Original Article

Is There an Association between Type 1 Diabetes in Children and Gallbladder Stones Formation?

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ABSTRACT

Background and Aims: A number of studies in adults have evaluated the prevalence of gallstones in the diabetic population and showed a significant association with type 1 diabetes (T1D) and type 2 diabetes. The pediatric literature is limited to a single small case series. We conducted a cross-sectional study to evaluate for the presence of association between T1D in children and gallstones formation. **Patients and Methods:** Children diagnosed with T1D in a diabetic clinic have been examined for existence of gall bladder stone formation from November 2008 through November 2009. All have been subjected to the following: History, physical examination, blood tests (liver function tests, lipid profile, glycosylated hemoglobin [HbA1C]), and an ultrasound (US) of the gall bladder. **Results:** One hundred and five children with T1D have been enrolled consecutively over a 1-year period: age ranged between 8 months and 15.5 years, 62 patients were females. The mean age at diagnosis was 6.3 ± 2.9 years (range 0.85-11 years), mean duration of T1D was 2.2 ± 2.1 years (range 0.2-8 years), mean body mass index was 16.5 ± 3.4, mean HbA1c was 10.7 ± 2.4%, and 61.3% of patients had a HbA1c level >10%. The mean serum cholesterol was 4.16 ± 0.75 mmol/L (normal 3.65-5.15 mmol/L) and mean serum triglyceride 1.02 ± 1.3 mmol/L (normal 0-1.7 mmol/L). Two patients had hyperlipidemia. US of the gallbladder did not show any case of gallstones or sludge formation. **Conclusion:** Data from our study do not show any association between T1D in children and gallstones formation, with diabetes duration of less than 8 years. The relatively short duration of diabetes and possibility that our study was underpowered might have been reasons for the absence of any association.

Key Words: Child, gall stones, Saudi Arabia, type 1 diabetes, ultrasound

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Type 1 diabetes (T1D) is a disorder of glucose metabolism that results from insulin deficiency secondary to autoimmune destruction of insulin secreting β cells. The resulting hyperglycemia commonly leads to alterations in the function of several organs in the human body such as the kidneys, eyes, nerves, gastrointestinal, and hepato-biliary organs. A number of studies in adults have evaluated the prevalence of gallstones in diabetic population and showed a significant association,[1-6] however, this has not been a consistent observation.[7-9] The pediatric literature is limited to a single small case series of 20 children with T1D, which showed preserved gallbladder function and no association between T1D and gall stone formation.[10] We conducted a cross-sectional study on a relatively larger number of children with T1D to answer the question: Is there an association between T1D in children and gallstones formation?

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PATIENTS AND METHODS

Children with T1D being who are followed in the diabetes clinic in our tertiary care center were consecutively enrolled into the study. Children and their parents who have attended the diabetic clinic at the Children's Hospital–King Saud Medical City, over the period from November 2008 through November 2009, and had accepted entry into the study, had been interviewed by the researchers and a consent was obtained. Diabetic children with a hemolytic condition or on drugs pre-disposing to gallstone formation (e.g., diuretics, ceftriaxone, octreotide) had been excluded. Children and their parents had been interviewed by co-investigators to collect data about demographics, duration of diabetes,

hepatobiliary symptoms (jaundice, biliary colic). Heights and weights have been measured by the clinic's nurses and plotted on a sex and age appropriate growth chart and body mass index (BMI) was calculated (kg/m^2). BMI ≥ 95th centile for age and sex defines obesity. All patients underwent assessment for clinical evidence of peripheral neuropathy by examining deep tendon reflexes (Achilles' and patellar tendon reflexes) and vibration sensation (application of a tuning fork to the wrist and ankle joints).

Blood has been collected for: Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase, gamma glutamyl transferase, total bilirubin, total protein and albumin, glycosylated hemoglobin (HbAIc), and fasting lipid profile (Hypercholesterolemia was defined as a serum cholesterol >5.15 mmol/L and hypertriglyceridemia was defined as a serum triglyceride >2.2 mmol/L). Liver ultrasound (US) was performed by a single senior pediatric radiologist, after 4 h of fasting. US was performed using a 3.5-7.5 MHz curvilinear transducer on Aloka prosound SSD 4000. The radiologist was blind to the clinical data of the patients.

RESULTS

Over the 1-year study period, 106 children with T1D were investigated. One patient with β-Thalassemia major and T1D was excluded. Table 1 shows the demographic, clinical, and laboratory characteristics of the 105 patients. Age ranged between 8 months and 15.5 years with a median of 9 years, 62 were females and 43 males. Median age at diagnosis was 7 years (range 0.85-11 years). The median duration of T1D was 2 years (range 0.2-8 years). Seven patients were enrolled within the first 6 months after diagnosis of diabetes. None of the patients had clinically evident autonomic neuropathy. Mean HbA1c was 10.7 ± 2.4%, and 61.3% of our cohort group had a HbA1c level more than 10%. Mean serum cholesterol was 4.16 ± 0.75 mmol/L (normal 3.65-5.15 mmol/L) and the mean serum triglyceride was 1.02 ± 1.3 mmol/L (normal 0-1.7 mmol/L). BMI was 16.5 ± 3.4. Two patients were obese. Only one child had hypercholesterolemia (serum cholesterol of 6.2 mmol/L) and another one had hypertriglyceridemia (serum triglyceride 3.5 mmol/L). None of the patients had elevated liver enzymes. US of the liver did not identify any single case of gallbladder stone or sludge formation.

Table 1: Clinical and laboratory characteristics of 105 children with type 1 diabetes

Variable	Patients (*n*=105) Mean±SD
Age (year)	8.5±2.8
Gender (female/male)	62/43
Age at diagnosis of T1D (year)	6.3±2.9
Duration of diabetes (year)	2.2±2.1
Body mass index (kg/m^2)	16.5±3.4
HbA1c (%)	10.7±2.4
Serum cholesterol (normal 3.65-5.15 mmol/L)	4.16±0.75
Serum triglyceride (normal 0-1.7 mmol/L)	1.02±1.3

HbA1c: Glycosylated hemoglobin, T1D: Type 1 diabetes

DISCUSSION

It is widely believed that gallstones occur more frequently in patients with type 2 diabetes and T1D than in the general population,[1-6] but this has not been borne out in all reports.[7-9] Chapman *et al*., screened a large population of diabetic patients and found a higher prevalence of gall stones in diabetic patients than controls (33% vs. 21%; $P < 0.001$). The prevalence of gall stones was higher in patients with type 2 than type 1 DM.[1] Hayes *et al*., found no differences in glycemic control (HbA1C) between diabetics with and without gallstones.[7] Thus, it seems that the prevalence of gall stones could be related to the type of diabetes and/or presence of certain potential confounders like obesity. Type 2 diabetes is usually found in obese individuals and obesity is a well-established major risk-factor for developing gallstones,[11] the basis being an increased hepatic secretion of cholesterol. Patients with type 2 diabetes have elevated plasma insulin levels; elevated insulin increases the saturation of bile by decreasing bile salt secretion or by abnormally uncoupling cholesterol and its solubilizing lipids in the fasting state.[12] Impairment of gall bladder emptying is another contributing factor for gallstones formation in diabetic subjects especially, in those patients with autonomic neuropathy.[13] Impaired post-prandial gall bladder contraction may result from either reduced cholecystokinin (CCK), which is a major humoral factor for gall bladder contraction, impaired CCK secretory capacity in the jejunum, or reduced sensitivity of the gall bladder to CCK.[13-15]

Neurotoxicity of the autonomic nervous system, secondary to longstanding hyperglycemia, is thought to be responsible for the gastrointestinal effects of diabetes.[16,17] Autonomic neuropathy increases with age and duration of diabetes mellitus. Therefore, diabetes mellitus in the first two decades of life is generally expected to be free of chronic micro-vascular and neuropathic complications, especially, the clinically apparent ones. However, there is increasing evidence from the pediatric literature of occurrence of diabetes related complications during childhood, including those related to the autonomic nervous system, even with short disease duration.[18] It has also been suggested that acute hyperglycemia, independent of autonomic neuropathy, impairs gastrointestinal motility.[16,17] Data

from our study, refute any association between T1D and gall stones formation despite that majority of our patients had poor glycemic control (61.3% of patients had HbA1C >10%). The rarity of obesity and hyperlipidemia, and absence of clinically evident peripheral neuropathy may have contributed to the absence of gall stone formation in our cohort group. Furthermore, insulin deficiency in T1D might have a protective role against formation of gall stones.[12] Our data are in agreement with the data reported by Arslanoğlu *et al.*,[10] that showed no association between T1D and gall stones in a small cohort of 20 children with T1D, with mean duration of diabetes of 3.1 ± 2.7 years. However, the significantly dilated gallbladder during fasting in diabetic children compared to controls led the authors to conclude that this finding could be an early sign of gastrointestinal autonomic neuropathy and a risk-factor for gall stone formation.[10]

The relatively short duration of diabetes in our study (2.2 ± 2.1 years) might have been a reason for absence of association between T1D and gall stone formation. Autonomic neuropathy increases with age and duration of diabetes mellitus. Therefore, diabetes mellitus in the first two decades of life is generally expected to be free of chronic micro-vascular and neuropathic complications, especially, the clinically apparent ones. The mere performance of deep tendon reflexes and vibration sensation cannot confirm or exclude the diagnosis of peripheral neuropathy. The diagnosis of peripheral neuropathy requires the performance of clinical diabetic neuropathy score supported by nerve conduction study, a procedure that we have not carried out, which is another limitation in our study. Although, our sample size is 5 times more than the number of patients included in the single pediatric study (20 patients),[10] it is still possible that our study was not powered enough to detect any association. The lack of data on prevalence of gall stones formation in pediatric T1D has precluded accurate estimation of adequate sample size.

CONCLUSION

We could not find any association between T1D in children and gallstones formation, at least with diabetes duration of less than 8 years. Large, prospective, controlled studies on type 1 diabetic children with long duration of diabetes are needed to make a conclusive statement on association between T1D and gallstone formation.

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