

Childhood Obesity and Familial Hypercholesterolemia
Genetic Diseases that Contribute to Cardiovascular Disease

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Abstract

Childhood obesity occurs as the result of an imbalance between caloric intake and energy expenditure. Genetic risk factors for obesity have become an area of research due to its permanency. Mutated genes such as Fat Mass and Obesity Associated (FTO), Leptin (LEP), Leptin Receptor (LEPR), Melanocortin 4 Receptor (MC4R), Adiponectin C1Q and Collagen Domain Containing (ADIPOQ), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), and Peroxisome Proliferator-Activated Receptor Gamma (PPARG) all contribute to the development of childhood obesity. In the presence of high cholesterol caused by obesity, the genetic condition known as familial hypercholesterolemia is exacerbated. Familial hypercholesterolemia is caused by a mutation in the following genes: Low Density Lipoprotein Receptor (LDLR), Apolipoprotein B (APOB), Low Density Lipoprotein Receptor Adaptor Protein 1 (LDLRAP1), and the Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9). Familial hypercholesterolemia and childhood obesity both contribute to elevated serum cholesterol levels resulting in the accelerated progression of atherosclerosis in children. Another sequela of hypercholesterolemia, atherosclerosis, is an arterial disease that contributes to the development of cardiovascular disease in children. Nurses play a prominent role in the prevention of childhood obesity through education within the community and school setting. As a result of childhood obesity and familial hyperlipidemia, both genetically-linked, cardiovascular disease has become prevalent in the pediatric population.

Childhood Obesity and Familial Hypercholesterolemia: Genetic Diseases that Contribute to Cardiovascular Disease

Childhood obesity has reached epidemic levels in the United States, now becoming the main health concern for children. Although obesity is caused by both modifiable and nonmodifiable risk factors, research has recently focused on the genetic background of obesity due to its permanency. Childhood obesity results from the overconsumption of calories combined with a decreased caloric expenditure; genetic mutations that contribute to obesity are located within this spectrum of energy balance. Additionally, childhood obesity is closely correlated with a diet high in fat, leading to the development of high cholesterol in children. In the presence of high circulating cholesterol levels familial hypercholesterolemia, a genetic lipid regulation disease is exacerbated resulting in increased cholesterol levels. Each of these conditions contributes to the development and progression of atherosclerosis in children. Familial hypercholesterolemia and childhood obesity, both genetically linked disease processes, are major risk factors for the development of atherosclerosis and the development of cardiovascular disease in children and adolescents.

Childhood Obesity

Definition

Pediatric obesity is a rapidly growing disease process that affects children of all ages. Obesity is defined as “the result of chronic energy imbalance in a person who consistently takes in more calories from food and drink than are needed to power their body’s metabolic and physical functions” (Centers for Disease Control and Prevention,

2013a, para.1). Excess intake of calories with decreased physical activity leads to the accumulation of fat. Childhood obesity is known as obesity that occurs in children and adolescents ages 2 to 19 years old. This condition is determined based on the child's body mass index (BMI). Body mass index (BMI) indirectly measures body fat based on the child's weight and height; age and sex-specific percentiles are used to determine BMI in children, rather than categories which are used for adults (Centers for Disease Control and Prevention, 2012). Percentiles represent how the child's weight and height correlate to other children of the same age and gender (American Heart Association, 2011). A child is deemed overweight if the BMI is between the 85th and 95th percentile, and obese if the BMI is above the 95th percentile (Centers for Disease Control and Prevention, 2012). Figure 1 illustrates how a child's height, weight, and age determine body mass index (BMI), the measuring tool for obesity.

Statistics

Unfortunately, childhood obesity has become a common occurrence in children across the United States, becoming more accepted and even expected in culture. Currently, one-third of children in the United States are either overweight or obese, tripling the amount of obese children from the past decades (American Heart Association, 2011). Approximately 13 million children ages 2 to 19 years old are obese, accounting for 16.9% of children in the United States. Divided into age groups, 8.4% of children ages 2 to 5 years old are obese, 17.7% of 6 to 11 year-olds are obese, and 20.5% of 12 to 19 year-olds are obese (Food Research and Action Center, 2010).

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The effects of childhood obesity extend across the borders of the United States and affect many children worldwide. According to the World Health Organization, “childhood obesity is one of the most serious public health challenges of the 21st century” (World Health Organization, 2014, para.1). As of 2010, the amount of overweight children under the age of five was approximately 42 million worldwide, with 35 million in developing countries (World Health Organization, 2014). Globally, instead of the focus being on underweight and malnourished children, the focus has shifted to overweight and obese children. Figure 2 depicts the increasing trend of obesity from 1963 to 2008 among various pediatric age groups. Figure 3 depicts the number of obese high school students in the USA based on state and location. The effect of obesity is not specific to one age group, but rather affects children of all ages, races, and gender (American Heart Association, 2011). Additionally, these drastic increases in obesity prevalence have occurred in a relatively short time period of 30 years.

Childhood obesity has become the primary health concern for children across the nation due to association with chronic disease that previously has not been seen until adulthood (American Heart Association, 2011). Chronic diseases are many times preventable and unfortunately are now occurring in childhood. Before the wide prevalence of obesity, childhood was always thought to be the healthiest time period in life; however, this ideal is changing. This disease process has exploded into epidemic proportions, and as a result, children are now at risk of dying before their parents.

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Figure 2: Increase in obesity among children ages 2 to 19 in the USA seen from 1963-2008 (American Heart Association, 2011)

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Figure 3: Percentage of obese high school students in 2011 based on state (Centers for Disease Control and Prevention, 2013a)

Former Surgeon General Richard Carmona stated, “because of the increasing rates of obesity, unhealthy eating habits and physical inactivity, we may see the first generation that will be less healthy and have a shorter life expectancy than their parents” (American Heart Association, 2011, p.1). Studies have shown that one-third of obese children will become obese adults, indicating that lifestyle and health in childhood is a major predictor of health as an adult (Bouchard, 2009). As a result of obesity, children are living lower quality of lives and have an increased risk of mortality at an earlier age.

Pathophysiology

Childhood obesity begins at the cellular level and occurs as a compensatory mechanism for an increase in caloric consumption. Energy metabolism is measured in calories, which are units of heat derived from food sources (Pleuss & Matfin, 2009).

Approximately 90% of energy in the body is stored in adipose tissue. Adipocytes are fat cells, located throughout the body, and are responsible for the accumulation, synthesis, storage, and utilization of lipids, which are the primary source of energy for the body. Mature, or differentiated adipocyte cells do not divide; however, immature adipocytes or pre-adipocytes are capable of division; therefore, pre-adipocytes are responsible for fat deposition throughout the body. In the process of fat tissue production, an increase in the consumption of lipids causes an increase in the amount of pre-adipocytes, which are capable of fat storage (Pleuss & Matfin, 2009).

Two varieties of adipose tissue are present in the human body: white fat and brown fat. White fat is the most prevalent form of fat tissue in the child and adult body. Triglycerides, produced by white fat, are a major source of energy for the body. Brown fat found in neonates, produces heat for the body, and is not involved in lipid storage. Adipocytes are also responsible for the production of leptin, a hormone indicated in the regulation of food intake and energy expenditure. Leptin attaches to leptin receptors and functions by increasing energy expenditure and decreasing food intake. In the absence of obesity, adipocytes remain at a relatively consistent amount; however, when obesity occurs, more adipocytes are required for fat storage and utilization. Childhood obesity is a result of the dysfunction of the body's normal fat storage process (Pleuss & Matfin, 2009).

Risk Factors

Modifiable risk factors. Obesity in childhood results from the combination of modifiable and non-modifiable risk factors. Modifiable risk factors include risk factors

that can be altered or changed such as diet, sedentary lifestyle, psychological factors, socioeconomic factors, and parental obesity (Pleuss & Matfin, 2009). Diet is a major risk factor for childhood obesity due to the consumption of foods high in fat and sugar, larger portion sizes, and increased intake of fast foods. Sadly, french fries are the most common source of vegetable consumed by children (American Heart Association, 2011). Children many times do not control their diet and eat what is provided; therefore, parents have a responsibility to insure a balanced and nutritious diet is consumed. Along with a poor diet, many children also live a very sedentary lifestyle, spending many hours watching television, playing video games, and using the computer. The average child spends 44.5 hours a week using the television, computer, and video games. Studies have shown that people usually eat while watching television and that each additional hour in television viewing is associated with consuming 167 calories. An increased amount of time watching television leads to overconsumption of calories creating a cycle of sedentary activity and overeating. Lastly, parental obesity is a main risk factor for childhood obesity. Children with one parent who is obese have a 79% likelihood of becoming overweight as an adult (Pleuss & Matfin, 2009). Many times a child cannot control parental weight or lifestyle behavior; however, parental obesity is a risk factor that can be changed. Although childhood obesity has become prevalent in society, modifiable risk factors such as diet, sedentary lifestyle, and parental obesity can be changed.

Non-modifiable risk factors. Non-modifiable risk factors for childhood obesity are permanent and cannot be changed. These risk factors include genetics, race, and a family history of obesity (Pleuss & Matfin, 2009). Due to the permanency of these risk

factors, they have become a subject of study to determine the impact they have on childhood obesity. Genetic factors include genetic mutations that alter physiologic processes and predispose to obesity. Race is a non-modifiable risk factor for obesity. Studies have shown that African American, Hispanic American, and Native American children have a higher prevalence of obesity than Caucasian children. Obesity rates for females ages 2 to 19 years old based on race include: 15.6% of Caucasians, 20.5% of African Americans, and 20.6% of Hispanic Americans (Food Research and Action Center, 2010). Obesity rates for males ages 2 to 19 years old based on race include: 12.6% of Caucasians, 19.9% of African Americans, and 24.1 % of Hispanic Americans. Native American children obesity data is not available. It is unclear whether the increased prevalence is related to racial factors or socioeconomic status. A family history of obesity may be the result of a genetic predisposition within the family; however, a child will typically follow the role models within the family (Pleuss & Matfin, 2009). Non-modifiable risk factors cannot be changed; therefore, it is important to screen children for the presence of these factors in order to understand their risk of becoming obese.

Genetic Links of Childhood Obesity

Due to the increasing prevalence of childhood obesity, research is currently focusing on genetic links that lead to the development of obesity. Genes provide detailed instructions for the body to carry out required daily functions. Additionally, genes instruct the body how to react to positive and negative changes within the environment (Centers for Disease Control and Prevention, 2013b). Mutations in specific genes alter the function of the gene and what it is responsible to produce. Although genetic

alterations in the human population occur at too slow of a rate to be responsible for the current obesity epidemic, variations in how individuals respond to similar environments indicate that genes play a role in the development of obesity. Obesity most likely is not a monogenetic condition, but is most likely a result of multiple genes and interactions within the individual's environment. Genes cannot be completely responsible for obesity, but in the presence of an obesogenic environment, these mutated genes are enhanced, and a child's probability of becoming obese greatly increases. An obesogenic environment offers easy access to high-calorie foods with limited physical activity (Centers for Disease Control and Prevention, 2013a).

Approximately 5% of childhood obesity cases are the result of a mutated gene, and less than 5% of these implicated genes have been discovered (Bouchard, 2009). Human genome studies have revealed over 50 genes that are associated with obesity (Centers for Disease Control and Prevention, 2013a). As research continues concerning genetic links to obesity, the amount of genetic mutations responsible for obesity is likely to increase. Genes that have been studied and contribute to obesity include: Fat Mass and Obesity Associated (FTO), Leptin (LEP), Leptin Receptor (LEPR), Melanocortin 4 Receptor (MC4R), Adiponectin C1Q and Collagen Domain Containing (ADIPOQ), Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1), and Peroxisome Proliferator-Activated Receptor Gamma (PPARG) (Centers for Disease Control and Prevention, 2013a). Childhood obesity results from a mutation of the various genes which all encode instructions for differing processes.

Fat mass and obesity associated gene. Fat Mass and Obesity Associated (FTO) is a discovered gene that contributes to the development of childhood obesity. Fat Mass and Obesity Associated gene, also known as ALKBH9, is located on the long arm of

chromosome 16 shown in Figure 4, and is a nuclear protein of the AlkB non-haem iron and 2-oxoglutarate-dependent oxygenase superfamily (Genetics Home Reference, 2013b). The exact physiologic function of the FTO gene is unknown, but is thought to regulate metabolic rate,

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Figure 4: FTO Gene
(Genetics Home Reference, 2013b)

energy expenditure, energy balance, body size, and body fat accumulation (UniProt, 2014). Mutations in the FTO gene interrupt the normal function and thus predispose to childhood obesity. When the FTO gene is mutated, it is associated with increased energy consumption and impairs the individual's response to satiety (Garver, 2011). As a result, children's ability to determine satiety is altered, resulting in hyperphagia. Additionally, current society promotes increased serving sizes, further exacerbating the problem of hyperphagia. Studies have shown FTO gene variants predispose an individual to an increased consumption of calorie-dense foods that are high in fat (Garver, 2011). A diet high in fat also contributes to high cholesterol, an associated condition with childhood obesity. The FTO gene predisposes children of all ages to obesity.

Leptin gene. Leptin (LEP) gene mutation contributes to the development of childhood obesity. The leptin gene, located on the long arm of chromosome 7 shown in

Figure 5, encodes a protein that is secreted by white adipocytes and assists to regulate

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body weight (Genetics Home Reference, 2013c). As stated above, white adipose tissue is responsible for fat storage. This protein functions via the leptin

Figure 5: LEP Gene (Genetics Home Reference, 2013c)

receptor and operates as a

signaling pathway that can inhibit food intake and regulate energy expenditure to maintain a balance of adipose mass. Due to a gene mutation, the LEP gene's ability to inhibit food intake is altered predisposing a child to severe obesity. The LEP gene is unable to inhibit food intake, predisposing to overconsumption of calories and an increase in adipose tissue (Genetics Home Reference, 2013c).

Leptin receptor gene. The Leptin Receptor (LEPR) gene helps to regulate body weight; however, when the gene is mutated, this contributes to childhood obesity. This gene is located on the short arm of chromosome 1 shown in Figure 6 and provides instructions for the

production of leptin

receptor, a protein

involved in body

weight regulation

(Genetics Home

Reference, 2013d).

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Figure 6: LEPR Gene (Genetics Home Reference, 2013d)

Leptin receptor proteins are found on cells throughout the body, and are activated by the binding of leptin. The binding of leptin to leptin receptors activates a chemical signal and produces satiety. Normally, adipose cells secrete leptin in direct proportion to the size and amount of adipose cells. An increased amount of adipose tissue results in the increased production of leptin. Mutations in LEPR gene result in leptin receptor deficiency, which leads to excessive hunger and significant weight gain. Deficiency of leptin receptors results in hyperphagia and subsequently, obesity (Genetics Home Reference, 2013e). Leptin receptor deficiency is an inherited autosomal recessive condition and is responsible for approximately 3% of individuals with childhood obesity and overeating. Autosomal recessive inheritance requires both parents to pass on the mutated gene to their offspring in order for the mutation to present clinically. Based on the inheritance pattern, children are born with this condition, predisposing them from birth to be overweight and obese (Genetics Home Reference, 2013e). Leptin receptor gene mutation is a minor yet concrete contributor to the development of obesity in the pediatric population.

Melanocortin 4 receptor gene. Melanocortin 4 Receptor (MC4R) gene contributes to childhood obesity through the dysfunction of energy balance. Located on the long arm of chromosome 18 shown in Figure 7, the MC4R gene is involved in energy homeostasis and somatic growth (Genetics Home Reference, 2014e). Melanocortin 4 Receptor is a membrane-bound protein receptor that interacts with adrenocorticotrophic (ACTH) and melanocyte-stimulating hormone (MSH). This protein is activated by binding with MSH, and results in a reduction of caloric intake and an increase in energy

expenditure via thermogenesis (Garver, 2011). Mutations of the MC4R gene cause individuals to consume an increased amount of food, specifically a preference for total and saturated fats. Mutations of this gene predispose children to the development of high cholesterol as a result of increased fat consumption. Additionally, MC4R mutations result in a decreased feeling of satiety and an increase in weight accumulation and thus, the resulting childhood obesity. Melanocortin 4 Receptor mutation, along with an obesogenic environment and prevalence of high-fat food, increases a child's risk of becoming obese (Garver, 2011).

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Figure 7: MC4R Gene
(Genetics Home Reference, 2014e)

Adiponectin C1Q and collagen domain containing gene. Adiponectin C1Q and Collagen Domain Containing (ADIPOQ) gene contributes to the development of

childhood obesity through the dysfunction of fat metabolism (Genetics Home Reference, 2013a).

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Figure 8: ADIPOQ Gene (Genetics Home Reference, 2013)

Adiponectin C1Q and

Collagen Domain Containing gene, located on the long arm of chromosome 3 shown in Figure 8, is involved in metabolic processes. This gene is solely present in adipose tissue and encodes for a protein that is involved in fat metabolism and insulin sensitivity.

Adiponectin C1Q and Collagen Domain Containing gene stimulates AMPK

phosphorylation in the skeletal muscle in the liver, resulting in glucose and fatty-acid combustion and metabolism. Mutation of the ADIPOQ gene is associated with adiponectin deficiency. Adiponectin deficiency impairs fat metabolism, therefore predisposing fat accumulation and obesity. Decreased fat metabolism contributes to the accumulation of adipose tissue, the defining factor in obesity (Genetics Home Reference, 2013a).

Proprotein convertase subtilisin/kexin type 1 gene. Childhood obesity occurs partially as a result of the mutation of the Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1) gene. This

gene is located on the long arm of chromosome 5 shown

in Figure 9, and plays a role in the production of

insulin (Genetics Home Reference, 2014f). Normally, PCSK1 encodes for a protein, a type 1 proinsulin-processing enzyme that activates latent precursor proteins to their usable state. The type 1 proinsulin-processing enzyme regulates insulin biosynthesis. Mutations of this gene contribute to the development of obesity, due to dysfunctional insulin synthesis. As a result of PCSK1 gene mutation, children are predisposed to obesity (Genetics Home Reference, 2014f).

Peroxisome proliferator-activated receptor gamma gene. Peroxisome Proliferator-Activated Receptor Gamma (PPARG) gene mutation results in the loss of

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Figure 9: PCSK1 Gene (Genetics Home Reference, 2014f)

control of fat tissue differentiation. Peroxisome Proliferator-Activated Receptor Gamma is located on the short arm of chromosome 3 shown in Figure 10 (Genetics Home Reference, 2014h). Normally, the PPARG gene encodes various nuclear receptors of the peroxisome

proliferator-

activated receptor

subfamily (PPAR):

PPAR-alpha,

PPAR-delta, and

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Figure 10: PPARG Gene (Genetics Home Reference, 2014h)

PPAR-gamma. Specifically, the PPARG gene encodes for PPAR-gamma, which is involved in the regulation of adipocyte differentiation. As stated above, adipocyte differentiation includes mature, or differentiated adipocytes, and immature adipocytes (Pleuss & Matfin, 2009). Differentiated adipocytes do not divide, and immature adipocytes are capable of division; therefore, pre-adipocytes are responsible for fat deposition throughout the body. With a mutation in adipocyte differentiation, pre-adipocyte cells can divide uncontrollably and increase the amount of adipose tissue. Obesity, diabetes, atherosclerosis, hypertension, and cancer are all associated with a mutation of the PPARG gene (Genetics Home Reference, 2014h). As a result of PPARG gene mutations children are predisposed to various chronic diseases, including obesity.

Hypercholesterolemia

Gene mutations implicated in childhood obesity occur in the process of energy balance. Many mutations as stated above predispose children to a high fat diet, a known

contributor to childhood obesity and hypercholesterolemia. High cholesterol in children is known to be associated with childhood obesity (The Cleveland Clinic Foundation, 2013). Hypercholesterolemia occurs when high levels of cholesterol are in the bloodstream (Genetics Home Reference, 2014b). This condition can result from genetic mutations, primary hypercholesterolemia, or lifestyle factors referred to as secondary hypercholesterolemia (Matfin, 2009). Familial hypercholesterolemia is primary hypercholesterolemia as a result of genetic mutations. Secondary hypercholesterolemia in children is linked with diet and obesity (The Cleveland Clinic Foundation, 2013). An obese child's diet is many times composed of foods high in fat and sugar, and deficient in essential nutrients. This diet is associated with secondary hypercholesterolemia as a result of excess cholesterol availability, leading to increased cholesterol in the bloodstream.

Cholesterol. Cholesterol is a fat-like substance that is abundant in the diet of obese children. Functionally, cholesterol is a building block of cell membranes, hormones, and produces compounds that are involved in fat digestion (Genetics Home Reference, 2014b). Sources of this substance include foods such as egg yolks, meat, poultry, fish, and dairy products. The digestive tract absorbs cholesterol, and then transports it into the vasculature via lipoproteins; lipoproteins are composed of a lipid in the interior and proteins surrounding the exterior (National Human Genome Research Institute, 2013). There are two variations of lipoproteins: low density lipoprotein (LDL) and high density lipoprotein (HDL); appropriate levels of LDL and HDL are shown in Figure 11. LDL and HDL function oppositely within the body.

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Figure 11: Cholesterol levels in children (Eiland & Luttrell, 2010)

LDL cholesterol. Low density lipoproteins, referred to as *bad cholesterol*, is the primary carrier of cholesterol and is composed of 10% triglycerides, 50% cholesterol, and 25% protein (Matfin, 2009). LDL is removed from the bloodstream mainly via LDL receptors, but also by monocytes or macrophages. Body tissues are able to control their cholesterol intake by increasing or decreasing the amount of LDL receptors. The amount of plasma LDL is directly controlled by the removal of LDL by monocytes and macrophages; when LDL is absorbed by macrophages, located in the walls of arteries, the development of atherosclerosis begins. Increased LDL levels are the main contributor to the development of atherosclerosis, which is discussed later (Matfin, 2009).

HDL cholesterol. High density lipoprotein is beneficial to the body and helps to control cholesterol. HDL, known as *good cholesterol*, is composed of 5% triglycerides, 20% cholesterol, and 50% protein (Matfin, 2009). Functionally, HDL cholesterol operates opposite of LDL by removing cholesterol from tissues and transporting it to the liver for excretion. By promoting the removal of LDL from the body, HDL helps to decrease to risk of atherosclerosis. HDL has arterial protective functions by preventing

the uptake of LDL by macrophages therefore decreasing atherosclerosis. Overall, children need adequate levels of HDL to combat the effects of LDL (Matfin, 2009).

Familial Hypercholesterolemia

Definition.

High cholesterol in children can be caused by diet or genetic mutations. Familial hypercholesterolemia is a genetically linked disease that is exacerbated by the presence of childhood obesity and high cholesterol. Familial hypercholesterolemia is an “inherited condition that causes high levels of LDL cholesterol levels beginning at birth and heart attacks at an early age” (National Human Genome Research Institute, 2013, para.1). Circulating high cholesterol within the vasculature, combined with the dysfunction in LDL removal results in extremely high levels of serum cholesterol predisposing children to cardiovascular events.

This condition is an autosomal dominant disease, which “refers to a gene on one of the 22 pairs of autosomes (non-sex chromosomes) [and]

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Figure 12: Autosomal Dominant inheritance pattern of Familial Hypercholesterolemia (FH Foundation, 2014)

describes a trait or disorder in which the phenotype is expressed in those who have inherited only one copy of a particular gene mutation” (Seal, 2011, p. 62). Due to the inheritance pattern, if one parent has this genetic defect they have a 50% chance of passing the disease to their offspring. Figure 12 illustrates familial

hypercholesterolemia's inheritance pattern. Familial hypercholesterolemia results from mutations of LDLR, APOB, LDLRAP1, and PCSK9 genes (Genetics Home Reference, 2014b). Gene mutations cause an inability to remove LDL from the bloodstream resulting in high levels of LDL cholesterol (National Genome Research Institute, 2013).

According to the American Academy of Pediatrics, FH screening is recommended in children after age 2 and before age 10 "if a family has a pattern of early heart attacks or heart disease defined as before age 55 for men and 65 for women" (FH Foundation, 2014, para. 8). Children are diagnosed with familial hypercholesterolemia if their total cholesterol is above 250 mg/dL and LDL is above 200 mg/dL. This condition affects approximately one in 500 people worldwide (Genetics Home Reference, 2014b). Familial hypercholesterolemia is a result of genetic mutations, altering the body's normal function.

Genetic Links to Familial Hypercholesterolemia

Low density lipoprotein receptor gene. Low Density Lipoprotein Receptor (LDLR) mutation is the main cause for the development of familial

hypercholesterolemia. LDLR, located on the short arm of chromosome 19 shown in Figure 13, provides instructions for the production of low-density lipoprotein receptors (Genetics Home Reference, 2014c). Normally, low density lipoprotein receptors are located on the outer surface of cells and bind with LDL circulating in

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Figure 13: LDLR Gene
(Genetics Home Reference, 2014c)

the bloodstream to transport them into the cell. Once transported into the cell, LDL is then degraded and releases cholesterol, which is then available to be used, stored, or excreted. After releasing cholesterol within the cell, LDL receptors return to the surface of the cell and the process begins again. Due to their integral part in LDL transport, LDLRs regulate the amount of cholesterol in the bloodstream. Familial hypercholesterolemia is a result of a mutated LDLR gene; over 1,000 mutations have been discovered concerning this gene. Mutations decrease the number of LDL receptors produced, causing an inability to remove LDL from the vasculature, resulting in high cholesterol levels. If a child inherits one mutated LDLR gene, one affected gene from one parent and one normal gene from the other parent, the child has an increased risk of cardiovascular disease beginning in their 40s or 50s. If two mutated LDLR genes are inherited, one mutated gene from each parent, a severe form of hypercholesterolemia is present in childhood. Unfortunately, LDLR gene mutations result in familial hypercholesterolemia and predispose children to high cholesterol (Genetics Home Reference, 2014c).

Apolipoprotein B gene. Apolipoprotein B (APOB) is involved in the removal of LDL from the vasculature. This gene is located on the short arm of chromosome 2 shown

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Figure 14: APOB Gene (Genetics Home Reference, 2014a)

in Figure 14, and provides instructions for making Apolipoprotein B (Genetics Home Reference, 2014a). Two forms of Apolipoprotein B are available: Apolipoprotein B-48 and Apolipoprotein B-100; both forms compose lipoproteins which transport cholesterol in the bloodstream. Apolipoprotein B-48, produced in the intestines, is a component of chylomicron; after digestion of a meal, chylomicrons are formed to transport fat and cholesterol from the intestine to the blood stream. Apolipoprotein B-100, synthesized in the liver, is a component of very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and low-density lipoproteins (LDL) all of which carry fat and cholesterol in the vasculature. Apolipoprotein B-100 allows VLDL, IDL, and LDL to attach to receptor sites, specifically within the liver. Altered Apolipoprotein B prevents LDL from attaching to receptor sites, decreasing the amount of LDL and cholesterol removed from the blood stream. Mutations of APOB cause increased levels of serum cholesterol and an increased risk of cardiovascular disease (Genetics Home Reference, 2014a).

Low density lipoprotein receptor adaptor protein 1 gene. Low Density Lipoprotein Receptor Adaptor Protein 1 (LDLRAP1) plays an integral role in the transport of cholesterol into the cell. Figure 15 illustrates the position of the LDLRAP1

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Figure 15: LDLRAP1 Gene (Genetics Home Reference, 2014d)

gene on the short arm of chromosome 1, which codes for a protein that removes cholesterol from the bloodstream (Genetics Home Reference, 2014d). The LDLRAP1 protein is involved in moving LDLR bound to LDL from the surface of the cell to the interior of the cell where the cholesterol is released. Gene mutations lead to the synthesis of a small dysfunctional LDLRAP1 protein or deficiency of the LDLRAP1 protein. In the absence of the LDLRAP1 gene, LDLR is unable to transport LDL from the bloodstream into the cell effectively. Although LDL is still able to bind with LDLR, the LDL is not properly transported within the cell causing the LDL to remain in the vasculature. The mutation of LDLRAP1 contributes to the development of familial hypercholesterolemia (Genetics Home Reference, 2014d).

Proprotein convertase subtilisin/kexin type 9 gene. Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) contributes to the development of familial hypercholesterolemia in children due to a mutated gene. This gene found on the short arm of chromosome 1 shown in Figure 16, codes for a protein that helps to regulate the

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Figure 16: PCSK9 Gene (Genetics Home Reference, 2014g)
amount of cholesterol within the vasculature (Genetics Home Reference, 2014g). PCSK9 helps to control the amount of LDL receptors present on the surface of liver cells to determine the rate of cholesterol removal from the blood. Cholesterol levels are

controlled by PCSK9 through the degradation of LDL receptors before they reach the surface of the cell. In the presence of a mutated PCSK9, one amino acid is altered resulting in the enhanced activity of PCSK9. Overactive PCSK9 results in a decreased amount of LDL receptors on the cell surface causing increased LDL levels in the blood vessels. As a result of deficient LDL receptors, cholesterol increases contributing to familial hypercholesterolemia (Genetics Home Reference, 2014g).

Atherosclerosis

Definition

Familial hypercholesterolemia and excess cholesterol contribute to the development and progression of atherosclerosis. Atherosclerosis is hardening of the arteries from the accumulation of fatty lesions in arteries, particularly the coronary arteries (Matfin, 2009). This is a degenerative disease that originates in childhood (Raghuveer, 2010). Risk factors for the development of atherosclerosis include both modifiable and non-modifiable risk factors such as hypercholesterolemia, family history of heart disease, obesity, and male gender (Matfin, 2009). The presence of obesity and familial hypercholesterolemia in a child greatly increases the risk of developing heart disease at an early age.

Classification of Atherosclerosis

Three types of atherosclerosis exist: fatty streaks, fibrous atheromatous plaque, and complicated lesions.

Fatty streaks. Children as young as one year old begin developing fatty streaks, independently of other predisposing risk factors (Matfin, 2009). Fatty streaks are

composed of macrophages and smooth muscle cells which are part of the vessel wall that have become infiltrated with lipids, forming foam cells. As cholesterol levels increase in the blood stream, monocytes engulf cholesterol and attach to the endothelium, where they then transition through the wall and transform into macrophages. Within the vasculature fatty streaks increases until a child reaches age 20, then either decrease or remain constant. The Bogalusa Heart Study discovered that 50% of children and 85% of young adults had fatty streaks within their arteries, supporting the belief that atherosclerosis development begins early in childhood (Eiland & Luttrell, 2010). After the development of fatty streaks, atherosclerosis progresses to fibrous atheromatous plaques (Matfin, 2009).

Fibrous atheromatous plaques. Fibrous atheromatous plaques contribute to the cardiovascular effects of atherosclerosis. Clinically, these plaques are the most common cause of atherosclerosis (Matfin, 2009). Lipids and vascular smooth muscle are the basis for fibrous atheromatous plaques, which cause the formation of scar tissue and eventually calcification of the plaque. The core of the plaque is composed mainly of cholesterol then encapsulated by a fibrous cap and a layer of smooth muscle. As the lesion grows, it occludes blood flow within the arteries causing a blockage. As a result of impeding blood flow, a myocardial infarction (heart attack) or ischemic infarction (stroke) can occur (Matfin, 2009).

Complicated lesions. Complicated lesions are a result of the combination and progression of atherosclerosis. As the fibrous plaque presents with hemorrhage and ulceration, platelets accumulate and scar tissue is formed (Matfin, 2009). Activated

macrophages release free radicals that oxidize LDL, which is damaging to the endothelial wall and causes hemorrhage. Hemorrhage activates the inflammatory response, resulting in the aggregation of platelets and fibrin to the damaged area, which can further occlude the blood vessel. As blood flows near the plaque, turbulence occurs, resulting in thrombosis or blood clots. Atherosclerosis is a process that occurs throughout time. The earliest manifestation of atherosclerosis is a fatty streak accumulation of lipid-filled macrophages within the arterial intima. Progressive lipid accumulation over time results in macrophage and smooth muscle proliferation and development of a fibrous plaque, ... plaque increases in size over years ... which leads to slow occlusion of the vessel or sudden occlusion of a distal vessel because of plaque embolization. (Raghuveer, 2010, pp. 3S-4S)

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Figure 17:
Atherosclerosis Disease
Process beginning at
age zero and
progressing to age 70
(Raghuveer, 2010, p.1516S)

As fatty streaks start accumulating in childhood, the presence of excess cholesterol aggravates arterial disease and predisposes to myocardial infarction. Atherosclerosis results in the occlusion of blood flow to various tissues throughout the body that can result in various disease processes. Figure 17 reveals the progression of atherosclerosis from birth to age 70 and the disease processes that can result. At birth, atherosclerosis is absent, but begins to develop throughout childhood until it is clinically present in middle age (Matfin, 2009).

Pharmacotherapy in Pediatrics

As a result of the increased prevalence of childhood obesity and familial hypercholesterolemia, pharmacotherapy is implemented to decrease cardiovascular disease. Childhood obesity with a high fat diet can exacerbate familial hypercholesterolemia. Treatment of hypercholesterolemia with pharmacologic agents in the pediatric population is controversial due to side effects of medications. Among all medications used to control adult cholesterol levels, statins have been found to be effective and safe in the treatment of familial hypercholesterolemia in the pediatric population (Eiland & Luttrell, 2010). Statins are pharmacologically classified as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, which reduce blood levels of triglycerides and LDL by inhibiting HMG-CoA reductase. Pharmacological therapy of familial hypercholesterolemia is relatively new; therefore, no specific dosing and treatment criteria have been established. The American Academy of Pediatrics recommends treating high cholesterol in children eight years and older if the following conditions are met: LDL

greater than 190 mg/dL in patients with no risk factors for cardiovascular disease if diet modification has been unsuccessful ... LDL greater than 160 mg/dL who have a family history of premature onset of cardiovascular disease or other risk factors including obesity, hypertension, or cigarette smoking, ... and LDL greater than 130 mg/dL who have diabetes. (The Cleveland Clinic Foundation, 2013, para. 4)

Treatment includes both lifestyle interventions and medication therapy, although diet and exercise interventions should be done for six months to one year before initiating medication (Eiland & Luttrell, 2010). One exception to this recommendation is that since familial hypercholesterolemia is a genetic disease, children may not respond to dietary intervention and may require medication earlier. Pravastatin has been approved by the FDA for use in children eight years old and up; lovastatin, simvastatin, fluvastatin, atorvastatin, and rosuvastatin have been approved by the FDA for children ten years and older. Overall, statins have been shown to reduce LDL cholesterol 17 to 50% from a child's baseline level. Side effects of statin use include headache, myalgia, and gastrointestinal symptoms, all of which decrease with continued use. Myalgia, known as muscle aches and soreness, is the most concerning side effect in children. Children suffering from myalgia may have a decreased level of activity, further contributing to childhood obesity and an increase in cholesterol levels, which was the initial basis for treatment. Nurses must educate children and parents concerning pharmacotherapy to enhance their compliance. Overall, it is important to manage cholesterol levels in children to decrease their risk of cardiovascular disease (Eiland & Luttrell, 2010).

Cardiovascular Disease

In the presence of familial hypercholesterolemia and childhood obesity, children are at an increased risk of developing cardiovascular disease. Across America, obesity has become the leading cause of premature heart attack (American Heart Association, 2011). Extreme body fat seen in obesity is correlated with high cholesterol and hypertension, both of which add an increased workload on the heart. Excess cholesterol in the bloodstream increases an individual's risk of developing heart disease and atherosclerosis (Genetics Home Reference, 2014b). Damage to the vasculature caused by atherosclerosis can result in coronary artery disease or myocardial infarction. Statistics reveal that overweight children between the ages of 7 to 13 years old are already at an increased risk of developing heart disease beginning at age 25 (American Heart Association, 2011). Research shows that 60% of overweight children between the ages 5 to 10 years old already have one risk factor for heart disease such as high cholesterol, high triglycerides, high insulin, or hypertension; 25% of children ages 5 to 10 already have two or more heart disease risk factors. As a result of choices made in childhood, children are at risk of developing cardiovascular disease that will be present for the remainder of their lives. Adolescents who are both obese and have high triglyceride levels have arteries similar to 45 year-olds. Childhood obesity affects the vasculature, leading to the premature onset and acceleration of atherosclerosis (Raghuveer, 2010). Acceleration of atherosclerosis results in cardiovascular effects, such as myocardial ischemia and myocardial infarction occurring in children. Unfortunately, due to the increase in childhood obesity in past years, coronary artery disease is expected to increase

5 to 16% by 2035. The atherosclerosis disease process begins early in childhood and progresses into adulthood (American Heart Association, 2012). In the presence of childhood obesity and familial hypercholesterolemia, atherosclerosis is exacerbated which leads to cardiovascular disease. Childhood obesity and familial hypercholesterolemia, both genetic based diseases, contribute to the development of cardiovascular disease in children.

Nurse Role in Preventing Childhood Obesity

Nurses play a key role in the prevention of modifiable risk factors and education of the genetic risk factors of childhood obesity. Education of the entire family unit is essential to the prevention of childhood obesity (Rabbitt & Coyne, 2012). Children are generally unable to change their eating and health habits alone; therefore, the family unit must be involved and participate in changes.

The nurse can prevent and reduce the occurrence of childhood obesity through community and school nursing. In both avenues the nurse can implement education of a healthy diet and adequate exercise program for children. A diet high in fruits, vegetables, whole grains, low-fat dairy products, and lean meats should be encouraged; additionally, a diet low in saturated and trans fats, cholesterol, sodium and added sugars should be followed (National Institute of Child Health and Human Development, 2012). Healthcare workers can refer families to ChooseMyPlate.gov which is a program developed by the USDA to promote healthy eating habits. Adequate exercise for children must also be promoted. Children and adolescents need at least 60 minutes of physical activity each day (National Institute of Child Health and Human Development, 2012). It is important to

tailor the exercise program to the child and include the child in the decision-making process to optimize the success of the exercise program. Along with the promotion of physical activity, the nurse should insist that sedentary activities be limited to two hours per day (Rabbitt & Coyne, 2012). Limiting the amount of time spent playing video games, watching television, and playing on the computer will create time for children to play outside and be physically active. It is essential that the nurse promotes healthy behaviors and does not focus on restrictive diets and over exercising, which could predispose a child or adolescent to an eating disorder (Rabbitt & Coyne, 2012).

Nurses also play a role in educating the public about the role of genetics in the development of childhood obesity. Human Genome Research verifies that genes play a role in the development of childhood obesity; however, specific environmental factors must also be present (Seal, 2011). Not only are nurses involved in education, but also have “a crucial role in the prevention and treatment of obesity by identifying the modifiable risk factors, evaluating individuals and their families, and collecting detailed family health histories” (Seal, 2011, p. 65). Health histories include at least three generations and plot out family members and diseases to search for an inheritance pattern. Family members should be provided with information about genetic testing which is currently only available for monogenic and syndromic forms of obesity. Although genetic testing will not prevent childhood obesity, it will allow families to be aware that they have a predisposition to obesity. Overall, the nurse plays an integral role in the prevention and education of childhood obesity.

Childhood obesity has become an epidemic in the United States of America within recent years. Research has focused on the genetics of pediatric obesity in order to identify gene mutations that disrupt the body's normal functioning and predispose children to disease. Obesity within the pediatric population has led to a surge of high cholesterol levels within children, so much so that medications are now administered to children to manage this condition. High cholesterol also exacerbates familial hypercholesterolemia, a genetically based disease that occurs in children. As a result of dysfunction in cholesterol utilization and storage, cholesterol remains within the blood stream, increasing the risk of atherosclerosis development. Childhood obesity, familial hypercholesterolemia, and atherosclerosis all contribute to the development of cardiovascular disease in children. The childhood obesity epidemic must be stopped before it steals the lives of America's children.

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