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Genes Involved in Cellular Uptake of Long-Chain C24 Sulfatide in Relation to Pathogenesis of Type 1 Diabetes

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Abstract

The very long-chain C24 sulfatide is important for inhibiting the development of diabetes in NOD mice. Due to its long-chain structure, C24 sulfatide may require facilitation by transport proteins such as fatty acid transport proteins (FATP) and ABC transporter subfamily D (ABCD). We analyzed the mRNA expression of four fat transporters, FATP2, FATP5, FATP6, and ABCD2, in human pancreatic islets from individuals with type 1 diabetes, type 2 diabetes, and control donors via data from the DiViD and nPOD studies. FATP2 was decreased in newly diagnosed type 1 diabetes patients, with values that were only 69% of the control values (p=0.034). FATP5 was also decreased in newly diagnosed type 1 diabetes patients, with 68% of the control values (p=0.0048). Additionally, we found that FATP6 was increased by 60% in type 2 diabetes patients compared with controls (p=0.0039). ABCD2 expression was substantially higher in newly diagnosed type 1 diabetes patients showing, 142% of healthy controls (p=0.0058). ABCD2 is found on the peroxisomal membrane and facilitates lipid degradation. These findings suggest impaired C24 sulfatide levels in type 1 diabetes patients, potentially compromising beta-cell protection from immune attack.

Keywords: C24 sulfatide, Long chain fatty acids, Type 1 Diabetes, T lymphocytes.

Abbreviations

ABCD: ATP-binding cassette subfamily D

DiViD: Diabetes Virus Detection

DRiP: defective ribosomal product

FATP: fatty acid transport protein

LCFA: long-chain fatty acids

nPOD: network for Pancreatic Organ Donors

SLC27A: solute carrier family 27

T1D: type 1 diabetes

VLCFA: very-long-chain fatty acids

Introduction

Recently, we have published a study indicating the importance of the sphingolipid C24 sulfatide [1]. In the present study we generate experimental

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data as a follow-up again focusing on this sulfatide isoform. The sphingolipid sulfatide plays an important role in the function of beta cells. The physiological part of helping insulin performance, storage and secretion is facilitated by C16 sulfatide which acts as a chaperone for all these processes [2]. C24 sulfatide plays an equally important role by protecting beta cells from attacks of T cells and thereby inhibiting an autoimmune process leading to Type 1 Diabetes [3]. The synthesis of C24 sulfatide requires the availability of long-chain fatty acids (LCFA) or very-long-chain fatty acids (VLCFA). Due to their extended chain length, these fatty acids may not readily cross the cell membrane and thus require facilitation by specific transporter proteins. Fatty acid transport across cellular membranes is an active process mediated by several transporters, including the fatty acid transport proteins (FATPs), also known as solute carrier family 27 (SLC27A). FATPs function both as transporters and acyl-CoA synthetases, coupling the uptake of LCFAs with their metabolic activation. This activation, converting LCFAs into acyl-CoA thioesters, is essential for their subsequent use in sphingolipid synthesis pathways, such as the formation of C24 sulfatide in beta cells [4]. There are six FATP isoforms (FATP1-6) [5]; FATP1 and FATP4 are widely distributed, while FATP2 and FATP5 are predominantly expressed in the liver and kidney [6]. FATP2 is also present at lower levels in human and rodent pancreatic islets, where it can influence beta cell lipid composition and insulin secretion [7]. Dysregulation of LCFA transport, particularly via FATPs, can disrupt lipid homeostasis and has been associated with insulin resistance [8].

In parallel, ATP-binding cassette subfamily D (ABCD) transporters are responsible for the intracellular transport of LCFAs. There are four ABCD isoforms: ABCD1, ABCD2, and ABCD3 are localized to peroxisomes, while ABCD4 is found in lysosomes [9]. ABCD1-3 facilitate the import of LCFAs into peroxisomes, where they undergo beta-oxidation and lipid degradation [10]. Notably, ABCD2 plays a significant role in the degradation of VLCFAs [11]. Peroxisomal transport is particularly relevant for the synthesis and turnover of C24 sphingolipids, including sulfatide, and changes in ABCD transporter activity may alter the balance between lipid synthesis and degradation in beta cells [12]. Together, these transporters regulate the balance in LCFA uptake, activation and peroxisomal degradation of LCFA – steps crucial for generating long-chain sphingolipids such as C24 sulfatide. We therefore hypothesized that altered expression of FATPs and ABCD2 in pancreatic islets may contribute to disturbed C24 sulfatide metabolism in diabetes. In this study, we analyzed mRNA expression data for all isoforms of both FATPs and ABCDs in pancreatic islets obtained from the DiViD and nPOD studies, focusing on their relation to type 1 and type 2 diabetes.

Materials and Methods

RNA analysis of human pancreatic islets

The human pancreatic islet RNA analysis was done as earlier described [13] but explained briefly. Human pancreatic tissue samples used in this investigation were obtained from two sources: the Diabetes Virus Detection (DiViD) study [14], which included newly diagnosed type 1 diabetes patients (mean disease duration: 35 days; aged 24-35 years; n=5), and the network for Pancreatic Organ Donors (nPOD) study [15]. Data access requests should be addressed to lars.krogvold@gmail.com. The nPOD material represents pancreases collected from deceased organ donors following accidental death, while the DiViD study utilized biopsies from living participants. The nPOD dataset includes 18 non-diabetic control donors (9F/9M; 36.2 ± 15.6 years), 12 autoantibody-positive persons (5F/7M; 20.4 ± 8.4 years) – 8 with one autoantibody and 4 with multiple autoantibodies – 19 individuals with established type 1 diabetes (> 5 years; 10F/9M; 33.2 ± 17 years), and 8 donors diagnosed with type 2 diabetes (5F/3M; 39.8 ± 13.4 years). From each sample, 25 pancreatic islets were randomly selected for laser capture microdissection, pooled from two to five sections, and processed for RNA extraction using the Arcturus PicoPure RNA Isolation Kit (Applied Biosystems, Grand Island, NY, USA). RNA quantification was evaluated on a Bioanalyzer 2100 system (Agilent Technologies, Santa Clara, CA, USA). Gene expression analysis was carried out using Affymetrix Human Gene 2.0 ST arrays (Gene Chip Human Gene 2.0 ST, Thermo Fisher), with normalization by global scaling. All experimental handling was performed in a same laboratory environment to maintain uniformity across datasets. RNA quality was confirmed with RIN values >3.5.

Statistical analysis

Statistical analyses were performed in R (version 2025.09.0+387) using the *tidyverse* and *ggpubr* packages. Data visualization was performed with *ggplot2*. mRNA expression was analyzed using an unpaired two-tailed t-test to compare control and treatment groups. Statistical significance was considered at $p < 0.05$.

Ethics statement

Ethical approval for the DiViD and nPOD studies was granted by the Norwegian Regional Committee for Medical and Health Research Ethics (reference 2009/1907) and the Institutional Review Board of the University of Tennessee Health Science Center (reference 10-00848-XM). All procedures adhered to applicable institutional and national guidelines and regulations. We confirm that all experimental protocols received prior approval from both ethics bodies noted above. Additionally, written informed consent was obtained from all participants and/or their legal guardians.

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Results

We examine genes involved in long-chain fatty acid absorption. For the *FATP2* gene, mRNA expression in human islets was 20.54 in control persons and 14.16 in newly diagnosed type 1 diabetes patients from the DiViD study, representing a reduction to 69% of control levels (p=0.035) (**Fig. 1**).

For the *FATP5* gene, mRNA expression was 43.11 in controls and 29.29 in newly diagnosed type 1 diabetes patients, corresponding to only 68% of control levels (p=0.0048) (**Fig. 2**).

For the *FATP6* gene, mRNA expression was 6.80 in controls and 10.89 in type 2 diabetes patients, thus showing a 60% increase in type 2 diabetes patients (p=0.0039) (**Fig. 3**).

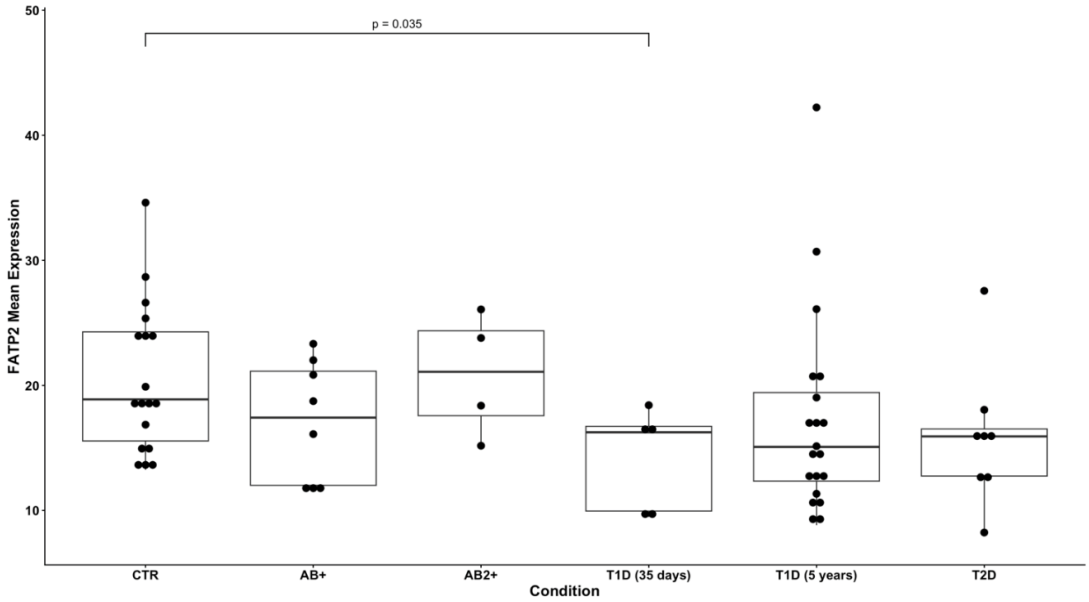

Figure 1: ***FATP2 gene expression.*** CTR: non-diabetic controls (n = 18); AB+: non-diabetic autoimmune single autoantibody-positive donors, nPOD (n = 8); AB2+: non-diabetic autoimmune double autoantibody-positive donors, nPOD (n=4); T1D (median disease duration, 35 days): donors with newly diagnosed type 1 diabetes, DiViD (n = 5); T1D (median 5 years): donors with intermedium diagnosed type 1 diabetes, nPOD (n = 20); T2D (median 2 years): donors with type 2 diabetes, nPOD (n = 8). Boxes indicate 25% and 75% quartiles and whiskers 1.5 × interquartile ranges.

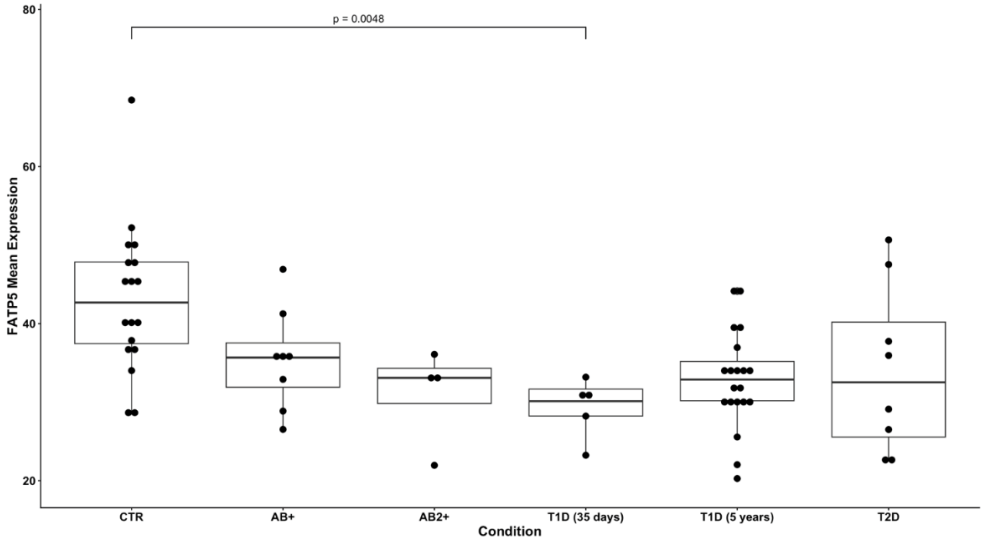

Figure 2: ***FATP5*** **gene expression**. CTR: non-diabetic controls (n = 18); AB+: non-diabetic autoimmune single autoantibody-positive donors, nPOD (n = 8); AB2+: non-diabetic autoimmune double autoantibody-positive donors, nPOD (n=4); T1D (median disease duration, 35 days): donors with newly diagnosed type 1 diabetes, DiViD (n = 5); T1D (median 5 years): donors with intermedium diagnosed type 1 diabetes, nPOD (n = 20); T2D (median 2 years): donors with type 2 diabetes, nPOD (n = 8). Boxes indicate 25% and 75% quartiles and whiskers 1.5 × interquartile ranges.

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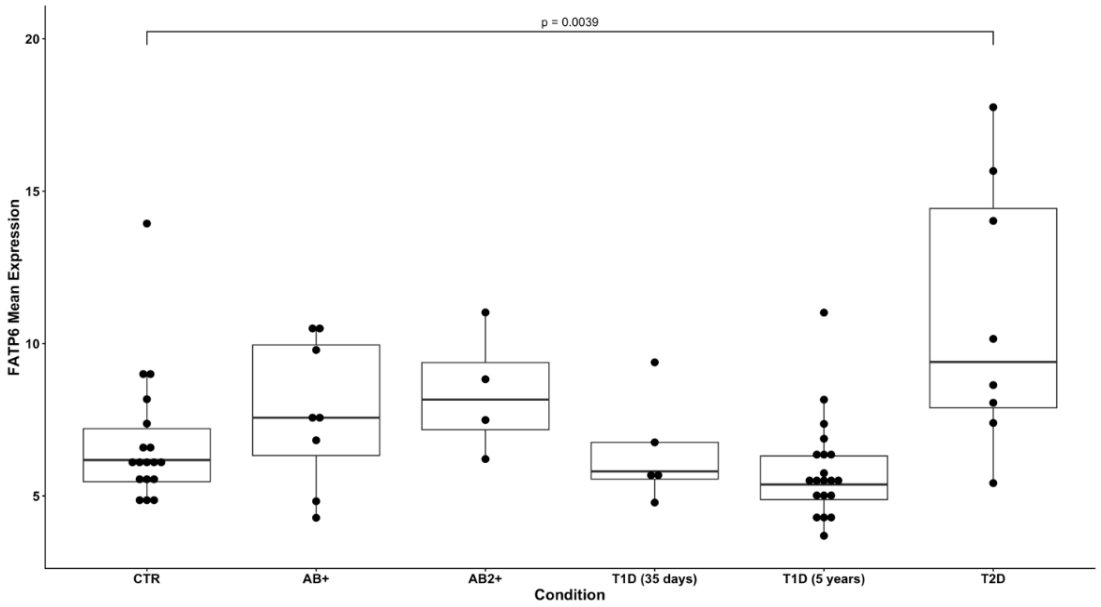

Figure 3: *FATP6* gene expression. CTR: non-diabetic controls (n = 18); AB+: non-diabetic autoimmune single autoantibody-positive donors, nPOD (n = 8); AB2+: non-diabetic autoimmune double autoantibody-positive donors, nPOD (n=4); T1D (median disease duration, 35 days): donors with newly diagnosed type 1 diabetes, DiViD (n = 5); T1D (median 5 years): donors with intermedium diagnosed type 1 diabetes, nPOD (n = 20); T2D (median 2 years): donors with type 2 diabetes, nPOD (n = 8). Boxes indicate 25% and 75% quartiles and whiskers 1.5 × interquartile ranges.

Regarding long-chain fat transport into peroxisomes, we examine ABCD genes. For the *ABCD2* gene, mRNA expression was 6.85 in healthy control persons and 9.76 in newly diagnosed type 1 diabetes, showing a 42% increase in expression (p=0.0058) (**Fig. 4**).

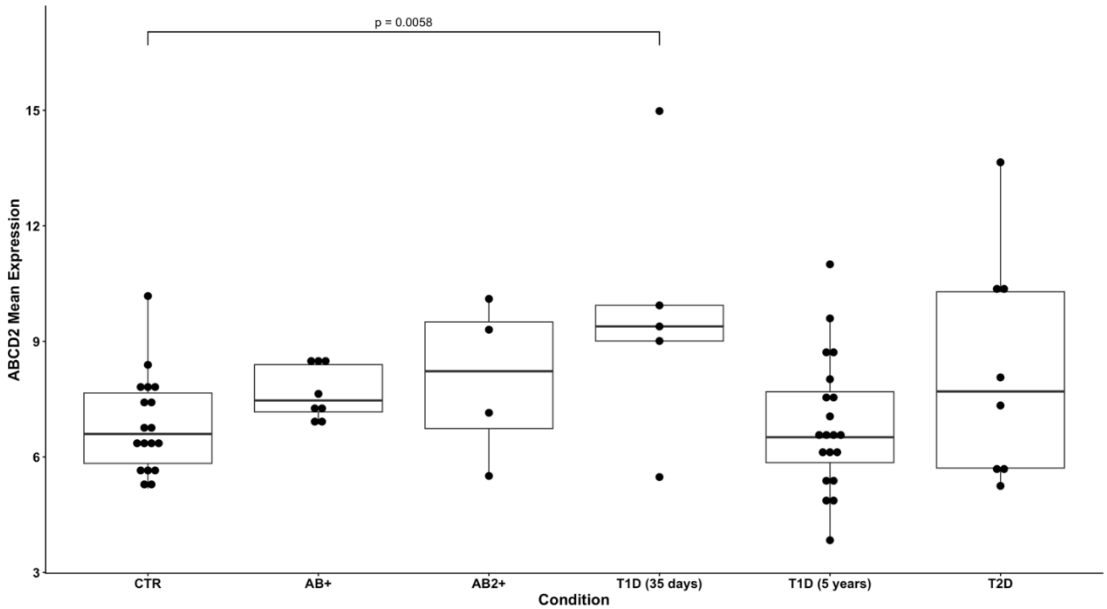

Figure 4: *ABCD2* gene expression. CTR: non-diabetic controls (n = 18); AB+: non-diabetic autoimmune single autoantibody-positive donors, nPOD (n = 8); AB2+: non-diabetic autoimmune double autoantibody-positive donors, nPOD (n=4); T1D (median disease duration, 35 days): donors with newly diagnosed type 1 diabetes, DiViD (n = 5); T1D (median 5 years): donors with intermedium diagnosed type 1 diabetes, nPOD (n = 20); T2D (median 2 years): donors with type 2 diabetes, nPOD (n = 8). Boxes indicate 25% and 75% quartiles and whiskers 1.5 × interquartile ranges.

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Discussion

In this study, we found that FATP2 and FATP5 expression levels in newly diagnosed type 1 diabetes patients were reduced to 68% of control values, while FATP6 expression was increased by 60% in type 2 diabetes patients. Additionally, ABCD2 expression was 42% higher in type 1 diabetes patients compared to controls. The absorption of long-chain fatty acids likely depends on their availability in the blood, which is expected to correlate positively with the expression of fat transporter molecules. This, in turn, should facilitate the uptake of very long chain sphingolipids such as C24 sulfatide, and an increased supply may help inhibit the development of type 1 diabetes. Highly interestingly, it has been found that NOD mice on a high fat diet almost completely avoid development of type 1 diabetes [16]. Furthermore, C24 sulfatide concentrations can be increased by lowering cholesterol levels [17]. This may explain why fenofibrate, which lowers cholesterol, enhances C24 sulfatide levels in beta cells and suppresses diabetes development in mice, [18], as it can correct for the reduced sulfatide levels typically observed in type 1 diabetes patients [19]. Our previous work showed that total sulfatide levels in newly diagnosed diabetic patients were only 23% of those in healthy controls [19]. Given that C24 sulfatide constitutes 36% of total sulfatide in rat islets, it is likely that C24 sulfatide is also substantially reduced in type 1 diabetes patients [20].

FATP2 is upregulated in human islets upon high glucose-stimulation [21], potentially to increase sulfatide synthesis for beta-cell protection. Type 2 diabetes is characterized by both insulin resistance and, in the early stages, increased insulin production. This suggests that there may be an optimal range for the expression of fat absorption facilitators such as FATPs: insufficient expression in beta cells may limit C24 sulfatide uptake, while excessive expression could promote insulin resistance, hyperinsulinemia, and progression toward type 2 diabetes. The factors determining the precise expression levels of these transport proteins remain unclear but may include the availability of relevant fatty acids. Furthermore, obese individuals, who typically have elevated levels of fatty acids, are more prone to developing type 2 diabetes, whereas individuals who develop type 1 diabetes are often lean and tall.

C24 sulfatide may play a crucial role in preventing T-cell mediated attacks on beta cells, which produce the highly immunogenic insulin protein. Insulin may sometimes be incorrectly synthesized due to alternative reading frames or improper assembly, resulting in defective ribosomal product (DRiP) molecules, that are highly immunogenic [22]. If this is the case, reduced protection by C24 sulfatide may increase susceptibility to T cell attacks. Interestingly, type 2 diabetes patients exhibit high levels of fat absorption molecules which may contribute to T cell inhibition, and they do not experience T-cell mediated inflammation. In animal models of type 2 diabetes such as db/db and ob/ob, C16 sulfatide is absent but C24 sulfatide is preserved [23] which correlates with the lack of T cell inflammation. Another gene of interest in fat absorption is Apolipoprotein E, which may function in parallel with FATPs and ABCDs. However, investigation of Apolipoprotein E was beyond the scope of the present study and has been addressed in several other publications [24].

Conclusion

In conclusion, our findings suggest that reduced expression of FATP2 and FATP5 in type 1 diabetes may impair the uptake of C24 sulfatide in beta cells, potentially contributing to disease pathogenesis. The observed elevation of ABCD2 expression in type 1 diabetes, a peroxisomal lipid degradation transporter, further supports this notion. Additionally, increased FATP6 expression in type 2 diabetes patients may represent an adaptive response to higher lipid intake.

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Author Contributions

KB conceptualized the project and wrote the original manuscript draft. LK, IG, and KD-J provided the DiViD material, analyzed and performed the human RNA expression data. KB, LK, RT, KD-J, IG, and CHFH edited, reviewed, and approved the final manuscript. KB is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest

The authors declare that no conflict of interest exists.

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