Studies on the role of glycosphingolipids in metabolism
Langeveld, M.

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Chapter 3

**Very low serum adiponectin levels in patients with type 1 Gaucher disease without overt hyperglycemia**

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H.P. Sauerwein, P. Simons and J.M. Aerts

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Abstract

Objectives and background
Gaucher disease (glucocerebrosidase deficiency) is characterized by massive accumulation of lipid-laden macrophages in various tissues. Gaucher patients show a hitherto unexplained increased hepatic glucose output. Since adiponectin is thought to influence hepatic glucose output, we studied its serum concentration in a cohort of Gaucher patients.

Results
Serum adiponectin was indeed found to be markedly reduced in patients (median value 3.1 µg/ml, range 1.4 - 6.3) as compared to healthy subjects (median value 5.6 µg/ml range 1.9 - 14.0). Successful therapy of Gaucher patients was accompanied by an increase in serum adiponectin, from 3.1 to 3.6 µg/ml (p=0.002). In healthy individuals low levels of circulating adiponectin, are generally associated with obesity. In Gaucher patients however adiponectin levels correlated not with body mass index.

Conclusions
The hypoadiponectinemia in Gaucher patients is most likely attributable to their low-grade chronic inflammation. The characteristic storage macrophages produce inflammatory cytokines such as TNF-alpha that is known to suppress adiponectin production. It is of interest that the very low adiponectin levels in Gaucher patients are not accompanied by hyperglycemia, contrary to their effect in obese individuals. It is hypothesized that the excessive hepatic glucose production in Gaucher patients balances the assumed increased glucose consumption by the massive amounts of storage macrophages. Hypoadiponectemia may play a regulatory role in preventing hypoglycaemia in this condition.
Introduction

Gaucher disease is caused by deficiency of the lysosomal enzyme glucocerebrosidase (EC 3.2.1.45). In the most common, non-neuronopathic (type 1) variant of Gaucher disease, clinical manifestations are restricted to the viscera. The disorder is characterized by massive accumulation of glucosylceramide in tissue macrophages. The characteristic lipid-laden storage cells (Gaucher cells) predominantly accumulate in spleen, liver and bone marrow. Their presence results in hepatosplenomegaly, cytopenia and bone complications.

Gaucher disease can be efficiently treated by chronic intravenous administration of recombinant glucocerebrosidase. This so-called enzyme replacement therapy (ERT) results in fast removal of storage cells, as is indicated by the prominent reduction of plasma markers for Gaucher cells, the hydrolase chitotriosidase and the chemokine CCL18. More recently, an alternative treatment based on inhibition of glycosphingolipid biosynthesis by oral administration of the iminosugar N-butyldeoxynojirimycin has shown to be effective in type I Gaucher disease. This so-called substrate reduction therapy (SRT) also results in major clinical improvements and leads to reduction in storage macrophages. The disappearance of storage cells upon therapy can be visualized by monitoring of triglyceride content of the lumbar spine bone marrow by Dixon Quantitative Chemical Shift Imaging (QCSI). In severely affected Gaucher patients the adipocyte content of the bone marrow is extremely low due to infiltration of Gaucher cells. Successful ERT or SRT gradually normalizes the bone marrow adipocyte content.

Gaucher patients show intriguing alterations in metabolism. Their resting energy expenditure is dramatically elevated. The hepatic glucose output is about 30% increased, however without concomitant abnormalities in blood glucose concentrations. A simple hormonal explanation for the high glucose turnover in Gaucher patients is so far lacking. Glucagon, (nor)epinephrine, cortisol and growth hormone levels do not differ between healthy control subjects and Gaucher patients after 16 hours of fasting. Insulin is significantly higher in Gaucher patients compared to healthy control subjects. The role of the prominent macrophage storage cells in the abnormalities in glucose metabolism of Gaucher patients is so far unclear. The effect of removal of storage cells by ERT on metabolic abnormalities has only partially been investigated. Clinical improvement of Gaucher patients coincides with a rapid and clear reduction in resting energy expenditure. Contrary to this, even after six month of
treatment only a modest correction in excessive hepatic glucose output occurs 12.
In recent times much attention is paid to the importance of adiponectin in the control
of glucose and whole body metabolism. Adiponectin is an abundant circulating hormone
produced by adipocytes. Plasma levels in healthy non-diabetic subjects are reported to
be 7.9±0.5 μg/mL in men and 11.7±1.0 μg/mL in women13. Adiponectin consists of an
N-terminal collagenous repeat and a C-terminal globular domain that resembles the
structure of tumor necrosis factor alpha. In muscle cells both the globular as well as the
full-length adiponectin are able to stimulate fatty-acid oxidation and glucose uptake
whereas in hepatocytes only full-length adiponectin is active in inhibiting gluconeogenesis14.
Adiponectin occurs in different complexes, including low molecular weight (LMW) trimers,
middle molecular weight (MMW) multimers, and high molecular weight (HMW) multim-
ers15,16. The biological importance of these different species is controversial. Most of the
features activated by adiponectin seem to involve the AMPK pathway.
Low circulating levels of adiponectin are considered to constitute a risk factor for develop-
ing impaired glucose tolerance and eventually type II diabetes17. Low adiponectin levels are
negatively correlated to hepatic glucose production18. It may be conceived that the increased
hepatic glucose output of symptomatic Gaucher patients is mediated by an abnormal low
level of adiponectin. We therefore studied serum adiponectin concentrations in a cohort of
type I Gaucher patients before and during treatment with EST or SRT. The outcome of this
investigation is here reported and discussed.

Patients and methods

Patients
All consecutive patients that were referred to our hospital between 1993 and 2001 with
symptomatic disease necessitating the initiation of treatment and of whom enough material
was available for analysis were included in this study. Twenty-eight (18 males, 10 females)
type I Gaucher patients and twenty-six control subjects matched on age (± 5 years), sex
and BMI (± 1 kg/m²) were investigated. In all patients a diagnosis of Gaucher disease was
confirmed on the basis of deficient glucocerebrosidase activity in leukocytes. None of the
patients were known to have diabetes or impaired fasting glucose levels. Before the initia-
tion of ERT, glucose and insulin levels in the postabsorptive state were available in 8 patients of whom 7 have been reported earlier\textsuperscript{10}. In addition, random glucose levels were available for 16 patients. 26 patients received enzyme replacement therapy (ERT) (imiglucerase, Cerezyme, Genzyme Corp., Mass., USA), and two patients received substrate reduction therapy (SRT) (N-butyldeoxynojirimycin, Zavesca, Actelion Pharmaceuticals). Samples were taken prior to initiation of treatment. A second serum sample was taken after several years of therapy (median 114 months of treatment, range 49 to 143). Samples were collected with consent of the patients.

**Disease severity assessment**

Before start of treatment and during follow up, various disease parameters were assessed, as depicted in table 1. Liver and spleen volume were measured by spiral CT scan. Bone marrow fat fraction of the lumbar spine was measured by Dixon quantitative chemical shift imaging (QCSI) as described in detail by Maas et al and Hollak et al\textsuperscript{19,20}. Chitotriosidase activity in plasma was determined by the standard enzyme activity assay with 4 MU-chitotriose (4-methylumbelliferyl β-D-N,N',N''-triacytethylchitotriose; Sigma) as substrate, as previously described\textsuperscript{2}.

**Adiponectin measurements**

Total serum adiponectin concentration was measured using an enzyme linked immuno-
nosorbent assay. Commercially available anti-human adiponectin capture and detection antibodies and recombinant adiponectin as standard were used (R&D systems, Minneapolis, USA). The inter- and intra-assay coefficients of variation in our laboratory were <16% and <4% respectively. If the adiponectin level was measured more than once the mean of the measurements is presented.

**Immunoblotting**

SDS-PAGE was performed according to the standard Laemmli’s method. Sample buffer was 3% SDS, 50 mM Tris-HCl pH 6,8 and 15% glycerol. The sample was diluted 1:10 with PBS and then mixed with 3 x sample buffer and incubated for 1 hour at room temperature. For immunoblotting proteins separated by SDS-PAGE were transferred to nitrocellulose membranes. The membranes were blocked with commercially available blocking buffer (Pierce,
Rockford, USA) supplemented with 0.1% Triton X-100, followed by overnight incubation with the primary antigen (biotinylated anti-human adiponectin antibody, R&D systems, Minneapolis, USA) 1:500 diluted in blocking buffer. After washing the membranes were incubated with streptavidin horseradish peroxidase antibody 1:10,000 for one hour at room temperature and then washed and incubated with ECL-solution and exposed to X-ray film.

**Statistical analysis**
Results are given as median and range. For comparison of independent groups (e.g. patients versus healthy control subjects) a Mann-Whitney test was used. For comparison between paired data (measurements before and after therapy) a Wilcoxon signed rank test was used. Correlations were calculated using rank correlation (Spearman’s rho). In all cases a p-value <0.05 was considered statistically significant.

**Results**

**Adiponectin levels**
Table 1 shows the characteristics of the studied type 1 Gaucher patients at baseline and after the prolonged period of ERT. The control population was successfully matched for gender, BMI (p=0.68) and age (p=0.95) to the Gaucher patients (only the ERT treated patients were matched).

Serum adiponectin levels were significantly lower (p<0.001) in untreated type I Gaucher patients compared to healthy controls. The median value in serum of patients was 3.1 µg/ml (range 1.4 - 6.3) versus 5.6 µg/ml (range 1.9 - 14.0) in the control subjects (figure 1). Adiponectin levels are known to be lower in men than women. This difference was also observed in the Gaucher population: median plasma adiponectin in male patients was 2.7 µg/ml (range 1.4 - 5.0) and in female patients 5.3 µg/ml (range 2.5 - 6.3) (figure 1) (p= 0.00). Both female and male Gaucher patients showed significantly lower adiponectin levels than matched controls.

The median BMI in the patient group was 22 kg/m² (range 17 -28). The patient group included only two obese patients (BMI above 25 kg/m²). Adiponectin levels in untreated Gaucher patients did not correlate with their BMI (r=-0.11, p=0.59) (figure 2).
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Table 1  Age, BMI, adiponectin levels, liver volume, spleen volume, chitotriosidase activity, bone marrow fat fraction measured at start of ERT. Change in BMI during ERT; m=male, f=female, n.k.= not known, Sx= splenectomy.

* chitotriosidase deficiency ** carrier of chitotriosidase mutation
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Table 1 (continued)  
Age, BMI, adiponectin levels, liver volume, spleen volume, chitotriosidase activity, bone marrow fat fraction measured at start of ERT. Change in BMI during ERT. m=male, f=female, n.k. = not known, Sx=splenectomy. * chitotriosidase deficiency  
** carrier of chitotriosidase mutation

**Figure 1** Adiponectin serum concentrations (µg/ml) in untreated male (n=18) and female (n=8) Gaucher patients and in age and BMI matched male (n=18) and female (n=8) control subjects

**Figure 2** Correlation between BMI (kg/m²) and serum adiponectin level (µg/ml) in untreated Gaucher patients (r=-0.11, p=0.59)
Glucose levels before the initiation of ERT were normal in all but 1 patient (median 5.0 mmol/l, range 4.4-6.9). For all patients in the postabsorptive state, (n=8), glucose levels were normal. In these 8 patients, insulin levels in the postabsorptive state were slightly elevated as previously reported (median 51.8 range 41.4-75.9 pmol/l)\(^\text{10}\). No correlation was found between glucose levels and adiponectin levels (r = 0.2, p=0.37) and insulin and adiponectin levels (r = 0.5, p=0.20).

**Relation between adiponectin levels and indicators of disease severity**

There was no significant difference between adiponectin levels in patients who underwent splenectomy compared to non-splenectomized patients (p=0.4) (data not shown). Liver volume and spleen volume were not significantly correlated to plasma adiponectin levels (r=0.134, p=0.51, and r=0.482, p=0.06, respectively). Adiponectin levels did not correlate with plasma chitotriosidase activity (r=-0.032, p=0.88). The triglyceride content of lumbar spine bone marrow as assessed by quantitative chemical shift imaging (QCSI) also did not correlate to the serum adiponectin levels of Gaucher patients (r=-0.13, p=0.527).

**Effects of treatment on adiponectin levels, BMI and organomegaly**

After several years of treatment with ERT (median 114 months, range 49 to 143) the adiponectin level in Gaucher patients increased marginally, but significantly (median serum adiponectin: 3.6 µg/ml, range 1.3 - 9.8) compared to baseline (median value 3.1 µg/ml range 1.4-6.3). The adiponectin levels of Gaucher patients receiving ERT increased slightly but did not reach the level of BMI-matched controls (p=0.02). BMI increased during therapy from a median of 22 (range 17-28) to 23.5 (range 21-32), which was highly significant (p<0.00). In treated patients, the normal negative correlation between body weight (BMI) and adiponectin levels was restored (figure 3).

Serum adiponectin levels were also determined in two female Gaucher patients who received substrate reduction therapy. On therapy initiation both had a normal BMI (<25 kg/m\(^2\)) and low adiponectin levels (7.3 and 4.5 µg/ml). In both patients the serum adiponectin increased during therapy (with increments of 3.3 and 0.84 µg/ml, respectively). No correlations could be established between absolute or relative reductions in organomegaly, bone-marrow fat fraction or chitotriosidase and adiponectin levels (data not shown).
Figure 3  Plasma adiponectin levels (µg/ml) in Gaucher patients before (n=24) and after treatment with enzyme replacement therapy. The dotted line indicates the median control adiponectin level (A) correlation between BMI (kg/m²) and plasma adiponectin level (µg/ml) in treated Gaucher patients (B).

Figure 4  Separation of low molecular, middle molecular and high molecular forms of adiponectin by SDS-PAGE. Profile of adiponectin forms in six healthy control subjects (3 male, 3 female) and seven Gaucher patients (5 female and 2 male) before (b) and after (a) enzyme replacement therapy.
Adiponectin isoforms

Adiponectin circulates as LMW, MMW and HMW form. No striking differences could be detected by Western blot analysis in the distribution of adiponectin forms in serum samples of Gaucher patients as compared to corresponding healthy control subjects (figure 4). Treatment with ERT in Gaucher patients did not markedly change the distribution of adiponectin forms, although the increase in LMW adiponectin was prominent in some patients.

Discussion

Our investigation revealed that type 1 Gaucher patients show remarkably low serum levels of adiponectin. Hypoadiponectinemia is common in obese individuals\(^2^1\). However, in Gaucher patients low adiponectin levels are clearly not caused by the presence of excess adipose tissue. The bodyweight of Gaucher patients does not correlate with adiponectin levels. This is further emphasized by the fact that successful therapy of patients often results in an increase in adiponectin as well as in bodyweight. Also, a negative correlation between circulating adiponectin levels and insulin resistance has been demonstrated, but preliminary results in our study do not indicate a relationship between adiponectin and insulin levels. The cause for the low adiponectin levels in symptomatic patients is not precisely known. Serum adiponectin levels in Gaucher patients do not strictly correlate to Gaucher cell burden as reflected by plasma chitotriosidase level, liver and spleen volume or by QCSI analysis of bone marrow infiltration by storage cells. Enhanced clearance of serum adiponectin by an increased mass of macrophages in Gaucher patients offers therefore no likely explanation for the observed low serum adipocytokine level. Low-grade systemic inflammation is a hallmark of Gaucher disease\(^2^2\). Massive storage of glucosylceramide in macrophages leads to specific activation of these Gaucher cells, manifested by the release of cytokines (TNFα, IL6, IL10) and other factors\(^2^,\(^3^,\(^2^3^,-^2^6\). In vitro, high concentrations of TNFα and IL6 are known to inhibit adiponectin production by isolated human adipose tissue\(^2^7\). It might be speculated that the (locally) altered cytokine profile in adipose tissue of Gaucher patients inhibits adiponectin production and causes the low serum adipocytokine levels. Obesity is another condition in which low adiponectin is associated with low grade systemic inflammation and
elevated circulating levels of TNFα and IL6, partially produced by macrophages residing in white adipose tissue.

Despite the impressive clinical improvement of Gaucher patients receiving ERT, this is accompanied by relatively modest corrections in adiponectin levels. No correlation could be established between decreases in organomegaly and increase in adiponectin levels. It has to be realized that ERT or SRT treatments result in only partial removal of Gaucher cells, without complete correction of low grade systemic inflammation. This may contribute to persistent suppression of adiponectin formation and prevent complete normalization of the serum adiponectin level. Our earlier observation that hepatic glucose production remains high in Gaucher patients receiving ERT for one half year is consistent with the persistence of reduced adiponectin levels.

More recently attention has been paid to the multimeric composition of adiponectin. Adiponectin may occur as LMW or HMW form. The HMW multimer is specifically involved in the activation of AMPK in hepatocytes. In contrast only the LMW trimer is able to activate AMPK in muscle. It has been proposed that particularly the HMW adiponectin suppresses hepatic glucose output. We observed no abnormalities in the distribution of multimeric adiponectin isoforms. Moreover therapy did not result in marked changes in the distribution of various isoforms.

Hypoadiponectinemia is generally considered an unfavorable condition associated with obesity, insulin resistance and type II diabetes. Intriguingly, symptomatic Gaucher patients, despite their very low adiponectin levels, do not develop apparent hyperglycemia. We hypothesize that in Gaucher disease, there is an increased glucose consumption by the massive amounts of storage macrophages and that the liver responds with an increase in glucose production. Hypoadiponectinemia could therefore play a role by preventing hypoglycemia.

In conclusion, symptomatic type 1 Gaucher patients show remarkably low serum adiponectin levels. Nevertheless, Gaucher patients are generally far from overweight and show no overt hyperglycemia. Consistent with their low adiponectin levels, hepatic glucose output in Gaucher patients is high. Further investigations on insulin responsiveness of Gaucher patients and the factors mediating low adiponectin production are warranted. It is of interest to note in this connection that very recently Ikonen and co-workers reported impaired insulin receptor activation in a mouse model for Niemann-Pick type C, another lysosomal storage disorder characterized by the presence of lipid-laden macrophages.
References

