Original article

Normal adiponectin levels despite abnormal glucose tolerance (or diabetes) and inflammation in adult patients with cystic fibrosis

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Abstract

Rationale. – Circulating adiponectin levels are negatively associated with glucose intolerance, inflammation and central adiposity. Since these conditions are common in cystic fibrosis (CF), we examined whether adiponectin values are altered in these patients.

Aim. – To determine if CF patients have altered adiponectin levels and if these levels correlate with glucose tolerance categories (normal, impaired glucose tolerance (IGT) and cystic fibrosis-related diabetes (CFRD)), insulin resistance or inflammatory markers such as fibrinogen and C-reactive protein (CRP).

Methods. – Oral glucose tolerance tests (OGTTs) were performed and adiponectin levels were measured in 90 CF patients not known to be diabetic and 15 healthy controls matched for age, sex and body mass index (BMI). Inflammatory markers, serum albumin concentrations and the clinical status of CF patients (i.e. pulmonary function) were also examined.

Results. – CF pathology was characterized by a high prevalence (43.5%) of glucose tolerance abnormalities: 26.5% of IGT and 17.0% of newly diagnosed CFRD. CF patients also presented systemic inflammation as revealed by a significant increase of fibrinogen (P = 0.029) in all patients and higher CRP levels in CFRD patients compared to the controls (P < 0.05). On the other hand, CF and control subjects had similar albumin serum concentration. While CF patients and controls had similar serum adiponectin values, women had significantly higher hormone levels than men (P < 0.001). Adiponectin levels did not correlate with glucose tolerance, inflammatory markers or insulin resistance. On the other hand, they correlated positively with both total and HDL–cholesterol (P < 0.001).

Conclusion. – CF patients did not show any alterations in adiponectin levels despite insulin resistance, glucose intolerance and sub clinical chronic inflammation. Thus, CF appears to be one of the rare conditions in which discordance between adiponectin values and insulin resistance or inflammation is evident.

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Adiponectin, one of the physiologically active polypeptides secreted by adipose tissue, is involved in a number of metabolic processes, including glucose and fatty acid metabolism [1]. Adiponectin increases insulin sensitivity by stimulating fatty acid oxidation and decreasing triglyceride accumulation in skeletal muscles [2,3]. It can also suppress glucose production by the liver [4]. Serum adiponectin levels are reduced in conditions associated with increased risk of cardiovascular disease, such as diabetes and central fat accumulation. Circulating adiponectin is negatively associated with insulin resistance, and decreased levels of the hormone have been found in humans and animal models of obesity and type 2 diabetes [5]. Furthermore, low adiponectin levels have been shown to be a good predictor of diabetes development [6]. Adiponectin concentration is also influenced by energy balance, and a negative correlation between hormone levels and energy intake has been reported in both severely malnourished patients [7] and young healthy subjects [8].

Cystic fibrosis (CF) is an autosomal recessive disease characterized by chronic lung infection as well as chronic malabsorption secondary to pancreatic insufficiency. The disease is associated with weight loss, but coexists with preferential central fat accumulation, chronic low-grade inflammation, insulin deficiency, increased energy expenditure and frequent glucose tolerance abnormalities [9]. Furthermore, diabetes is diagnosed in 40% of adult CF patients, while another 35% have impaired glucose tolerance (IGT). Thus, the CF population represents a group of patients with multiple conditions usually associated with altered adiponectin concentration. Therefore, we evaluated serum adiponectin levels in CF patients and healthy controls matched for age, sex and body mass index (BMI), and characterized for glucose tolerance, insulin resistance and nutritional as well as inflammatory markers.

2. Subjects and methods

2.1. Subjects

Ninety CF patients and 15 controls with normal glucose tolerance (NGT) and matched for age, sex and BMI (kg/m²) participated in this study. The protocol was approved by the Research Ethics Committee of the Centre hospitalier de l’Université de Montréal (CHUM), and all subjects received a signed copy of the written consent form. Male and female CF patients over 18 years of age were included in the study. The exclusion criteria were the presence of exacerbation in the previous month defined by: changes in sputum production (volume, color, consistency), new or increased hemoptysis, cough, increased dyspnea, fatigue or lethargy, fever > 38 °C, anorexia, sinus pain, a 10% decrease in pulmonary function determined by forced expiratory volume in 1 s (FEV₁) from previously recorded values (done every 3 months), intravenous antibiotic treatment, medication or conditions that interfere with glucose metabolism, steroids (oral or intravenous), growth hormone, megace, or pregnancy. Exacerbation was identified on the same day by a trained CF-pneumologist blinded to the metabolic parameters.

2.2. CF status

Pulmonary function was measured by spirometry on the day of the oral glucose tolerance test (OGTT) using FEV₁ (l/s) and predicted %FEV₁ (Medgraphic 1870, St. Paul, MN, USA) as variables. Genotype status was extracted from the medical...
files. Pancreatic insufficiency was defined by current enzyme supplementation.

2.3. OGTT

All subjects underwent a 2-h OGTT. After an overnight fast, they ingested, in less than 5 min, a glucose solution: 1.75 g/kg of body weight to a maximum of 75 g according to American Diabetes Association guidelines [10]. Blood samples were taken at 0, 30, 60, 90 and 120 min to measure plasma glucose and insulin concentrations. Plasma glucose was determined immediately in duplicate with a Glucose Analyzer (Beckman, Fullerton, CA, USA). All new cases of diabetes were confirmed by a second OGTT within 2 months.

2.4. Insulin sensitivity assessment

Insulin sensitivity was evaluated on the basis of insulin and glucose values of the OGTT. We chose the Stumvoll’s index because it has been validated for insulin sensitivity against the golden standard method: euglycaemic hyperinsulinemic clamp [12] and since used in various populations. Moreover, our unpublished data suggest that evaluation of insulin sensitivity using the Stumvoll index, unlike other fasting or post-challenge indices, is well correlated with direct measurement using the euglycaemic hyperinsulinemic clamp in the CF population.

2.5. Biochemical dosages

Insulin levels were measured in duplicate by a radioimmunoassay (Linco Research Inc., St. Charles, MO, USA). Total adiponectin levels were also evaluated using a commercial radioimmunoassay from Linco Research Inc. since at the time of the study no commercial kit were available to evaluate the multiple forms of adiponectin. The inflammatory profile included plasma fibrinogen and C-reactive protein (CRP) concentrations and was determined by nephelometric assay using Beckman (Beckman Coulter Canada Inc., Mississauga, Ont., Canada). Glycated haemoglobin, an index of blood glucose control, was measured by immunoturbidimetric assay using the ADVIA1650 (Bayer Health Care Diagnostics, Toronto, Ont., Canada). Total cholesterol, triglycerides and HDL–cholesterol were measured by enzymatic reaction (ADVIA1650, Bayer Health Care Diagnostics). Biochemical evaluation included albumin, total blood count and routine chemistry.

2.6. Statistical analysis

The data are expressed as mean ± S.D. One-way analysis of variance (Anova) was performed to analyze mean differences among the groups. When significant differences were found, a Tukey post hoc test was used to identify group differences. Significance was accepted at $P < 0.05$.

3. Results

3.1. Characteristics of CF patients

The results are presented for 90 CF patients and 15 healthy controls similar for age and BMI. The characteristics of the CF patients and control subjects are reported in Tables 1 and 2. All control subjects had NGT.

Our cohort of stable CF patients showed a moderate decrease in FEV$_1$, which was more pronounced in cystic fibrosis-related diabetes (CFRD) subjects, and a high prevalence of pancreatic insufficiency (Tables 1 and 2). According to conventional criteria, CF patients were classified into three groups based on their glucose tolerance during the OGTT. As described previously [9], even in a group of CF patients not known to be diabetic, the prevalence of glucose tolerance abnormalities was high (43.5%) [11,13]. Thus, in this cohort, 26.5% of CF patients had IGT while 17.0% presented newly diagnosed CFRD. Compared to the controls, in CF patients, deterioration of glucose tolerance (from NGT to CFRD) was associated with a significant and progressive increase of glycated haemoglobin (HbA1c) and fasting glucose levels, a reduction of fasting insulin concentrations and a degradation of insulin sensitivity (Table 2).

CF was also associated with systemic inflammation, as shown by a significant increase of fibrinogen levels in all CF groups compared to the controls ($P = 0.029$). We also observed higher CRP in the NGT and CFRD group ($P < 0.05$) and a tendency toward increased CRP in the IGT group ($P = 0.07$) versus control subjects. On the other hand, there was no differ-

![Table 1](https://example.com/table1.png)

### Table 1
Physical characteristics of CF patients and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>NGT (56.5%)</th>
<th>IGT (26.5%)</th>
<th>New CFRD (17%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex M/F (N)</td>
<td>8/7</td>
<td>31/20</td>
<td>11/13</td>
<td>8/7</td>
</tr>
<tr>
<td>Age (years)</td>
<td>24.3 ± 4.3</td>
<td>27.5 ± 8.2</td>
<td>29.1 ± 9.2</td>
<td>28.8 ± 8.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.4 ± 9.8</td>
<td>60.5 ± 10.5</td>
<td>61.5 ± 11.3</td>
<td>60.4 ± 12.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.8 ± 1.8</td>
<td>21.5 ± 2.9</td>
<td>22 ± 3.4</td>
<td>20.4 ± 5.3</td>
</tr>
<tr>
<td>Pancreatic enzyme supplementation</td>
<td>0%</td>
<td>80%</td>
<td>82%</td>
<td>100%</td>
</tr>
<tr>
<td>% FEV$_1$</td>
<td>—</td>
<td>69.8 ± 21.1</td>
<td>78.8 ± 21.1</td>
<td>61.0 ± 11.1</td>
</tr>
</tbody>
</table>

Data are presented as mean ± S.D. NGT: normal glucose tolerance; IGT: impaired glucose tolerance; CFRD: cystic fibrosis-related diabetes; FEV$_1$: forced expiratory volume in 1 s.
Adiponectin concentrations were similar in CF patients and controls (Table 2 and Fig. 1), and eliminating one outlier with high adiponectin values in the diabetes group did not alter the results. However, there was a strong gender effect with significantly higher adiponectin levels in women compared to men (P < 0.001; Fig. 1). Previous studies have shown that type 2 diabetes is associated with lower adiponectin levels [5]. However, and as shown in Fig. 1, adiponectin values were similar among different glucose tolerance categories as well as between the controls and CF patients. Adiponectin concentration has also been reported to be inversely correlated with markers of chronic subclinical inflammation and insulin resistance [14]. However, we did not observe any correlation between adiponectin and either CRP or fibrinogen levels, or insulin sensitivity (Fig. 2). Furthermore, in CF patients, adiponectin values were not associated with markers of nutritional status, such as serum albumin concentration, BMI or body weight, nor with pulmonary function (FEV1) (data not shown).

Liver disease, a frequent complication of CF [9], could contribute to elevated adiponectin levels as shown by studies in patients with advanced cirrhosis [16]. The conventional markers associated with hepatocellular injury and biliary tract disorders include aminotransferases (AST, ALT) and gamma-glutamyltransferase (GGT) [17]. As shown in Table 2, the ALT, AST and GGT of CF patients were in the normal clinical range. On the other hand, all CF groups had an increased AST concentration compared to control (P < 0.05) (Table 2). Furthermore, we did not observe any correlation between adiponectin and AST, ALT or GGT levels (data not shown). On the other hand, and as reported previously in other populations [15], there was a positive correlation between adiponectin levels and both HDL and total serum cholesterol concentrations (Fig. 3).

### 4. Discussion

CF patients present numerous conditions that could affect and/or be associated with lower adiponectin concentrations, such as chronic inflammation, central fat distribution and insulin resistance. Because of adiponectin’s role in glucose metabolism [18], alteration of the hormone’s levels could contribute to the glucose abnormalities reported in the CF population. We investigated whether CF status modulated adiponectin levels in a cohort of patients characterized for glucose tolerance, insulin sensitivity and inflammatory profile. The present results demonstrated that there was no significant difference in serum adiponectin concentrations in a stable adult CF population compared to healthy controls. Furthermore, in this cohort,
Adiponectin levels did not correlate with glucose intolerance, insulin resistance, inflammatory markers such as CRP and fibrinogen, or pulmonary function (FEV1). On the other hand, and as established [6], adiponectin levels were significantly higher in women compared to men (Fig. 1) and correlated positively with total and HDL-cholesterol (Fig. 2).

The present work highlighted the already reported high prevalence of glucose intolerance in the CF population (Table 1) [11]. A number of studies have described either normal [19, 20], reduced [21–25] or increased [26,27] insulin sensitivity in CF patients. The differences between these various studies may be due to the methodologies used to evaluate insulin sen-
sitivity and the frequent absence of a control group. Using validated indices derived from the OGTT in a large group of patients, we were able to document insulin resistance in IGT and CFRD but not in NGT subjects (Table 2). Thus, besides the well-documented insulin deficiency in CF patients [28], insulin resistance could play a role in the degradation of glucose tolerance.

Circulating adiponectin levels are reduced in humans with insulin resistance and type 2 diabetes [29]. Furthermore, low serum adiponectin concentration has been shown to be predictive of diabetes development [5]. Because the CF population presented both a high prevalence of glucose tolerance abnormalities and insulin resistance (Tables 1 and 2), we expected to observe decreased serum adiponectin concentrations, at least in IGT and CFRD subjects. However, despite a wide spectrum of glucose and insulin sensitivity abnormalities, we did not find any association between adiponectin concentrations and glucose tolerance categories or insulin sensitivity in CF patients (Fig. 2). Discrepancy between insulin sensitivity and adiponectin levels has been observed before. In fact, insulin sensitivity improvement in non diabetic insulin resistant, or in IGT obese subjects during caloric restriction was not associated with increased adiponectin concentrations [30,31]. Using the Homeostasis Model Assessment (HOMA) fasting-based index to quantify insulin sensitivity, Moriconi et al. [32] did not observe the presence of insulin resistance in CF patients, nor did they find any correlation between adiponectin levels and insulin sensitivity. Thus, we extend previous findings by demonstrating that neither glucose tolerance status, nor insulin sensitivity can predict circulating adiponectin levels in CF patients. Unlike type 2 diabetes, for which low adiponectin levels have been shown to be an independent predictor of diabetes development in prospective studies [33,34], the predictive value of low adiponectin concentration for the risk of future diabetes probably does not apply to CFRD.

CF patients frequently present inflammation, even without proven pulmonary exacerbation, and there is a well-described inverse correlation between adiponectin concentration and inflammatory markers [35]. Despite higher serum CRP and fibrinogen concentrations in CF patients, we did not observe any association between these inflammatory markers and adiponectin levels in our cohort (Fig. 2). Together, these data suggest that adiponectin levels are not reduced in stable CF patients presenting low-grade inflammation. Thus, as described recently for type 1 diabetic patients with nephropathy [36], CF appears to be one of the rare situations in which there is discordance between adiponectin concentration and insulin resistance, elevated glucose and inflammation.

Significant variations in adiponectin levels have been reported for patients with energy deficits due to eating disorders, such as anorexia nervosa and bulimia nervosa [29,35], with a gradual rise in adiponectin related to the magnitude of caloric deficiency [7,37]. This negative relationship between energy intake and adiponectin concentrations has been recently extended to an apparently healthy young population [8]. Chronic energy deficiency is prevalent in CF patients [38] and could thus contribute to increased and/or preserved adiponectin concentrations. Recently, Moriconi et al. [32], reported a negative correlation between serum albumin and adiponectin concentrations in CF patients, suggesting that the relationship between denutrition and adiponectin concentration is preserved in CF. In contrast, we did not observe any correlation between serum albumin and adiponectin concentrations. The discrepancy between these two studies could be related to the fact that our cohort might have represented an earlier stage of the disease than the one included in the Moriconi study, based on better mean pulmonary function (FEV1) as well as higher albumin concentrations (Tables 1 and 2). It is tempting to speculate that in CF patients, adiponectin concentration is modulated by various stimuli acting in opposite directions. While chronic inflammation, glucose tolerance abnormalities such as diabetes and insulin resistance may favor its reduction even a moderate energy deficit could counterbalance this effect. In severely affected CF patients, the energy deficit stimulus may predominate resulting in elevated adiponectin levels. The increase in adiponectin concentrations may be a protective mechanism to prevent further deterioration of insulin resistance and protein catabolism in already malnourished patients. Further prospective studies using more accurate measure of energy balance and malnutrition, may be able to determine whether deterioration of the nutritional status of CF patients is associated with increased circulating adiponectin levels.

Some limitations of our study should be taken into consideration when analyzing the data. We did not evaluate factors that have been reported to modulate adiponectin levels, such as physical activity, energy expenditure or body composition. Lower physical activity [39] and preferential central fat mass accumulation, despite low body weight [32], have been documented in the CF population. However, this should further contribute to reduced adiponectin levels and thus reinforce our observation of preserved adiponectin concentration in CF patients.

In conclusion, our large cohort of CF patients did not show any alterations in adiponectin levels despite insulin resistance, a high prevalence of glucose intolerance and subclinical chronic inflammation. CF appears to be one of the rare conditions in which there is discordance between insulin resistance or inflammation and adiponectin levels. The mechanisms and physiological relevance of these higher than predicted adiponectin levels deserve further investigation.

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