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Energy balance, glucose and lipid metabolism, cardiovascular risk and liver disease burden in adult patients with type 1 Gaucher disease☆

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ABSTRACT

Gaucher disease (GD), the most prevalent lysosomal storage disease, is characterized by systemic accumulation of macrophages engorged with glycosphingolipid-laden lysosomes. Even though both lysosomes and sphingolipids play a pivotal role in metabolic homeostasis, little is known on metabolic abnormalities associated with GD. In this review, we discuss the peculiarity of energy balance and glucose and lipid metabolism in adult type 1 GD patients. Moreover, we evaluate the potential relationship between these metabolic derangements, cardiovascular risk and chronic liver disease. The limited data available show that adult type 1 GD is characterized by a hypermetabolic state, peripheral insulin resistance and hypolipidemia with markedly reduced HDL-cholesterol levels, partially reverted by enzyme replacement therapy (ERT) or substrate reduction therapy (SRT). Although this unfavorable metabolic profile has not been associated with increased incidence of type 2 diabetes and premature atherosclerosis, a natural history study has shown that cardio-cerebrovascular events and malignancy are the leading causes of death in treated type 1 GD patients. Hepatomegaly is frequently observed in GD and ERT/SRT are highly effective in reducing liver volume. Nevertheless, patients with GD may be at increased risk of long-term liver complications including cirrhosis and hepatocellular carcinoma. The role that ERT/SRT and/or lifestyle habits may have on such metabolic features of GD patients, and subsequently on long-term prognosis, deserves further investigations. To gain more insights into the peculiarity of GD metabolism may serve both surveillance and treatment purposes by helping to identify new markers of disease severity and define an updated natural history of GD.

1. Introduction

Gaucher Disease (GD) is the most frequent lysosomal storage disease with a prevalence of 1:40.000 individuals. It is caused by mutations in lysosomal acid beta-glucosidase (GBA) whose deficient activity leads to glycosphingolipids storage in cells of the reticulo-endothelial system and inflammation. The most prevalent phenotype, type 1, is characterized by spleno-hepatomegaly with hematologic abnormalities, coagulopathy and bone disease with severe skeletal complications [1–3].

The available treatments, in particular enzyme replacement therapy (ERT) and substrate reduction therapy (SRT), are very effective on visceral, hematologic and bone complications and have significantly improved the risk of complications, expectancy and quality of life in patients with GD [4–8], thus exposing these patients to the common unhealthy lifestyle and risk factors of the general population in the western countries, including the metabolic syndrome (MS) and MS-related disorders. Indeed, recent data emerging from international registries showed that cardiovascular and chronic liver diseases currently stand among the leading causes of death also in GD patients [9]. These findings suggest that one of the primary goal in the management of GD patients should be to assess and control the hepato-metabolic and cardiovascular risk factors, further to treatment of classical GD manifestations.

There is compelling evidence that lysosomes are a signal hub for many pathways that regulate cellular homeostasis, being involved, among their broad functions, in nutrient sensing, transcriptional regulation and energy metabolism, further to be the terminal end of cellular catabolic pathways [10–12]. For example, it has been demonstrated that lysosomes, through a calcium signaling mechanism, regulate the activities of TFEB, a master transcriptional regulator of lysosomal biogenesis and autophagy [13]. The TFEB pathway controls the starvation response by sensing nutrient levels, and by inducing a metabolic switch

Abbreviations: ApoAI, apolipoprotein AI; ApoB, apolipoprotein B; ApoE, apolipoprotein E; BMI, body mass index; ERT, enzyme replacement therapy; GBA, acid beta-glucosidase; GD, Gaucher disease; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein; MS, metabolic syndrome; REE, resting energy expenditure; SRT, substrate reduction therapy; TFEB, transcription factor EB; VLDL, very-low-density lipoprotein.

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that allows the cell to generate energy from stored lipids [10,11,14]. That same pathway is activated under lysosomal storage conditions [11,15]. Therefore, it is not surprising that lysosomal dysfunction and subsequent metabolic derangements have been associated with several human diseases, such as lysosomal storage diseases, GD being the prototype of these inherited disorders, as well as with obesity and MS [10,16–20]. In principle, while metabolic abnormalities due to lysosomal dysfunction could be partially reverted by ERT/SRT in GD, overnutrition and unbalanced diets could exacerbate them.

Moreover, compounds of the sphingomyelin-ceramide-glycosphingolipid pathways have been studied as potential secondary messengers affecting directly or indirectly the intracellular and intercellular cross talks, and being involved in various pathological conditions, such as insulin resistance and fatty liver disease [21].

Unfortunately, despite these premises, little is known on energy balance, glucose and lipid metabolism, cardiovascular risk and liver disease burden in GD patients either at baseline or during long-term ERT/SRT. Moreover, whether ERT/SRT and/or lifestyle habits induce significant changes in these metabolic features, and subsequently on long-term prognosis, has not been well established so far.

Aim of this review is to shed some light on the metabolic features of type 1 GD by discussing the peculiarity of energy balance and glucose and lipid metabolism and their modifications during ERT/SRT in adult GD patients. Finally, we evaluate the potential relationship between these metabolic aspects, cardiovascular risk and chronic liver disease, including hepatocellular carcinoma (HCC), in adult GD patients. In order to carry out the review, we extensively searched PubMed database for pertinent articles published through 1st September 2016 by using the following key-words “type 1 Gaucher disease” combined with “energy metabolism” or “glucose metabolism” or “lipid metabolism” or “metabolic syndrome” or “cardiovascular risk” or “liver disease” or “hepatocellular carcinoma”.

2. Energy balance in GD

GD is characterized by systemic inflammation, growth retardation and increased energy expenditure. In the late 1980s Barton et al. observed that resting energy expenditure (REE) of 25 U.S. patients with type 1 GD measured by indirect calorimetry was approximately 44% higher than that predicted for patient's age, sex and anthropometric measures. This increase in the caloric requirements was supposed to determine growth retardation and thinness in children and reduced muscle mass in adult patients with GD. Interestingly, the Authors showed that the excess energy expenditure was directly related to liver and spleen volumes. These findings led them to suggest that the hypermetabolic state in GD was secondary to the large mass of Gaucher's cells and that measurement of REE could have been a useful tool for monitoring GD progression and the effect of therapy [22]. Some years later Hollak et al. confirmed that REE measured by indirect calorimetry was significantly higher than predicted REE and measured REE in weight- and age-matched healthy controls in a European cohort of type 1 GD patients. Of note, the elevated REE decreased after 6 months of treatment with alglucerase, although it still remained higher as compared with controls. In contrast with the previous study, despite a significant reduction in liver and spleen volumes during ERT, this study failed to demonstrate a relation between the decrease in organ volumes and the decrease in hypermetabolism. These Authors suggested that the increase in REE in GD more probably reflected macrophage activation and production of pro-inflammatory cytokines [23]. This seminal study by Hollak and colleagues also showed that the decrease in hypermetabolism during ERT was associated with an increase in weight and in fat mass [23]. Several subsequent studies from all over the world confirmed a consistent weight gain and increase in body mass index (BMI) of type 1 GD patients while on ERT (Table 1) [24–26]. Langeveld et al. showed a mean increase of 6 kg or 2.4 kg/m^2 during 11 years of ERT in 35 Dutch patients with type 1 GD and the prevalence of overweight increased from 16% at baseline to 56% after treatment. Weight gain was not correlated with the duration or the dose of enzymatic therapy nor to the response to treatment. Of note, 7 untreated patients from the same centre showed a similar weight gain during a follow-up of 8 years. Moreover, irrespective of treatment, weight gain over time in GD patients followed the course of the control general population from the Netherlands [25]. These findings suggest that aging GD patients have the same trend in weight gain over time as compared to aging healthy individuals, probably due to excess nutrients intake and sedentariness as the general population. Unfortunately, to the best of our knowledge, no studies have examined dietary habits and lifestyle in GD patients.

3. Glucose metabolism in GD

GD has been associated with insulin resistance (Table 2). Several experimental studies have clearly demonstrated that altered sphingolipid metabolism is crucial in insulin resistance development in many human diseases [27]. Sphingolipids play a prominent role in cell signaling and are important constituents of cell membranes and lipid rafts. The nature of the sphingolipids in lipid raft domains may be central to proper insulin signaling. For instance, the ganglioside G_{M3} is one of the main sphingolipids believed to interfere with insulin signaling, by displacing the insulin receptor in lipid rafts, impairing insulin receptor interaction and decreasing insulin receptor dependent PI(3)K/Akt signaling pathway [27]. Of note, G_{M3} overproduction mediated by obesity-related increases in circulating saturated fatty acids and pro-inflammatory cytokines has been linked to obesity-associated insulin resistance and type 2 diabetes [28]. Consistently, G_{M3} is among the lipids which result altered in GD [29,30], and G_{M3} elevations have been associated with insulin resistance in GD experimental models [27].

Corssmit et al. were first in describing abnormal glucose metabolism in GD patients. They conducted a study with continuous infusion of radiolabeled glucose in 7 clinically stable untreated type 1 GD patients and found a 30% increase in basal glucose production in GD patients compared to controls, without concomitant abnormalities in blood glucose concentrations nor significant changes in glucoregulatory hormones levels [31]. The same Authors subsequently confirmed that GD patients had both increased glucose production and increased glucose clearance and higher levels of insulin, which were not significantly affected by alglucerase treatment. However, this population included mildly-to-moderately affected patients treated with low dose of alglucerase [23]. Altered paracrine macrophage-hepatocyte interactions and markedly low levels of adiponectin in GD patients have been suggested as potential mechanisms involved in the increased hepatic glucose output [23,31,32]. A more recent study failed to reproduce the earlier finding of increased hepatic glucose output in GD patients, probably due to the selection of patients with mild disease [33]. Nevertheless, this seminal paper found that GD patients had lower insulin-mediated glucose uptake, hence higher peripheral insulin resistance, as compared to healthy controls [33]. A retrospective longitudinal study described a 8.2% cumulative incidence of type 2 diabetes after 11 years of follow-up in 49 type 1 GD patients treated with ERT. The incidence of type 2 diabetes paralleled the increase in weight gain during the follow-up. Of note, there were no significant differences with the cumulative incidence of type 2 diabetes in control general populations [25]. Finally, a subsequent cross-sectional study form Turkey confirmed that insulin resistance is a common finding also in non-overweight GD patients treated with ERT, suggesting that abnormalities in glucose metabolism are not the consequence of the hypothesized larger than average weight gain described in GD patients treated with long-term ERT [34].

4. Lipid metabolism in GD

Plasma lipids and lipoproteins are altered in GD. The primary storage of glucosylceramide in GD leads to secondary alterations of lipid metabolism and trafficking that affect gangliosides (GM3), phosphatidylcoline and sphingomyelin [29]. Interestingly, glucosylsphingosine, the

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