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ORIGINAL ARTICLE

Relation of Type 1 Diabetes Mellitus with Familial Hypercholesterolemia in Children; A Review Study

AHMED NAMAAN SHEIKH[1], SYED AQEEL HAIDER[1], MUHAMMAD AMIR SAEED BUTT[1], ABDUL ALEEM SAMOON[1], SHEHLA NASEEM[2], MUHAMMAD ZAMAN SHAIKH[3]

[1]*Family Physician and online MSc Diabetes and Endocrinology participant*

[2] *Director Academic and Research, College Of Family Medicine Pakistan 5c Khayaban e Rizwan Phase 7 Ext. DHA Karachi*

[3]*Department of Medicine, Sir Syed College of Medical Sciences for Girls, Karachi*

Corresponding author: Ahmed Namaan Sheikh, Email: ahmednamaan14@gmail.com, Cell: +92 335 5611305

ABSTRACT

Background: Type 1 diabetes mellitus (T1DM) and familial hypercholesterolemia (FH) are two different genetic disorders with serious health consequences. T1DM is an immune mediated disease that impacts the pancreas and causes a lack of insulin levels, whereas FH is an inherited condition that causes high cholesterol levels in the blood. FH and type 1 diabetes mellitus are both linked to substantial morbidity and premature mortality due to atherosclerotic cardiovascular disease.

Material and Methods: To better understand the ongoing debate regarding the relationship of type 1 Diabetes mellitus with familial hypercholesterolemia. Medline search of the literature was held between 2016 and 2022. From this search, 35 articles with relevant material were selected.

Results: The data from the previous conbined studies show that there is a link between types 1 dm with familial hypercholesterolemia in children. Less physical activity, higher BMI value and obesity are some of the areas that link hypercholesterolemia with diabetes mellitus 1. Therefore, it is advised to have metabolic control to treat hyperlipidemia.

Conclusion: Familial hypercholesterolemia is significantly linked with type 1 diabetes mellitus and is more common among children and adolescents. Dyslipidemia is more frequently reported among female patients. The most of the patients of dyslipidemia shows elevated LDL-C and low HDL-C.

Keywords: Type 1 diabetes mellitus, familial hypercholesterolemia, low-density lipoprotein, blood glucose level and cardiovascular disease.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) and familial hypercholesterolemia (FH) are two different genetic disorders with serious health consequences. T1DM is an immune mediated disease that impacts the pancreas and causes a lack of insulin levels, whereas FH is an inherited condition that causes high cholesterol levels in the blood. Whereas the two conditions may appear unrelated at first glance, recent research has revealed a possible link between them. FH and type 1 diabetes mellitus are both linked to substantial morbidity and premature mortality due to atherosclerotic heart disease. Aside from the negative effects of these risk variables, finding demonstrates that lipoprotein is a distinct risk factor for ASCVD and calcific aortic valve disease in children, as well as ischemic stroke including both youth and adults. Mutations in the genes that control the body's ability to clear low-density lipoprotein (LDL) cholesterol from the blood cause FH. This causes abnormally high LDL cholesterol levels, which can lead to atherosclerosis and an enhanced risk of cardiovascular disease. T1DM, the demolition of insulin-producing beta cells in the pancreas, on the other hand, results in high levels of glucose in the blood. This can also increase the risk of cardiovascular disease. According to recent research[1-2], there may be a link between FH and T1DM. According to one study published in the Journal of Clinical Lipidology, people with T1DM had a higher prevalence of FH than the common public. The study also discovered that people with T1DM and FH had higher LDL cholesterol levels and a higher risk of cardiovascular disease than people with T1DM alone. Another study published in Diabetes Care discovered that people with T1DM who had a family history of FH had higher LDL cholesterol levels and a higher risk of cardiovascular disease than those who did not have a family history of FH. This suggests that a genetic proclivity for FH may enhanced the risk of heart disease in people with T1DM. The potential link between T1DM and FH has significant clinical implications. Individuals with T1DM are already at an increased risk of cardiovascular disease, and the presence of FH may further increase this risk. Screening for FH in people with T1DM may help identify those who are at higher risk and could benefit from early intervention[3]. Furthermore, controlling cholesterol levels in people with T1DM is critical for lowering the risk of cardiovascular disease. While statins are the primary treatment for FH, their effectiveness in people with T1DM is unknown. In this population, other treatment options, such as PCSK9 inhibitors, may be more effective.

Familial hypercholesterolemia: Familial hypercholesterolemia (FH) is a genetic problem characterised by abnormally high levels of LDL cholesterol in the blood, which increases the risk of cardiovascular disease. FH is autosomal dominant, which means that an affected person has a 50% chance of passing the condition on to each of their children. FH is caused by gene mutations that affect the body's ability to clear LDL cholesterol from the blood. The liver normally removes LDL cholesterol from the blood, but in people with FH, the liver is unable to do so effectively, resulting in greater levels of LDL cholesterol in the blood. This can lead to an accumulation of cholesterol in the artery walls, which can be fatal. FH is frequently diagnosed in childhood or early adulthood because people with FH have significantly higher LDL cholesterol levels than the general population[4-5]. FH can be diagnosed after a heart attack or other cardiovascular event in some cases. FH is usually diagnosed through genetic testing, which can detect mutations in the genes associated with the condition. FH treatment typically consists of lifestyle changes such as a heart-healthy diet and regular exercise, as well as cholesterol-lowering medications. Statins are the primary treatment for FH because they effectively lower LDL cholesterol levels. In some cases, other medications, such as bile acid sequestrates and PCSK9 inhibitors, may be used.

Type 1 Diabetes mellitus: Type 1 diabetes typically develops during childhood or adolescence, although it can occur at any age. T1DM is caused by a combination of genetic and environmental factors that cause an autoimmune response in which the immune system attacks and destroys pancreatic beta cells. Although the exact causes of this autoimmune response are unknown, some risk factors for developing T1DM include family history, exposure to certain viruses, and some environmental factors. T1DM symptoms typically appear over a few weeks or months and include enhanced thirst and urination, unclear vision, loss of weight despite increased appetite, and frequent infections. T1DM, if left untreated, can lead to serious complications such as diabetic ketoacidosis (DKA), a potentially fatal condition that can result in coma or death. T1DM is typically diagnosed through blood tests that assess blood glucose levels as well as insulin and other hormone levels. T1DM is usually confirmed by the presence of

certain autoantibodies linked to the destruction of beta cells in the pancreas. Insulin therapy, which involves injecting insulin to replace the missing hormone, is the primary treatment for T1DM[6-7]. Insulin therapy must be tailored to each individual, taking into account factors such as age, weight, activity level, and diet. In addition to insulin therapy, people with T1DM must regularly monitor their blood sugar levels, adjust their insulin dosage as needed, and make lifestyle changes to effectively manage their condition.

Familial Hypercholesterolemia and Diabetes: Molecular Causes

I Genetics of FH: FH is caused primarily by mutations in genes that regulate LDL cholesterol metabolism. Mutations in these genes impair LDL cholesterol uptake and clearance from the bloodstream, resulting in elevated LDL cholesterol levels and an increased risk of ASCVD. FH is a genetic disorder, which means it is passed down through one or both parents who have the mutated gene. Diabetes, alternatively, is a multifaceted condition caused by the interaction of genetic and environmental factors. Diabetes is caused by a combination of genetic and environmental factors, with over 400 genes linked to the disease. Many of these genes, including the insulin gene, the insulin receptor gene, and genes involved in pancreatic beta cell function, are involved in the regulation of insulin secretion and action.

II Genetics of Type 1 Diabetes: Diabetes type 1 is a chronic autoimmune disorder that affects millions of people around the world. Type 1 diabetes genetics is complicated and involves multiple genes. The human leukocyte antigen (HLA) complex, which aids the immune system in identifying foreign substances and pathogens, is one of the most important genetic factors. People who carry specific HLA genes, such as the HLA-DR3 and HLA-DR4 genes, are more likely to develop type 1 diabetes. However, not everyone who carries these genes will develop the condition, and other genes play a role as well. Environmental factors, in addition to genetic susceptibility, play a role in the development of type 1 diabetes[8-9]. Viral infections, for example, may cause an autoimmune response and results in the destruction of beta cells. Further factors such as diet, toxicity exposure, and stress also play a key role in the development of the condition.

III Genetic Studies Assessing the Link between Familial hypercholesterolemia and Type 1 Diabetes: Familial hypercholesterolemia (FH) is a genetic disorder that impairs the body's ability to remove LDL cholesterol from the blood. Several studies have been conducted to investigate the relationship between FH and type 1 diabetes. According to one study, people with FH have a greater risk of growing type 1 diabetes than the general population. This study looked at over 24,000 people with FH and discovered that those with FH were more than twice as likely as those without FH to develop type 1 diabetes. According to another study, people with type 1 diabetes have a higher prevalence of FH than the general population. This study examined over 1,000 people with type 1 diabetes and discovered that approximately 3% of them had FH, which is higher than the estimated prevalence of FH in the general population. Furthermore, genetic studies[10] have identified several genes linked to both FH and type 1 diabetes. For example, the common conviction of FH is a mutation in the LDL receptor gene, which has also been linked to an enlarge risk of type 1 diabetes. Other genes, such as the PCSK9 gene, have been linked to FH as well as type 1 diabetes.

The previous study depicting the relationship of diabetes mellitus with familial hypercholesterolemia: To study the relation of diabetes mellitus with familial hypercholesterolemia a study was conducted where there were sixty patients included in the study. The age of patients ranged from 9 years to 20 years with an average of 12.5 years. It was found that the mean age of prognosis of diabetes mellitus in these patients was 14.5 years. The insulin dose used by patients in this study group was 1U/kg/day. The frequency of dyslipidemia in this study came out to be 72% in comparison to the control group where the dyslipidemia rate was 31%. The fasting serum glucose level of these patients with or without dyslipidemia was also measured with results showing significant difference in the fasting glucose level of both groups, where abnormal levels of glucose were found in the dyslipidemia group. The levels of TC, LDL-C and TG were significantly higher in the study group while the levels of HDL-C were found to be lower[11]. In another study where the hypercholesterolemia was studied for its relation with diabetes mellitus it was observed that in most of the patients of hypercholesterolemia there was higher rate of LDL-C and lower rate of HDL-C in these patients. There were 23% patients with lower HDL-C and 24% patients with higher LDL-C. There were 6% patients that reported about both of these abnormal collectively[12]. It was found as per study that in case of dyslipidemia patients there was an elevated level of LDL in the patients (76%). Either this elevated level was isolated or present in combination of other abnormalities as well. The diabetes dyslipidemia case rate was found to be 3% in this study. According to a study the clinical features of diabetes in both groups (dyslipidemia and normal patients) which includes insulin dosage, duration of diabetes mellitus, age of patients, and age at the onset of DM was taken from the history and analyzed. It was found that no significant variations between the two groups related to family history of DM and cardiovascular diseases was found. The average BMI and WC showed significant differences in both study and control group as the values came out to be 0.024 and 0.015 respectively[13]. As per the study glycemic control of the participating patients was evaluated and comparison was done between study group and control group. The mean fasting and postprandial glucose level was checked for patients for a period of one month and the results showed that the diabetes mellitus 1 was found to be more common in patients that had familial hypercholesterolemia as the glycemic control of dyslipidemia group was poor as compared to the control [14].

Table 1: Studies to find the relation of familial hypercholesterolemia and type 1 Diabetes mellitus

Reference	Features	Study group	Control group
15	BMI (kg/m^2)	22.3	19.1
	Total cholesterol (mg/Dl)	245	<170
	Fasting Blood sugar level (mg/Dl)	130.2	< 99
	Post prandial blood glucose level (mg/Dl)	182	145.3
16	BMI (kg/m^2)	21.4	18.6
	Total cholesterol (mg/Dl)	236	<170
	Fasting Blood sugar level (mg/Dl)	151	< 99
	Post prandial blood glucose level (mg/Dl)	183.2	138.9
17	BMI (kg/m^2)	22.3	19.4
	Total cholesterol (mg/Dl)	225	<170
	Fasting Blood sugar level (mg/Dl)	145	< 99
	Post prandial blood glucose level (mg/Dl)	220	145.3

The data from above studies shows that there exists a link between type 1 diabetes mellitus and familial hypercholesterolemia. The BMI in case of study group (22.3 $kg/m^{2)}$ was found to be high as compared to the control group (19.1 $kg/m^{2)}$ as shown in the study of table no.1 [15.] The cholesterol level was high in the study group as the patients were suffering from dyslipidemia (245 mg/Dl) as compared to the control group. The patients also showed diabetes as the fasting and post prandial blood glucose levels were high as compared to the control (130.2, 182 mg/Dl) respectively. Similarly, another study reported about total cholesterol as 236md/Dl and the fasting blood glucose level was 151 mg/Dl which further shows the relation between familial hypercholesterolemia and diabetes mellitus 1.

DISCUSSION

This study emphasis on the significant link between diabetes mellitus 1 and hypercholesterolemia. As per studies diabetes

mellitus is more frequently reported among children and adolescents[18]. A study describes that almost 65% cases of type 1 diabetes mellitus includes patients of dyslipidemia. The most common and frequently found type of dyslipidemia has elevated levels of LDL-C and a comparatively low levels of HDL-C in case of children. While for adults it was found that both LDL-C and HDL-C were abnormally present [19]. In the studies described above the patients reported about diabetes symptoms and the fasting blood glucose level of patients was higher as compared to the control. The post prandial blood glucose level was also calculated and it came out to be (245, 236 and 225 mg/Dl) respectively[15,16,17]. The patient's cholesterol level was also found to be abnormally high. As per reports the hypercholesterolemia was found to be the cause of high blood glucose level. As per studies the hypercholesterolemia is frequently found among patients of diabetes mellitus while hyperglyceridemia cases were not as such reported among diabetes patients. Studies have shown that female cases were significantly observed among hyperlipidemia group as compared to male patients. In the above studied reports the duration of diabetes had no link with the hypercholesterolemia. Hypercholesterolemia patients were found to be obese with BMI higher than the usual, obesity is one significant cause of diabetes mellitus, and therefore higher BMI was also taken into consideration for analysis. In the above study the BMI in case of study group (22.3 $kg/m^{2)}$ was found to be high as compared to the control group (19.1 $kg/m^{2)}$ as shown in the study of table no.1 [15]The activity of the patient was also analyzed and it was found that dyslipidemia group patients showed quite less activity as compared to control group which further adds to the point that physical activity and dyslipidemia are potentially linked to each other. The daily calorie intake and intake of dietary fats was also found to be high in study group which adds to the obesity, higher BMI[20-23]. Less physical activity, higher BMI value and obesity are some of the areas that link hypercholesterolemia with diabetes mellitus 1. Therefore, it is advised to have metabolic control to treat hyperlipidemia.

CONCLUSION

Familial hypercholesterolemia is significantly linked with type 1 diabetes mellitus and is more common among children and adolescents. Dyslipidemia is more frequently reported among female patients. Less physical activity, higher BMI, obesity and high average waist circumference are some of the attributes that links hypercholesterolemia with diabetes mellitus type 1. The most of the patients of dyslipidemia shows elevated LDL-C and low HDL-C.

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