Prevalence of dyslipidemia in adults with cystic fibrosis☆

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Abstract

Background: A high fat calorie diet is advocated for patients with cystic fibrosis (CF) however the lipid profiles of individuals with CF, including those with CF-related diabetes (CFRD), are not well studied.

Methods: We conducted a retrospective review of adult CF patients attending St Michael’s Hospital between January 2005 and December 2007.

Results: 334 patients (77% pancreatic insufficient (PI)) were included in the study. Mean HDL cholesterol was significantly lower in males (p<0.0001) with 44% of males having HDL cholesterol <38.7 mg/dL (1 mmol/L). Pancreatic sufficient patients were more likely than PI subjects to have total cholesterol ≥201 mg/dL (5.2 mmol/L) (p<0.01). 5% of subjects had triglyceride concentrations ≥195 mg/dL (2.2 mmol/L). Diabetes was diagnosed in 23% of subjects. Lipid profiles were similar between diabetics and non-diabetics. Total cholesterol and triglycerides both increased with increasing age and increasing BMI (p<0.01).

Conclusion: Dyslipidemia occurs in CF patients however no differences in lipid profiles were seen between those with diabetes and those without. Fasting lipids should be monitored in CF patients, particularly those with PS, older age, and high BMI. As survival in CF increases, the prevalence of dyslipidemia may increase resulting in clinically important complications.

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1. Introduction

The life expectancy of patients with cystic fibrosis (CF) has improved dramatically with median survival now over 37 years of age [1]. A high fat, high calorie diet is a long-established and integral part of CF management, particularly for pancreatic insufficient (PI) patients. This dietary regimen, in association with pancreatic enzyme supplementation, helps satisfy the dietary requirements of CF patients. However, it has been shown that even with enzyme supplementation, fat and fat-soluble vitamins are still malabsorbed [2]. It has previously been reported that CF patients have lower total cholesterol than the non-CF population despite their diet [3,4]. This is presumed to be secondary to decreased exogenous lipid absorption, however the effects of a high fat diet on overall lipid profiles in the adult CF population is not known. In the non-CF population, a high fat diet is associated with the development of dyslipidemia, which is a well-recognized risk factor for atherosclerotic disease [5]. The prevalence of ischemic heart disease in the CF population is reported to be lower than the general population [6]. A high fat, high calorie diet was first introduced in the Toronto CF clinic in the early 1970s [7] therefore many patients have now lived with this diet for over 40 years. As life expectancy for those with CF continues to improve, the repercussions of this diet on parameters other than nutritional markers and vitamin status need to be examined.

Also related to improved life expectancy of CF patients, CF-related diabetes (CFRD) has become a more frequent long-term
complication of CF [1]. Prevalence of CFRD (with or without fasting hyperglycemia) is associated with advancing age, affecting 35% of adults in their twenties and 43% of adults over the age of 30 [8]. Insulin resistance in the general population is associated with dyslipidemia, with the most common pattern being hypertriglyceridemia, low HDL cholesterol and normal LDL cholesterol [9], however the effect of CFRD on lipids is unclear. CFRD differs from both type I and type II diabetes in that it is a combination of insulin deficiency, as well as peripheral and hepatic insulin resistance [8,10]. Microvascular complications are well described in CFRD and appear to be related to time with the disease and diabetic control [11]. The lack of published literature on macrovascular complications has been hypothesized to be, at least in part, related to the presumed favorable lipid profile in CF, however the shorter life span may also be limiting this potential longer-term complication.

In this study we aim to characterize lipid profiles in a large cohort of adult CF patients and to identify potential subgroups at increased risk for dyslipidemia [12].

2. Subjects and methods

We conducted a retrospective cross-sectional review of adult CF patients attending St Michael’s Hospital between January 2005 and December 2007. Relevant data had been prospectively entered into the Toronto CF database during this period. All patients in whom a fasting lipid profile was measured during this period were included. If patients underwent double lung transplantation, subsequent lipid results were excluded from analysis. All included patients fulfilled the CF Foundation consensus criteria for the diagnosis of CF [13]. Patients provided informed written consent for their data to be submitted to the Toronto CF Patient Data Registry. The Research Ethics Board at St. Michael’s Hospital approved the study.

2.1. Predictor variables

Age, gender, BMI, forced expiratory volume in 1 second (FEV1), CFRD status and pancreatic status were documented for all patients on the same day that the lipid measurements were carried out. FEV1 percent predicted was calculated using the Hankinson equation [14]. Pancreatic status was determined by reviewing pancreatic enzyme usage, previous trypsinogen levels and fecal fat collection results.

Oral glucose tolerance tests (OGTT) were performed yearly on all CF patients without a diagnosis of CFRD. CFRD was defined as persistently elevated blood sugars and/or positive OGTT in a stable state of health where the final outcome was initiation of medical treatment for diabetes. OGTT was performed according to the 1999 Consensus Conference Report on CFRD [15]. The fasting plasma glucose (FPG) and 2-h plasma glucose (2hPG) was measured after an oral glucose load of 1.75 g/kg body weight (maximum 75 g). Patients were classified into glucose tolerance categories according to the OGTT results: normal glucose tolerance (NGT) if FPG<126 mg/dL (7.0 mmol/L) and 2hPG below 141 mg/dL (7.8 mmol/L); impaired glucose tolerance (IGT) if FPG<126 mg/dL (7.0 mmol/L) and 2hPG between 141 and 200 mg/dL (7.8 and 11.1 mmol/L); CFRD without fasting hyperglycemia (FH) if FPG<126 mg/dL (7.0 mmol/L) and 2hPG>200 mg/dL (11.1 mmol/L); and CFRD with FH if FPG>126 mg/dL (7.0 mmol/L) and 2hPG>200 mg/dL (11.1 mmol/L). In general, patients with IGT or CFRD with and without FH on an OGTT went on to have home glucose monitoring. Those with persistently elevated blood sugars proceeded to treatment at the discretion of the treating physician. Most individuals who started treatment had CFRD with FH. The majority of CFRD patients commenced insulin therapy however a small number were treated with oral hypoglycemic medications.

2.2. Outcome variable

Fasting lipid profiles were carried out annually as part of routine care. If subjects had more than 1 lipid profile done within the study time period, the lipid profile containing the most complete lipid parameters was chosen for the study. Lipid analysis was performed with either the Beckman Coulter Unicel DxC 600 or the Beckman Coulter LX20 analyzer. Cholesterol and triglycerides were analyzed using enzymatic methods. LDL cholesterol was calculated using the Friedewald equation [16]. Hyperlipidemia cut-off points were determined using recommendations from the National Cholesterol Education Program [17] and Canadian Recommendations for the Management of Dyslipidemia 2003 [18]. The Canadian recommendations use the total/HDL cholesterol ratio as well as LDL cholesterol to provide target lipid ranges dependent on cardiovascular (CV) risk. The total/HDL cholesterol ratio has a greater predictive value for CV risk than individual lipid parameters alone in the general population, with a ratio of <4.0 recommended for those at high risk of coronary artery disease or those with a history of diabetes.

2.3. Statistics

Descriptive statistics for continuous variables are given as means±standard deviations (SD) unless otherwise indicated. Categorical variables were analyzed using Fisher’s exact test. Student’s t test was used to compare mean values between 2 groups for continuous variables. Parametric and non-parametric testing was carried out to ensure consistent results. p-values of <0.05 are reported as significant in the results. Statistical analysis was performed with SAS software (version 9.1; SAS Institute Inc, Cary, NC).

3. Results

Baseline descriptive characteristics of the subjects are given in Table 1. Out of the 334 subjects with fasting lipid profiles, 328 (98%) had total cholesterol (TC) results, 326 (98%) had triglyceride results and 170 (51%) had HDL cholesterol, LDL cholesterol and Total/HDL cholesterol ratio results. The included subjects represented 90% of our clinic population. Males and females had similar demographics except that females had lower BMI (21.6±3.6 vs. 23.0±3.7 kg/m², p<0.01). Lipid results according to gender are shown in Table 2. The majority of mean
lipid values when evaluated by gender were within optimal limits as suggested by national guidelines. The notable exception was mean HDL cholesterol for males, which was below the recommended target minimum of 38.7 mg/dL (1 mmol/L) and significantly lower than females (37.5 ± 10.8 mg/dL (0.97 ± 0.28 mmol/L) vs. 46.8 ± 14.7 mg/dL (1.21 ± 0.38 mmol/L), p < 0.01). Furthermore, a significantly greater proportion of males compared to females had HDL cholesterol < 38.7 mg/dL (1 mmol/L) (44% vs. 23% respectively, p = 0.004).

3.1. Pancreatic status and lipids

Subjects were categorized by pancreatic status with 77% being PI. PS subjects were significantly older than PI subjects (38.2 ± 11.9 vs. 29.2 ± 8.8 years, p < 0.0001) with higher BMI (24.7 ± 4.5 vs. 21.7 ± 3.1 kg/m², p < 0.0001). PI subjects had significantly lower TC (138 ± 34 vs. 172 ± 36 mg/dL (3.56 ± 0.87 vs. 4.45 ± 0.94 mmol/L), p < 0.0001) and LDL cholesterol (74 ± 21 vs. 104 ± 27 mg/dL (1.91 ± 0.55 vs. 2.68 ± 0.71 mmol/L), p < 0.0001) compared with PS subjects. HDL cholesterol was slightly lower in PI patients (40 ± 12 vs. 46 ± 16 mg/dL (1.04 ± 0.32 vs. 1.19 ± 0.41 mmol/L), p = 0.04) but total/HDL cholesterol ratio was also significantly lower than PS patients (3.52 ± 0.98 vs. 4.02 ± 1.06, p = 0.02). A significantly higher percentage of PS subjects was found to have TC, LDL cholesterol, and total/HDL cholesterol above the optimal target range compared to PI patients (Table 3). Twenty percent of PS patients had TC > 201 mg/dL (5.2 mmol/L) and 57% had LDL cholesterol > 97 mg/dL (2.5 mmol/L). Notably, some PI subjects also had elevated lipid profiles, albeit in smaller numbers than PS patients. Despite the age difference between the 2 groups, TC, LDL cholesterol and total/HDL cholesterol results remained significantly different between the PI and PS subjects after correcting for sex and age.

3.2. CFRD and lipids

There were 77 (23%) subjects with CFRD. This group was compared to the PI patient group without CFRD (n = 181). PS subjects were excluded from this analysis as no PS subjects had CFRD. CFRD subjects were older (32 ± 10 vs. 28 ± 8 years, p = 0.005) with lower mean FEV1% predicted (50 ± 23 vs. 58 ± 20 %, p = 0.01) but similar BMI. No statistically significant difference was found in lipid profiles between CFRD and non-CFRD PI patients and the proportion of subjects with lipid levels above optimal targets did not differ between the two groups (Table 4).

3.3. BMI, age and lipids

TC and total/HDL cholesterol ratio all increased with increasing BMI (p < 0.001) and this trend remained significant (p = 0.01) after excluding PS subjects. On subgroup analysis of male PI subjects, we found the higher the BMI the more likely they were to have a total/HDL cholesterol ratio > 4 (p = 0.01). Fifteen male PI subjects with a BMI > 26 kg/m² had total/HDL cholesterol tested and 8 of these subjects (53.3%) had a ratio > 4 compared to 14.0% (6/43 subjects) of those with a BMI < 22 kg/m². In all subjects, and after excluding PS patients, TC and LDL cholesterol levels increased with increasing age (both p < 0.01).

3.4. Triglycerides

Sixteen percent of all subjects had triglycerides > 150 mg/dL (1.7 mmol/L) and 5% had triglycerides > 195 mg/dL (2.2 mmol/L). Triglycerides were not significantly higher in

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Table 1
Baseline characteristics for subjects (n = 334).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31 ± 10</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>59 ± 22</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>59</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.4 ± 4</td>
</tr>
<tr>
<td>CFRD (%)</td>
<td>23</td>
</tr>
<tr>
<td>PI (%)</td>
<td>77</td>
</tr>
</tbody>
</table>

Values are mean ± SD unless otherwise stated.

Table 2
Gender differences in lipid profiles.

<table>
<thead>
<tr>
<th>Variable (mg/dL)</th>
<th>Female</th>
<th>Male</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>154 ± 37.5</td>
<td>140 ± 36</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>97 ± 56</td>
<td>95 ± 57</td>
<td>0.8</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>47 ± 15</td>
<td>37 ± 11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>83 ± 26</td>
<td>80 ± 26</td>
<td>0.4</td>
</tr>
<tr>
<td>Total/HDL cholesterol¹</td>
<td>3.39 ± 0.96</td>
<td>3.85 ± 1.12</td>
<td>0.004</td>
</tr>
</tbody>
</table>

To convert mg/dL to mmol/L for TC, HDL, LDL multiply by 0.0259; for TG multiply by 0.0113.

Values are mean ± SD unless otherwise stated.

¹ Ratio has no units.

Table 3
Percentage of subjects with elevated lipid values, by pancreatic status.

<table>
<thead>
<tr>
<th>Variable (mmol/L)</th>
<th>PI</th>
<th>PS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>4</td>
<td>20</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>14</td>
<td>18</td>
<td>0.4</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>14</td>
<td>57</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>52</td>
<td>41</td>
<td>0.3</td>
</tr>
<tr>
<td>Total/HDL cholesterol &gt; 4*</td>
<td>24</td>
<td>43</td>
<td>0.03</td>
</tr>
</tbody>
</table>

To convert mg/dL to mmol/L for TC, HDL, LDL multiply by 0.0259; for TG multiply by 0.0113.

* Ratio has no units.

Table 4
Percentage of pancreatic insufficient subjects with elevated lipid values, by CFRD status.

<table>
<thead>
<tr>
<th>Variable (mmol/L)</th>
<th>CFRD</th>
<th>Non-CFRD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>5</td>
<td>4</td>
<td>0.7</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>19</td>
<td>12</td>
<td>0.2</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>20</td>
<td>11</td>
<td>0.2</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>57</td>
<td>49</td>
<td>0.5</td>
</tr>
<tr>
<td>Total/HDL cholesterol &gt; 4*</td>
<td>24</td>
<td>23</td>
<td>0.8</td>
</tr>
</tbody>
</table>

To convert mg/dL to mmol/L for TC, HDL, LDL multiply by 0.0259; for TG multiply by 0.0113.

* Ratio has no units.
PS subjects or those with CFRD. Triglycerides increased with increasing age (p<0.008) and increasing BMI (p < 0.0001). Male PI subjects with higher BMI were more likely to have triglycerides >150 mg/dL (1.7 mmol/L) compared to those with lower BMI (p<0.01). Of the 26 male PI subjects with a BMI>26 kg/m², 9 subjects (34.6%) had an elevated triglyceride concentration compared to only 9.7% of those with a BMI of 19–22 kg/m². None of the 24 male PI subjects with a BMI<19 had elevated triglycerides.

4. Discussion

This study examines the lipid profile of a large cohort of adults with CF and evaluates the association between lipid abnormalities and pancreatic and CFRD status. We found that PS subjects were more likely to develop dyslipidemia compared to PI subjects, specifically elevated TC, LDL cholesterol and total/HDL cholesterol. In PI subjects, TC, LDL and HDL cholesterol tended to be lower, however in 24% of subjects total/HDL cholesterol was >4. Increasing age and BMI were associated with elevated total/HDL cholesterol ratios in PI subjects. There were no differences in lipid profiles between those with CFRD and those without, even once PS subjects were excluded.

Previous investigators have reported lower serum TC concentrations in the CF patient population compared to the general population [3,4]. Figuero et al. reported a high prevalence of hypertriglyceridemia in their CF clinic population, with 16% of patients having triglycerides >195 mg/dL (2.2 mmol/L) [3]. In the current study 16% of subjects had triglycerides >150 mg/dL (1.7 mmol/L), but only 5% of subjects had triglycerides >195 mg/dL (2.2 mmol/L). The reason for this difference in prevalence of hypertriglyceridemia between these patient populations is unclear. The study population in the Figuero study included children as well as adults and had higher FEV1 than our patient population. However, they found no correlation between age or lung function in their study, suggesting that these factors are not an adequate explanation for the observed differences in prevalence of hypertriglyceridemia.

4.1. Association between gender and lipid profiles

Male subjects had lower HDL cholesterol compared to females in the current study. The gender difference with HDL cholesterol may be explained, at least partially, by the actions of estrogen. Estrogens are known to have profound effects on cholesterol metabolism in the non-CF population [19,20]. Estrogens increase HDL cholesterol by augmenting the secretion of apoA-I and also reduces HDL breakdown by reducing hepatic lipase activity [21]. HDL cholesterol has also been shown to have other properties including immune system regulation, anti-inflammatory, antioxidant, antithrombotic and antivasospastic effects [22]. ApoA-I and apoA-2 are the major apolipoproteins of HDL cholesterol with higher ApoA-1 protective against CV disease [23]. Given the low incidence of cardiovascular disease in the CF population despite low HDL cholesterol, further investigation of apolipoproteins levels in CF may prove of interest.

4.2. Potential explanations for dyslipidemia in CF

Lower lipid values seen in PI subjects in the current study could be explained by decreased exogenous lipid absorption. PI patients are known to malabsorb dietary fat despite adequate intake of pancreatic enzymes [2]. This is due to either incomplete intraluminal solubilization or reduced intestinal mucosal uptake of long-chain fatty acids [2]. Furthermore, chronic inflammation seen in CF may play a role in dyslipidemia [3]. Pro-inflammatory cytokines such as TNF-α are elevated in CF and are known to inhibit lipoprotein lipase activity and stimulate hepatic lipogenesis [24]. Levy et al. [4] showed a strong positive correlation between serum TNF-α and plasma triglycerides in CF adolescent patients. An alternate explanation for abnormal serum lipids in CF is dysfunction of the CF transmembrane conductance regulator (CFTR). Tissues deficient in CFTR have altered levels of fatty acids, with an increased ratio of arachidonic acid to docosahexaenoic acid. In addition, cultured epithelial cells from animal CF models show abnormal intracellular accumulations of unesterified cholesterol [25]. White et al. also reported increased levels of plasma membrane cholesterol and abnormal intracellular cholesterol trafficking in an in vitro CF cell model. Abnormalities in fatty acid profiles are seen in vivo in both PI and PS CF patients, but also in heterozygote parents of CF patients [26]. These findings suggest that mutations in CFTR may directly alter fatty acid metabolism.

The significant differences in lipid concentrations comparing PI and PS patients seen in the current study suggest that these differences could at least partly be explained by impaired lipid absorption. Prospective studies are required to confirm this suggestion and evaluate the contribution of the other potential mechanisms discussed.

4.3. Relevance of dyslipidemia with regards to cardiovascular risk in CF adults

In the non-CF population, low HDL and elevated total/HDL cholesterol ratio are independent predictors of cardiovascular disease [27]. However CF patients, despite their high fat, high calorie diet and high prevalence of CFRD, are yet to demonstrate an increased cardiovascular risk during their lifetime. Microvascular disease is seen in patients with CFRD, although to a lesser degree than in the non-CF diabetic population [11]. There have been individual case reports of CF adults with ischemic heart disease, but these reports are infrequent [6].

This apparent lack of significant atherosclerotic disease could be explained the low proportion of patients who survive into their fifth and sixth decades, when the incidence of cardiovascular disease is at its peak in the non-CF population. Another potential explanation is the finding by previous investigators that the majority of patients have normal or below normal levels of serum total cholesterol [3]. Indeed we have confirmed in the current study that the majority of PI patients have favorable lipid profiles. However, we have demonstrated that a considerable proportion of PS patients have elevated total cholesterol and total/HDL cholesterol ratios, which may increase their lifetime cardiovascular risk. It should
be mentioned that the proportion of CF patients who are PS may increase as more patients with milder disease are detected by newborn screening. In addition, CF infants born in the year 2000 are projected to have median survival of 50 years [28]. CF adults may therefore have higher prevalence of cardiovascular disease over coming decades.

4.4. Limitations

The retrospective study design limits the conclusions; however, the large sample size includes a wide range of disease severity increasing the generalizability of the results. Only 51% of our study population had HDL and LDL cholesterol levels measured, although this population did not differ in characteristics from the overall study group. Medications that could interfere with lipid profiles were not recorded for the study. However, less than 1% of our patients take prescription lipid-lowering therapy therefore it is unlikely that this affected the results. An important limitation in detecting the effect of CFRD on lipids relates to our definition of CFRD. Our definition provided a diagnostic cut-off point between CFRD and non-CFRD whereas blood sugar control in CF is more a fluctuating spectrum of degrees of glucose intolerance. Patients labeled as non-CFRD may have had a degree of glucose intolerance not captured with the present study. Furthermore, lipid profiles in CFRD patients may indeed be different than their non-CFRD counterparts but this may have been obscured by not taking into consideration the duration of disease.

4.5. Conclusions

Management of dyslipidemia in the CF population requires a different approach to the non-CF population, since a life-long high fat, high calorie diet is recommended. As prognosis of CF improves, the median age of the patient population will increase. We expect that this will result in higher prevalence of dyslipidemia in the CF patient population, which may translate into higher prevalence of cardiovascular disease. If this is the case, assessment and treatment of dyslipidemia, combined with monitoring of other cardiovascular risk factors, will become more relevant over the coming decades.

References