Cross-talk between Folic acid and MMP2 /Leptin genes Methylation in Childhood Obesity, Nutrigenomics approach

Thesis

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List of Abbreviations

ARC .....Arcuate nucleus

AgRP.....agouti-related protein

BAT .....brown adipose tissue

BBB .....blood brain barrier

DHF .....Dihydrofolate

FTO .....Fat mass and obesity associated gene

GWAS .....The genome-wide association studies

HFD .....high fat diet

Jak-2 .....Janus kinase-2

LEP.....leptin

LEPR .....leptin receptor

MC4R .....Melanocortin receptor-4

MMPs.....Matrix metalloproteinases

MMP-2 .....Matrix metalloproteinase-2

NPC-1 .....Niemann-Pick C1 gene

POMC .....Pro-opiomelanocortin

SAM.....S adenosyl methionine

SNPs .....single nucleotide polymorphisms

THF .....Tetrahydrofolate

WAT.....white adipose tissue

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Abstract

Introduction: Over the last few decades there has been a worldwide increase in pediatric obesity affecting both developed and developing countries ***(Popkin, 2006).*** Obese children are at increased risk of a number of health problems including diabetes, sleep problems, joint problems, early puberty or menarche, asthma and other respiratory problems.

Aim: To correlate between MMP2 /leptin genes expression and folic acid levels in sera of obese children in order to study the effect of folic acid on methylation of these genes.

Patients and methods: This case control study was conducted on 80 children and adolescents (37 boys and 43 girls), children age range (2-16 years), with simple obesity recruited from National Nutrition Institute, the nutrition clinic. The study was initiated and completed in the period from the June 2015 till October 2016.

Results: The present study included (80) children. They were stratified into (4) groups: Group (I): Obese children (12 boys and 18 girls) before starting special diet regimen or folic acid intake (n=30). Group (II): Obese children (17 boys and 13 girls) after completing a special diet regimen for 3 months but without folic acid intake (n=30). Group (III): Some of group I children who completed folic acid intake and the same diet regimen for 3 months (n=15). Group (IV): Age and sex matched children (12 girls and 8 boys) as control group (n=20). No age or sex significant differences were found when we compared the three groups of included children (groups I, II and IV).

Conclusion: Depending on the previous information, MMP-2 and leptin methylation could be important source of information about pathogenesis and complications of childhood obesity.

Keywords: *Cross-talk between Folic acid and MMP2 / Leptin genes Methylation in Childhood Obesity, Nutrigenomics approach*

INTRODUCTION

Over the last few decades there has been a worldwide increase in pediatric obesity affecting both developed and developing countries ***(Popkin, 2006).*** Obese children are at increased risk of a number of health problems including diabetes, sleep problems, joint problems, early puberty or menarche, asthma and other respiratory problems ***(Lee, 2009).***

The prevalence and severity of obesity have been increased in children and adolescents, as well as in adults ***(Wang and Beydoun, 2007)***, in the United States, as reported by ***(Ogden, 2014),*** the prevelance of obesity among children (2- 19 years) is 16.9% and that is referred to complex interactions between genetic and environmental factors.

In recent years, epigenetic modifications such as DNA methylation and histone modifications have been highlighted in chronic non-communicable diseases as obesity due to their role in chromatin structure and gene expression and their potential use as markers for disease onset, progression, diagnosis and prognosis was considered ***(Garver et al, 2013)***.

DNA methylation is the only known modification that targets the DNA itself. Compared to histones, which undergo a variety of post-translational modifications under different conditions, DNA methylation is relatively stable over a longer period. The methylation of cytosine residues at CpG dinucleotides in gene promoters or CpG islands is well described and known to have profound effects on the regulation of gene expression ***(Burdge and Lillycrop, 2010; Choi and Friso, 2010)***.Thus, the role of epigenetic modifications in obesity is a fruitful area for research.

Aim of the Work

1. To estimate serum folic acid in obese children
2. To evaluate methylation state of MMP2 /leptin genes before and after folic acid supplementation.
3. To correlate between MMP2 /leptin genes expression and folic acid levels in sera of obese children in order to study the effect of folic acid on methylation of these genes.
4. To validate these biomarkers as contributors in pathogenesis of childhood obesity.

Obesity

Obesity is the excessive accumulation of fat which results in an increased risk of developing associated pathologies, including mortality. Childhood obesity is defined as a BMI of 95th percentile or greater on standardized age-based growth charts ***(Davila et al., 2017)***. It is a disease state resulting from an imbalance between energy intake and energy expenditure Excess calories create a positive energy balance with the excess energy stored in the body ***(Mraz and Haluzik, 2014)***.

Child obesity has been progressively increasing over the last few decades, being considered a worldwide epidemic by the World Health Organization (WHO). Worldwide, it is estimated that 43 million children under 5 years are overweight and obese, 35 million in developing countries and 8 million in developed countries ***(WHO, ٢٠١0).***

Although reduced energy expenditure and increased consumption of highly caloric foods are important factors contributing to the current epidemic of obesity, studies suggest that the development of obesity and associated metabolic disorders involves complex interactions between genetic and environmental factors, which are underpinned by epigenetic mechanisms ***(Kuehnen et al., 2012).***