Rapid Rise in Hypertension and Nephropathy in Youth With Type 2 Diabetes. Diabetes Care. 36: 1735–1741.

13. MacIver DH, Clark AL. (2016). Contractile Dysfunction in Sarcomeric Hypertrophic Cardiomyopathy. J Card Failure. 22: 731–737.

14. Cohn JN, Ferrari R, Sharpe N. (2000). Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. J Am CollCardiol. 35: 569–582.

15. Moreno V, Hernández-Romero D, Vilchez JA, García-Honrubia A, Cambronero F, et al. (2010). Marin F.Serum levels of high-sensitivity troponin T: a novel marker for left ventricular remodeling and performance in Hypertrophic Cardiomyopathy.J cardiac failure. 16: 950-956.

16. Miao DM, Zhang LP, Yu HP, Zhang JY, Xiao WK, et al. (2014). Serum levels of high-sensitivity troponin T: a novel marker for left ventricular remodeling and performance in hypertensive subjects. 13: 5143-5153.

17. Jaisson S, Gillery P. (2014). Impaired proteostasis: role in the pathogenesis of diabetes mellitus. Diabetologia. 57: 1517–1527.

18. James HA, O'Neill BT, Nair KS. (2017). Insulin Regulation of Proteostasis and Clinical Implications. Cell Metab. 26: 310-323.

19. Araki E, Oyadomari S, Mori M. (2003). Endoplasmic Reticulum Stress and Diabetes Mellitus. Internal Med. 42: 7-14.

20. Demirtas L, Guclu A, Erdur FM, Akbas EM, Ozcicek A, et al. (2016). Apoptosis, autophagy & endoplasmic reticulum stress in diabetes mellitus. 144: 515-524.

21. Badreddin A, Fady Y, Attia H, Hafez M, Khairallah A, et al. (2017). What role does the stress response have in congestiveheart failure? J Cell Physiol: 1–8.