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General discussion

 Interruption of the enterohepatic circulation of bile acids can be pathophysiological feature of diseases, such as cystic fibrosis (CF), mostly via intestinal bile acid malabsorption. On the other hand, induction of bile acid malabsorption has emerged as a therapeutic option for specific conditions. Interruption of the enterohepatic circulation has implications beyond changes in the intestinal absorption of lipids an fat soluble vitamins. In this thesis we assessed both bile acid malabsorption in a disease state, CF, and as a possible therapy for hypercholesterolemia, obesity, type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD).

Clinical assessment of bile acid homeostasis and hepatic disease in cystic fibrosis

CF is an autosomal recessive genetic disorder resulting in dysfunction of the cystic fibrosis transmembrane regulator (CFTR) protein. CFTR functions as a transmembrane chloride transporter and its dysfunction leads to formation of abnormally thick, dehydrated mucus in various organs. Clinically, exocrine pancreas insufficiency leading to nutritional problems and pulmonary issues such as recurring infections and fibrosis have been the main cause of morbidity and mortality. Over the last 50 years, improved treatment options for CF have dramatically increased life expectancy from about 4 years to a currently predicted median survival of about 44 years (1). At this moment over 300 disease causing CFTR mutations have been identified (2). While most CFTR mutations are well known and can be categorized in genetic severity of disease, the clinical complications and course of the disease for individual patients is still highly variable. There is no good correlation between the type of CFTR gene mutation and specific aspects of the clinical phenotype, suggesting involvement of both genetic and environmental modifying factors (3). With the increase in life expectancy, the importance to address potential clinical problems beyond pulmonary and nutritional issues has increased. Complications of the hepatobiliary and gastrointestinal system are common, with liver disease now being the third leading cause of mortality in CF patients (4). Major complications, such as liver cirrhosis or intestinal obstruction, may overshadow less severe complications, such as constipation or general gastrointestinal discomfort, which, however, can still significantly impact quality of life (5). In chapter 2 we reviewed the liver involvement in cystic fibrosis (cystic fibrosis liver involvement; CFLI) and addressed the complex clinical approach to the pleiotropic nature of CFLI. The pathophysiology of CFLI is poorly understood but, especially in the case of liver
cirrhosis, it is a significant contributor to the CF related morbidity and mortality (6,7). We found that a combination of the heterogeneity of CFLI and the lack of consensus on the definition for CF liver disease (CFLD) or CFLI, hampers the design and execution of targeted diagnostics, therapies and (preclinical) studies (6,8). Unfortunately, preclinical studies of CFLI are also difficult, partly due to the fact that available animal models not consistently reflect the human pathophysiology (9). Another aspect of the clinical phenotype of CF is perturbed bile acid homeostasis which most likely affects CFLI and vice versa (10,11).

In chapter 4 we found that bile acid malabsorption in cystic fibrosis is measurable in plasma via the surrogate markers fibroblast growth factor 19 (FGF19) and 7α-hydroxy-4-cholesten-3-one (C4). FGF19 is released from the distal ileum upon activation of the nuclear farnesoid X receptor (FXR) by absorbed bile acids. C4 is an intermediate molecule in the bile acid synthesis pathway. Under conditions of bile acid malabsorption, plasma FGF19 levels decrease and, by compensatory increased bile acid synthesis, plasma C4 levels increase (12,13). We showed that the disruption of bile acid homeostasis correlates poorly to CFTR dysfunction in other organs/tissues, such as measured by sweat chloride levels, or pulmonary function (FEV1). This highlights the role for organ specificity and modifying factors in CF. It is not surprising that especially the intestine is subject to environmental modifiers. Gastrointestinal factors such as microbiota are directly affected by the environment (e.g. through differences in nutrition or antibiotic use). While this makes the gastrointestinal system in CF difficult to study, it is also attractive for potential therapies as intestinal factors may be more easily modifiable in comparison to targets directly related to the genetic mutation.

Treatment of bile acid malabsorption and gastrointestinal complications in cystic fibrosis

We showed in chapter 5 that treatment with the common laxative, polyethylene glycol (PEG) partially restored the interruption of the enterohepatic circulation in CF mice. PEG is a frequently prescribed treatment for constipation, both in CF and in non-CF patients. CF patients often suffer from constipation and in more severe cases distal intestinal obstruction syndrome (DIOS), defined as acute complete or incomplete faecal obstruction in the ileocaecum (14). In a cohort of pediatric CF patients, prevalence of constipation was 47% and this correlated to degree of fat malabsorption (5). The potential clinical significance of constipation and the use of PEG in CF patients should therefore not be underestimated. In CF mice it was previously shown that intestinal features including small intestinal bacterial
overgrowth and intestinal inflammation improved upon PEG treatment (15). Both CF mice and patients display an increased intestinal permeability (16–20). In a recent study, chow fed PEG treated mice were shown to be protected from development of significant dysbiosis (more *Escherichia Coli*) and CF-related cholangiopathy in the liver compared to CF mice fed with a liquid diet high in medium chain triglycerides, suggesting a role for dysbiosis and intestinal permeability in CFLI (21). The mechanism underlying the improvements upon PEG treatment is not understood. PEG treatment altered microbiota and decreased fecal excretion of secondary bile acids in (non-CF) rats (22). It is therefore tempting to speculate that in the CF condition PEG may also alter the microbiota and that this is related to its effects on the bile acid homeostasis. Alternatively, direct improvements of the viscosity of the intestinal mucus layer might be involved. In WT mice, (high doses of) PEG significantly changed the mucus layer and microbiota (23).

CF patients display aberrant intestinal microbiota compared to non-CF controls (24). Overt problems like intestinal dysbiosis and small intestinal bacterial overgrowth (SIBO) are common complications in CF. These problems in CF patients are complex since patients may not only be predisposed to dysbiosis due to consequences of the disease (changes in mucus and immune function) but also indirectly, as the result of frequent antibiotic use for pulmonary infections (25). Improving dysbiosis via probiotics (*Lactobacillus reuteri, Lactobacillus rhamnosus GG* or a mix of strains) has shown promising effects on gastrointestinal function by lowering fecal calprotectin levels, a marker for intestinal inflammation, and in decreasing the frequency of pulmonary exacerbations (26). A bi-directional relationship exists between bile acid homeostasis and intestinal microbiota (27). Changes in absolute or relative (intestinal) bile acid levels can alter the composition microbiota species as they can be toxic to certain species while providing provide others with reaction substrates. In turn, abundance of specific microbiota species with the ability to biotransform bile acids, changes the (intestinal) bile acid profile and subsequent bile acid activated receptor signaling. Therefore, improvement of bile acid homeostasis potentially alters microbiota but treatment of dysbiosis may also affect bile acid homeostasis. Furthermore, changes in microbiota and bile acid homeostasis modify gastrointestinal, hepatic, immune and metabolic functions (27,28). Based on current literature, we speculated on a multitude of potential effects of bile acid malabsorption in CF on these functions in chapter 3 (10).
Apart from improving bile acid homeostasis with PEG in CF mice, we demonstrated in chapter 4 that ivacaftor, a CFTR potentiator, improved key parameters of bile acid homeostasis in CF patients with a class III gating mutation. The improvements did not correlate with any other measured CF related outcomes, including sweat chloride levels, a surrogate marker for CFTR function (in sweat glands). Ivacaftor treatment has also been shown to improve other gastrointestinal factors in CF (29). In a case report of a 6-year old CF patient, ivacaftor treatment reduced histologic mucus inspissation in the small intestine (30). A recent study showed that ivacaftor treatment in CF patients decreased intestinal inflammation (as measured by fecal calprotectin) and induced changes in intestinal microbiota potentially related to the improvements in inflammation (increase in Akkermansia and decrease in Enterobacteriaceae species) (31). However, the underlying mechanism of these gastrointestinal improvements and bile acid homeostasis in CF remains unexplained. Based on current literature and our observations of improved bile acid homeostasis upon PEG or ivacaftor treatment, bile acid malabsorption could either be caused by 1) an altered mucus layer, 2) changes in microbiota, 3) a direct effect of CFTR on ASBT function or expression, 4) a direct effect of CFTR on FXR activation or expression, or a combination of any of these factors (Fig. 1). As all these factors are modifiable (i.e. FXR agonists, probiotics), research into the underlying mechanism could also potentially lead to novel drug based therapies.
Chapter 9

Figure 1. Overview of potential (in)direct effects of CFTR function on intestinal bile acid absorption. Lumenal BA are absorbed either actively via ASBT or passively after deconjugation over the membrane. Intracellularly, BA activate FXR for subsequent release of FGF15/19 into the blood. ASBT: apical sodium dependent bile acid transporter, BA: bile acids, FGF15/19: fibroblast growth factor 15/19, FXR: farnesoid X receptor.

The role of ASBT in intestinal cholesterol and fat absorption and the consequences for transintestinal cholesterol excretion (TICE)

In chapters 6 and 7 we demonstrated that genetic inactivation of ASBT nearly abrogates intestinal cholesterol absorption and significantly decreases overall fat absorption, with the most pronounced effects on the absorption of saturated fatty acids. Cholesterol is disposed from the body mainly via the feces in the form of acidic sterols (bile acids) or neutral sterols (cholesterol and its microbial metabolites). The fecal source of neutral sterols is either via the diet, the bile or the direct excretion through a pathway known as transintestinal cholesterol excretion (TICE). TICE has recently become recognized as a major contributing pathway to
cholesterol excretion in both mice and humans (32–34). To what extent cholesterol excreted into the intestine via the TICE pathway is subjected to reabsorption is not known. In chapter 6 we used ezetimibe, an NPC1L1 inhibitor, and genetic inactivation of Asbt (Asbt<sup>-/-</sup> mice) to investigate the contribution of cholesterol reabsorption to TICE. Previous data suggested that fractional cholesterol absorption is only partially decreased in Asbt<sup>-/-</sup> mice (35). However, we found that intestinal cholesterol absorption in Asbt<sup>-/-</sup> mice was completely abrogated, to the same extent as treatment with ezetimibe. Previous studies showed that ezetimibe increased fecal sterol excretion beyond what was expected based upon dietary and biliary input (36–38). This mechanism was majorly dependent on the presence of the cholesterol efflux transporters, ATP-binding cassette sub-family G members 5 and 8 (ABCG5/8). ABCG5/8 mediate both cholesterol efflux from the liver into bile and from the intestine directly into the lumen (39). We found no difference in intestinal expression of Abcg5/8 upon abrogation of cholesterol absorption. We argue based on our data that impairment of cholesterol absorption is a main driver of TICE because abrogation of cholesterol absorption using two different models, caused a similar change in TICE flux. Our interpretation of these observations is that there is a continuously present Abcg5/8 mediated TICE flux that, under physiological conditions, is predominantly reabsorbed (38). TICE has been recognized as a potential target for drugs in the treatment for hypercholesterolemia (40). Based on our interpretation, we proposed a new model of (intestinal) cholesterol fluxes where intestinal excretion (i.e. TICE) minus intestinal (re)absorption is represented by the net transintestinal balance (Fig. 2). This means TICE can be increased either by direct stimulation of involved efflux mechanisms and/or by inhibition of the intestinal (re)absorption. Our present results offer an explanation for the previously described major additional effect of treatment with an intestinal FXR agonist in conjunction with ezetimibe on fecal cholesterol excretion (41). Overexpression of Abcg5/8 was also shown to greatly induce biliary and intestinal cholesterol efflux (42). Therefore, we speculate that treatments that target both induction of TICE and inhibition of cholesterol (re)absorption could be very efficient for the prevention and management of hypercholesterolemia.
Figure 2. Proposed model of cholesterol fluxes contributing to fecal neutral sterol excretion. The net transintestinal (cholesterol) balance is represented by \([\text{excretion}]-[(\text{re})\text{absorption}]\) and is calculated by subtracting biliary and dietary cholesterol input from fecal neutral sterol output.

The mechanism underlying the effects of ASBT inhibition on cholesterol and fat absorption is likely mediated through a significantly decreased bile acid pool that is insufficient to facilitate lipid absorption (35). Bile acids are necessary for the formation of micelles that facilitate the transport of hydrophobic compounds over the unstirred water layer and need to be present in a critical micellar concentration (43,44). This hypothesis is supported by the findings in chapter 7 that the absorption of hydrophobic fatty acids (long chain saturated fatty acids, SFAs) is particularly impaired, whereas the absorption of unsaturated fatty acids is relatively preserved.

*The role of ASBT inhibition in diet induced obesity and glucose metabolism*

Modulating bile acids and their receptors has emerged as an interesting novel therapeutic target in the treatment of various hepatic and metabolic disorders (45,46). While, in chapters 3, 4 and 5 we explored bile acid malabsorption as a result of disease and its potential for treatment, in chapter 6, 7 and 8 we investigated the role of exploiting bile acid malabsorption to improve metabolic abnormalities. We demonstrated the potential of using ASBT inhibition to improve diet induced obesity, glucose metabolism and hepatic lipid accumulation.
General discussion and conclusions

Figure 3. Mechanism of the beneficial effects of ASBT inhibition on metabolism and NAFLD.

Beneficial effects of ASBT inhibition are likely mediated through a combination of altered intestinal bile acid levels and changes in bile acid pool size and profile leading to subsequent changes in lipid absorption, ceramides and FXR and TGR5 signaling. A potential role changed L-cell activation and microbiota might also be involved.

ASBT: apical sodium dependent bile acid transporter, FXR: farnesoid X receptor, FGF15/19: fibroblast growth factor 15/19, GLP-1: glucagon like peptide-1, TGR5: Takeda G-protein coupled receptor 5

Bile acid malabsorption has various beneficial effects on metabolism, and it is likely that changes in multiple processes contribute to these effects (Fig. 3). In chapters 7 and 8 we showed the potential role of decreased fatty acid absorption for the beneficial effects on diet induced obesity, insulin resistance and non-alcoholic fatty liver disease (NAFLD). ASBT inhibition, however, also changes bile
acid pool composition and receptor signaling. Prevention of ileal bile acid reabsorption results, much like bile acid sequestration, in higher colonic bile acid concentrations which are expected to change subsequent receptor signaling. More studies exist on the role of bile acid sequestrant therapy in metabolism than for ASBT inhibition, from which some lessons can be learned. First generation bile acid sequestrants (cholestyramine, colestipol) have a greater affinity for dihydroxy than trihydroxy bile acids while the more recently developed colesevelam binds all bile acid species with high affinity, via both hydrophobic and ionic sites (47). Upon bile acid sequestration bile acids that are not absorbed in the colon induce activation of the G-protein coupled bile acid receptor 1 (GPBAR1, GPCR19 also known as TGR5) and promote glucagon like protein-1 (GLP-1) release (48,49). However, the relationship between colonic bile acid concentrations and GLP-1 release is complex. Trabelsi et al. provided evidence that, in mice, the metabolic benefits of the bile acid binding sequestrant colesevelam are mediated by inhibition of FXR since the beneficial effects of colesevelam on glucose metabolism and GLP-1 disappeared upon genetic inactivation of FXR (50). However, an important difference between bile acid sequestrants and ASBT inhibitors is their effect on bile acid composition. Colesevelam in WT mice increased fecal bile acid excretion of all species, most notably for deoxycholic acid (DCA), while the bile acid pool size and biliary bile acid secretion rate remained unchanged due to compensatory synthesis (51). The biliary bile acid composition consisted of slightly more cholic acid (CA) but otherwise did not change compared to untreated WT mice. In mdr2−/− mice colesevelam increased absolute fecal concentrations of all bile acid species but mostly CA and DCA, thereby increasing hydrophobicity (52). Concomitantly, the biliary bile acid composition shifted towards a more hydrophilic, FXR antagonistic profile, containing more β and ω-muricholic acid (MCA). We have consistently shown in chapters 6, 7 and 8 that ASBT inhibition alters the bile acid profile in bile, plasma and feces towards a more hydrophobic profile, containing more CA and DCA at the expense of β-MCA. Bile acid binding via sequestrants likely alters properties of bile acids, thereby interfering with passive colonic reabsorption and preventing the subsequent increase in DCA concentrations in the plasma and bile. While DCA is a potent activator of TGR5, it is also a potent activator of FXR. In Zucker diabetic rats, treatment with an ASBT inhibitor increased plasma GLP-1 levels and decreased glucose levels (53). Co-treatment with an FXR agonist for two days did not attenuate the effects on glucose levels suggesting that, in contrast to the proposed mechanism of bile acid sequestrants, FXR inhibition is likely not involved in modulating the benefits of ASBT inhibition on glucose metabolism. How
changes in bile acid profile upon ASBT inhibition potentially affect FXR and TGR5 activation and subsequent GLP-1 secretion from the intestine remains elusive. We found that both absolute biliary and fecal concentrations of (tauro-)β-MCA, a potent FXR antagonist (54), decrease upon ASBT inhibition. Compared to colesevelam treatment, these differences in MCA species, could mitigate effects on GLP-1 release in mice. In humans, colesevelam increased the CA pool size at expense of chenodeoxycholic acid (CDCA) and DCA (55). However, these changes correlated poorly to improvements in metabolic parameters. It was suggested that another, indirectly involved mechanism might result in an increase of GLP-1 release through unabsorbed fatty acids activating L-cells in the more distal intestine (56).

We and others consistently demonstrated that ASBT inhibition or genetic inactivation in mice reduces ileal Fxr activation and the expression of its target genes including Fgf15 (35,57–60). Genetic (whole body) inactivation of FXR has been shown to reduce diet induced weight gain and improve glucose metabolism in mice, while specific hepatic FXR deletion did not (61). Moreover, treatment with a selective intestinal FXR inhibitor improved features of diet induced obesity and metabolism in mice via modulating thermogenesis (62). While we did not observe a statistically significant difference in energy expenditure between Asbt⁻/⁻ and WT mice in calorimetric cages (chapter 7), it is still possible that a slight change contributed to the overall beneficial metabolic phenotype.

As previously mentioned, a bi-directional relationship exists between bile acid homeostasis and microbiota (27). Changes intestinal bile acid concentrations alter microbiota composition. In turn, specific microbiota species biotransform bile acids and affect the bile acid pool composition. Because of its profound effects on bile acid homeostasis, ASBT inhibition likely also induces changes in microbiota. However, the specific changes upon ASBT inhibitor treatment have never been assessed and it is even harder to establish how potential changes relate to the observed benefits. Colesevelam treatment in mdr2⁻/⁻ mice significantly altered intestinal microbiota, but the consequences of these changes were not explained (52). In turn, modulating microbiota via a probiotic mixture (VSL#3) has been shown to enhance intestinal bile acid deconjugation, preventing their reabsorption and subsequently reducing Fxr-Fgf15 signaling in mice (63).

The role of ASBT inhibition in non-alcoholic fatty liver disease

We found that ASBT inhibition consistently lowered hepatic lipid accumulation in mice under various of experimental and dietary conditions (chapters 7 and 8) (59). The clinical progression of NAFLD is highly variable with only a minority of patients
with steatosis eventually developing fibrosis. The stage of fibrosis severity correlates well with clinical outcomes and is the strongest predictor for overall and liver-related mortality (64–66). Therefore, prevention of fibrosis has clinically become the most important target for NAFLD therapies. Unfortunately, it is not known what determines whether steatosis will develop into fibrosis. It likely involves a complex of genetic and environmental factors (67). The presence of non-alcoholic steatohepatitis (NASH) was suggested as an important factor increasing the risk of fibrosis but recent studies suggest it to be of limited prognostic value (68,69).

Mice do not readily develop fibrosis on a western type or high fat diet (HFD) unless fed for a considerably long time or combined with another hepatic injury (70). This fact makes preclinical studies on NAFLD – fibrosis progression difficult, although not impossible. In chapter 8 we used a choline deficient L-amino acid defined (CDAA) diet, shown to induce steatosis and subsequent fibrosis after 22 weeks in mice, to explore the effects of ASBT inhibition on development of NAFLD related fibrosis (71,72). We found that in the context of choline deficiency, some of the previously consistent effects of ASBT inhibition including reduction of intestinal lipid absorption and prevention of hepatic triglyceride accumulation (chapters 6 and 7) were attenuated. In addition, ASBT inhibitor treatment did not prevent the development of hepatic fibrosis. The mechanism underlying these effects remains unexplained. Furthermore, while intestinal fat absorption is likely an important contributor to the metabolic and especially hepatic benefits mediated by ASBT inhibition or inactivation, combined consideration of chapters 7 and 8 demonstrate that other factors are involved as well (Fig. 3). It would be interesting to see the effects of ASBT inhibition in different, recently developed, NAFLD mouse models that better mimic the human pathology (73,74).

As there are many similarities between the risk factors and pathogenesis of obesity and insulin resistance and NAFLD, the discussed changes upon ASBT inhibition that reduce diet induced obesity and metabolic abnormalities are likely to also affect NAFLD development (Fig. 2). However, both we, in chapter 8, and Rao et al. showed profound effects on hepatic lipid accumulation without similar effects on bodyweight or glucose homeostasis, suggesting some degree of liver specific effects of ASBT inhibition (59).

Lower intestinal Fxr activation and subsequent Fgf15 expression upon ASBT inhibition could be involved in modulating the effects on hepatic steatosis. In line with the observations on diet induced obesity, specific inactivation of intestinal Fxr in mice reduced HFD induced NAFLD development due to a reduction in ceramide
production (75). However, genetic inactivation of Fgf15 in mice promoted bodyweight gain and hepatic steatosis in a HFD model (76). Conversely, in another study using long-term HFD feeding to induce NASH, steatosis, inflammation and bodyweight gain were not affected, while fibrosis was reduced in Fgf15\(^{-/-}\) mice (77). Hepatic fibrosis was also reduced in Fgf15\(^{-/-}\) mice using carbon tetrachloride injections to induce hepatic fibrosis (78). How the absence of Fgf15 reduced fibrogenesis in these studies remained unexplained. Fxr\(^{-/-}\) mice on a methionine choline deficient (MCD) diet, showed decreased steatosis compared to controls but increased NASH and fibrosis (79). This was explained by increased hepatic bile acid concentrations, which is not observed upon ASBT inhibition, that resulted in hepatotoxicity. Another potential explanation for reduced hepatic lipid accumulation, proposed by Rao et al., involves the change in hepatic bile acid composition to contain more FXR agonistic species, changing hepatic specific FXR signaling and subsequently affecting mainly lipogenesis (59). Both whole body and hepatic specific Fxr\(^{-/-}\) mice display increased hepatic triglyceride and cholesterol accumulation even on a low-fat control diet (80,81). Hepatic transcriptome data of HFD fed mice treated for 16 weeks with an ASBT inhibitor showed most pronounced changes in genes involved in protein modification and lipid, fatty acid, and steroid metabolism (59). In general, FXR agonists have shown potential benefits in NAFLD and NASH (82). However, most of the studied FXR agonists concomitantly activate both hepatic and intestinal FXR and therefore the (long-term) specific effects of altering increasing hepatic FXR signaling (while decreasing intestinal FXR activation) remain unclear.
Conclusions

Intestinal bile acid malabsorption induces a pleiotropy of changes that, depending on the underlying conditions, can have either positive or negative consequences for health. CF is a monogenetic disease that results in a complex metabolic phenotype, illustrated by the highly variable presentation of liver disease. We showed that bile acid malabsorption is an important feature of CF. Treatment by directly targeting CFTR or by using a laxative improved bile acid homeostasis. Our data indicate that these treatments could affect the bile acid metabolism related gastrointestinal, metabolic and hepatic features of CF. Future studies are necessary to establish the mechanism underlying the bile acid malabsorption in CF and the potential clinical benefits of modulating bile acid homeostasis to improve other complications.

We demonstrated that bile acid malabsorption due to inactivation of ASBT abrogates cholesterol absorption, providing novel insights into the role of cholesterol absorption in the intestinal cholesterol fluxes, including TICE. We further found that the benefits on metabolic homeostasis and NAFLD observed upon ASBT inhibition are partly mediated through a reduction of intestinal fatty acid absorption. Initial studies of ASBT inhibitors showed promising results in primary biliary cirrhosis and T2DM patients, but further application has been limited by a high frequency of gastrointestinal side-effects, mainly diarrhea (83–85). However, SHP626 (formerly LUM002) is currently in phase 2 clinical trials for treatment of NASH (ClinicalTrials.gov Identifier: NCT02787304). In the future, development of novel ASBT inhibitors and possible combined treatments with bile acid sequestrants might improve their tolerability.

Taken together, this thesis highlighted the prominent role of bile acid homeostasis in gastrointestinal, metabolic and hepatic function. Modulating the enterohepatic circulation of bile acids either directly or indirectly is a powerful tool to improve clinical outcomes of various diseases, including CF, T2DM and NAFLD.
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