The Connection Between Bile Acids and Type 2 Diabetes Mellitus

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ABSTRACT

Bile acids (BAs) are steroid molecules that have a hydrophilic and a hydrophobic end, and are synthesized exclusively in the liver, being end product of cholesterol catabolism. Type 2 diabetes mellitus (DM2) is a chronic degenerative disease, with a pathophysiology characterized by insulin resistance (IR), insulin deficiency due to insufficient production of pancreatic ß-cells, and elevated serum glucose levels leading to multiple complications. BAs are related to several metabolic alterations, including metabolic syndrome and DM2. It is currently known that BAs act as a ligand for the nuclear farnesoid X receptor, a receptor with an important role in glucose metabolism, lipids and cellular energy production, as well as in the regulation of production, elimination and mobilization of BAs. BAs have also been reported to act as a signaling pathway through of Takeda G protein-coupled receptor 5. In this manuscript, we describe the interface between BAs and metabolic disorders, in particular DM2, including discussing possibilities in the development of therapeutic procedures targeting BAs as an optional pathway in the treatment of DM2.

Keywords: Bile Acids, FXR, TGR5, Type 2 diabetes mellitus.

INTRODUCTION

Bile acids (Bas) are steroid molecules that have a hydrophilic and a hydrophobic end, and are synthesized exclusively in the liver, being end product of cholesterol catabolism. It was originally thought that BAs would act only in the digestion and absorption of lipids in the small intestine (1). However, in recent years, the action of BAs as metabolic modulators has drawn attention, as studies have shown that Bas are also key players in metabolic control, as a signaling molecule in the regulation of carbohydrate and lipid metabolism (2).

It is currently known that BAs act as a ligand for the nuclear farnesoid X receptor (FXR), a receptor with an important role in glucose metabolism, lipids and cellular energy production, as well as in the regulation of production, elimination and mobilization of BAs (3). BAs have also been reported to act as a signaling pathway through of Takeda G protein-coupled receptor 5 (TGR5) (4).

FXR is quite evident in hepatocytes and enterocytes, controlling multiple metabolic pathways by controlling BAs production through upregulation of ileal fibroblast growth factor (FGF) and hepatic heterodimer, thus maintaining BAs homeostasis (5). Suppression of FXR, on the other hand, promotes glucose homeostasis

by inducing glucagon-like peptide-1 (GLP-1) production (6). TGR5 is most evident in enteroendocrine cells, brown adipose tissue and muscle tissue, and its activation stimulates energy expenditure by inducing GLP-1 release that will regulate blood glucose and reduce weight gain (7).

Thus, BAs as signaling molecules will play important endocrine functions in metabolism, because through the activation of signaling pathways they will regulate besides their own synthesis the metabolic homeostasis, especially of glucose and GLP-1. Therefore, BAs are related to several metabolic alterations, including metabolic syndrome and type 2 diabetes mellitus (DM2), and may include them with an interesting option in DM2 therapy, as well as serve as a research target for the development of drugs for the treatment of other metabolic alterations, based on the interconnection between various organs and systems with BAs and their receptors (8).

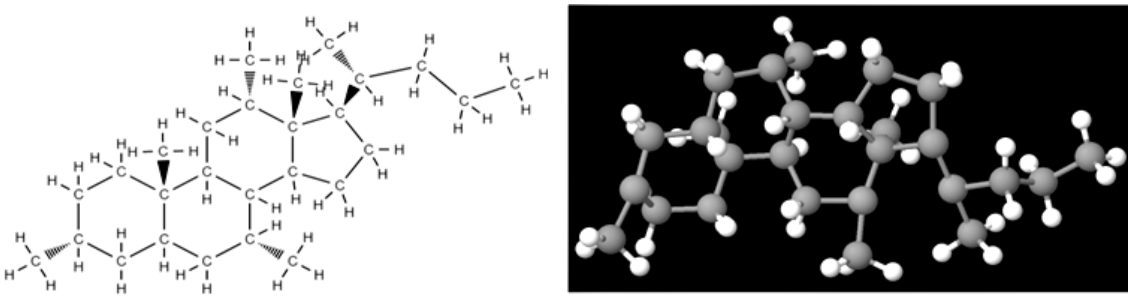
In this manuscript, we describe the interface between BAs and metabolic disorders, in particular DM2, including discussing possibilities in the development of therapeutic procedures targeting BAs as an optional pathway in the treatment of metabolic disorders.

BILE ACIDS

- **Chemistry**

The family of BAs integrates a set of molecular categories of acidic steroids with specific biological and physical-chemical properties. The BAs belongs to a group of chemically diverse steroids which presents a core structure constituted of seventeen carbon atoms organized in four linked rings as follows: one five-member cyclopentane ring and three six-member cyclohexane rings, over the course of a five-eight carbon side-chain which ends with a carboxylic acid and various hydroxyl and methyl conglomerates (9). BAs molecules are around 20 Å long, with a medium radius of approximately 3.5 Å (Figure 1) (10).

Figure 1. Chemical structure (A) and Molecular structure (B) of Bas.



A B

Source: Drawing chemical structures in https://molview.org/?smiles

- **Synthesis**

The synthesis the BAs is realized takes place only in the liver, where a sequence of enzymatic reactions will occur in the hepatocyte transforming the hydrophobic cholesterol in water-soluble amphiphatic groups. The synthesis of BAs occurs through two pathways, the classical pathway and the acidic pathway. The classical pathway resulting in the development of the primary Bas (cholic acid, chenodeoxycholic acid, and deoxycholic acid), and the alternative pathway that can be altered by intestinal flora controlled by the enzyme CYP27A1 transforming oxysterols to secondary Bas. BAs are biologically transformed into taurine and glycine conjugates through of an amidation reaction stimulated by an acyltransferase. Every day about 500 mg of cholesterol is transformed into BAs. Physiologically the primary BAs are the main BAs, comprising about 94% of the total BAs (11,12).

In the late 1990s, BAs recognized as the natural ligands for FXR, which acts as a biological mediator of BA synthesis through transcriptional stimulation of the small inhibitory nuclear receptor heterodimer, and can be stimulated through primary as well as secondary BAs, however chenodeoxycholic acid is possibly the strongest natural BAs ligand (13).

- **Physiology**

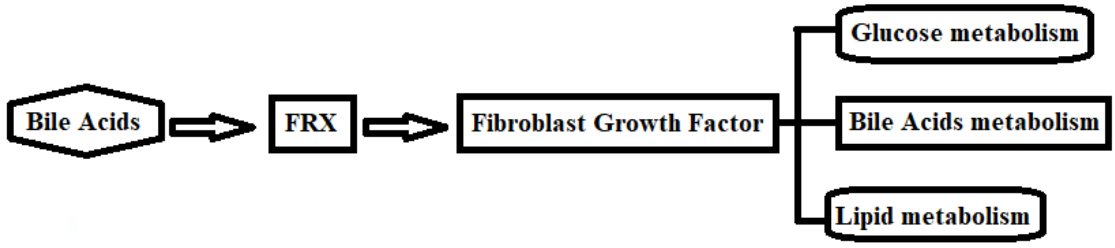
Studies produced in recent years show that in addition to their role in the digestive system, BAs perform the regulation of a diverse range of metabolic activities from lipid homeostasis to glucose metabolism.

Physiological activities of BAs include cholesterol homeostasis, emulsification of fats, metabolism of fat-soluble vitamins, and metabolic regulation (14).

It has been described that BAs have hormonal action through binding to nuclear receptors and modulating the expression of proteins involved in cholesterol

homeostasis. It has been described that BAs have hormonal action through binding to nuclear receptors and modulating the expression of proteins involved in cholesterol homeostasis. Among these nuclear receptors are included the FXR. Thus, the BAs-FXR complex binds to specific genes, stimulating or suppressing their transcription (15). Thus, activation of FXR at the gut level will stimulate FGF-19 synthesis, and through its downstream effect on FGF-19 will maintain glucose, lipid and BAs homeostasis (Figure 2) (16).

Figure 2. Bile acid-mediated modulation in lipid and glucose metabolism



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The BAs also through the TGR5, involved in intestinal motility, lead to the production of GLP-1 which in addition to glycemic control by its insulin stimulating effect on pancreatic ß-cells inhibits gastric emptying (17).

INTERFACE BETWEEN BILE ACIDS AND TYPE 2 DIABETES MELLITUS

DM2 is a chronic degenerative disease, with a pathophysiology characterized by IR, insulin deficiency due to insufficient production of pancreatic ß-cells, and elevated serum glucose levels leading to multiple complications (18).

As mentioned above, individuals with DM2 have alterations in the metabolism of BAs such as changes in synthesis, composition, and excretion. Thus, different sizes of BAs have been described in DM2 individuals when comparing treated and untreated individuals. Similarly the composition of BAs undergoes changes in individuals with DM2 (19). Furthermore, comparative studies between non-diabetic individuals and DM2 patients demonstrated that BAs levels were elevated in DM2 (20). Increases in BAs excretion are associated with glycemic levels in DM2 patients and may represent compensatory elevation in BAs signaling to maintain glucose homeostasis (21).

- **Bile acids and insulin secretion**

The β-cells of the pancreatic islets express TGR5 receptors, which when activated increase insulin secretion at both low and high circulating glucose levels (22).

Thus, BAs exhibit an impact on insulin secretion as a function of TGR5-mediated GLP-1 stimulation (23). At the pancreatic level GLP-1 promotes insulin secretion, β-cell enlargement, as well as acts by preventing apoptosis also of β-cells (24).

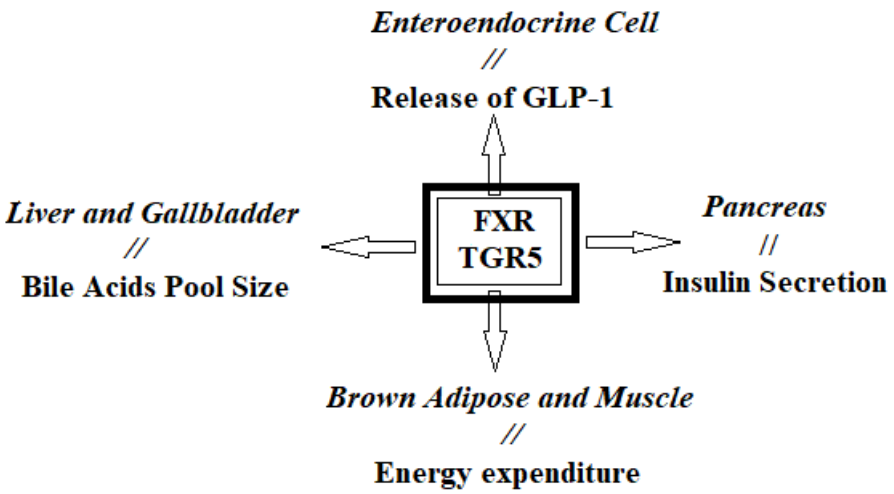
The mechanism of the FXR-dependent insulinotropic effect of the BAs, includes block of potassium channels, membrane depolarization and increased calcium concentration. For the stimulation of insulin secretion the cytosolic localization of FXR, and BAs–induced interrelation with potassium channels are indispensable (25).

- **Bile acids and insulin sensitivity**

Studies show that BAs activate FXR and TGR5 receptors and improve insulin sensitivity (26). The positive impact of BAs on glucose metabolism is mediated by means of the TGR5. TGR5 has high expression in the intestine, and its activation in enterocytes stimulate the secretion of the incretin GLP-1, promoting glucose-dependent insulin secretion (27). GLP-1 is a hormone produced in the intestinal L-cells as a result of food intake that stimulates the insulin secretion and blocks glucagon secretion, favoring the glucose homeostasis (19).

In summary, after ingestion of food, BAs are liberated into the intestine activating FXR and TGR5. FXR activation activates the FGF-19 that contributes to glycogen synthesis and gluconeogenesis. Thus, the activation of TGR5 raises the amount of GLP-1, promoting insulin secretion and reducing blood glucose. BAs returning via the enterohepatic circulation stimulate FXR in the liver, which will also participate in glycolysis and gluconeogenesis. FXR signaling although it does not infer on hepatic insulin sensitivity, does act on insulin sensitivity in skeletal muscle and brown adipose tissue (Figure 3) (28).

Figure 3. Bile acids - insulin secretion and insulin sensitivity



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- **Bile acids and Type 2 Diabetes Mellitus**

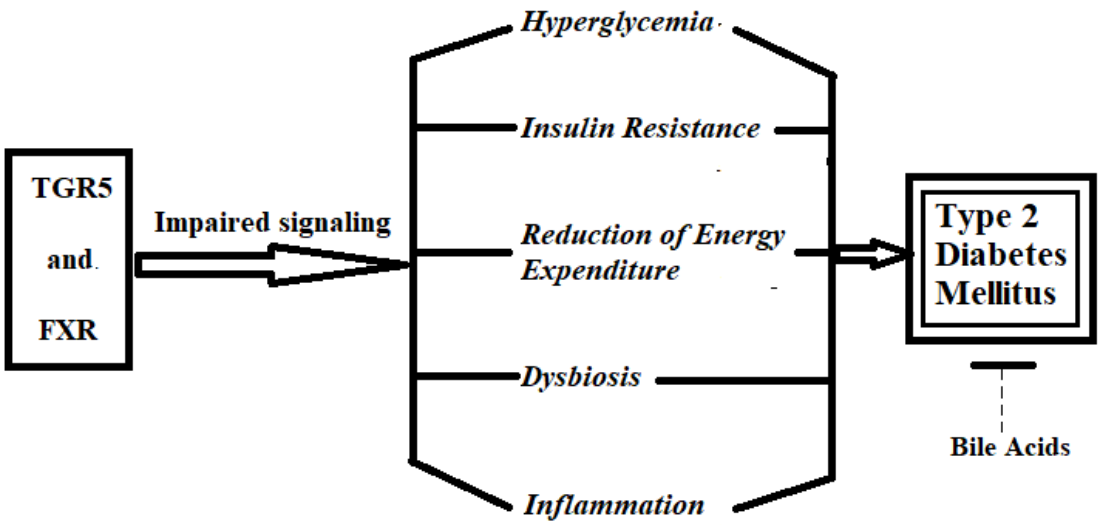
DM2 is resulting from both genetic and environmental conditions and is defined by an inappropriate reaction to insulin in such a way insulin is no longer enabled to activate the absorption of glucose into peripheral tissues such as muscle and fat, inducing IR. Thus, the increased IR decreased insulin sensitivity which will lead to hyperglycemia secondary to reduced secretion of insulin by the pancreatic ß-cells (29).

As described earlier, BAs have a pleiotrophic role in regulating metabolism including insulin secretion by the pancreas and stimulating incretins. Thus, BAs could potentially play the role of a marker of β-cell performance in DM2. Changes in the profile of circulating BAs will favor alterations in the homeostasis of metabolism being involved in the pathogenesis of IR and DM2 (30).

DM2 is related with an elevation in the hydrophobicity of the circulating BAs quantity in humans, and the low regulation of BAs maintains the hyperglycemic state and pancreatic ß-cells degeneration (24). Thus, the accumulation of toxic BAs, lead to inflammatory damage to pancreatic ß-cells, associating with the triggering of DM2.

BAs-TGR5 and FXR signaling modulates glucose homeostasis at the hepatic level which will implicate glycemic metabolism and energy production. Thus, alterations in BAs signaling associated with dysbiosis contribute to the onset or decompensation of DM2. Therefore, the regulation of BAs signaling pathway plays an important role in the metabolic control, and may contribute to the treatment of DM2 (Figure 4).

Figure 4. Bile acids and Type 2 Diabetes Mellitus



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TREATMENT OPTIONS FOR DM2 WITH BAs

The relationship between glycemic levels and serum levels of BAs demonstrated the feasibility of using BAs as part of the treatment of DM2. Thus, BAs have been used in the treatment of DM2 for some years, due to the activation of intestinal FXR and TGR5 receptors that lead to increased secretion of insulin and GLP-1 with consequent glycemic control (31).

Therapeutic plans for elevating BAs levels for glucose homeostasis in DM2 may include: targeting FXR, TGR5 targeting, and BAs sequestrants.

- **Targeting FXR**

FXR was cloned initially in 1995, and it was subsequently shown that the BAs activating it will regulate several metabolic pathways that will interfere with serum glucose levels (32).

GLP-1 is one of the pathways that connect FXR to glucose homeostasis. The stimulation of FXR agonist causes gut microbiome change, leading to the expression of TGR5 agonists which in turn stimulates an enhanced secretion of GLP-1. The upregulation of GLP-1 induces a reduction in blood glucose levels in the course of FXR inactivation (33). Thus, simultaneous stimulation of FXR and TGR5 with GLP-1 activation seems to be an adequate strategy in the metabolic control for DM2.

FXR also inhibits gluconeogenesis via the FXR-FGR-19 pathway, as also FXR activation enhances gluconeogenesis gene transcription and gluconeogenesis in hepatocytes via glucagon, restoring glucose homeostasis (34).

FXR interferes with insulin signaling by increasing insulin secretion as well as insulin sensitivity. FXR acts insulin signaling through the FXR-Kruppel-like factor 11 pathway contributing to preservation of pancreatic β-cell function (35). It has also been shown that FXR agonist treatment causes increment in insulin secretion as a result of inhibition of membrane potassium channels with increased calcium flux through calcium channel in the pancreatic β-cells leading to increased glucose-induced insulin secretion (36). FXR agonists improve insulin sensitivity as well as improve IR insulin in individuals with DM2 through FXR-specific activation. The use of FXR agonists has been shown to restore insulin sensitivity by reducing IRS phosphorylation on Ser(312) and increasing AKT phosphorylation on Ser(437) at the muscle and liver level, triggering insulin transcription and release (37).

Therefore, the action of FXR agonist on glucose homeostasis in DM2 presents itself as an important therapeutic prospect in DM2 as well as serving as a basis for the development of new drugs for this purpose.

- **TGR5 targeting**

Although treatment with TGR5 agonists needs further evaluation, published studies show evidence of therapeutic possibilities related to its modulation, making it an interesting therapeutic target for the treatment of DM2.

TGR5 is G protein-coupled receptors, which is associated with stimulatory G protein being activated by BAs. TGR5 is present in several tissues, including liver, gallbladder, brown adipose tissue, and the intestine, and insulin action can be enhanced by TGR5 activation in macrophages preventing IR. In L cells of the intestine, TGR5 stimulates the secretion of GLP-1 and the anorectic hormone peptide YY (38). Thus, TGR5 may play an important role in the control of DM2, and several chemical compounds with chemical structures diverse have been described as TGR5 agonists for the treatment of DM2.

One of the most important roles of TGR5 is to maintain normal glucose levels and increase in energy expenditure. Among eleven forms of BAs the taurolithocholic acid, as well as fexaramine activates TGR5 agonists which improves IR and glucose tolerance. Furthermore, the activation of TGR5 in muscle and brown adipocytes will activate the enzyme deiodinase 2 converting thyroxine into triiodothyronine stimulating energy expenditure (39).

Studies have shown that the use of TGR5 agonists on high-fat food induced intestinal GLP-1 secretion with restoration of normal glycemic levels. Thus, TGR5 agonist therapy may represent an alternative to the use of incretin and dipeptidyl peptidase IV inhibitors in the treatment of DM2 (40).

What has been shown in the literature is that TGR5 agonists in hyperglycemic situations rearrange pancreatic α cells to produce GLP-1 and increase β-cell mass, resulting physiologically in improved insulin sensitivity, weight reduction and improved IR. Thus, TGR5 agonists present a novel mechanism in glucose homeostasis in DM2 patients.

- **BAs sequestrants**

The collaboration of BAs to the normalization of glycemic feedback in DM2 was especially evidenced by the impacts of BA sequestrants, which interfere with both glucose levels and the profile of BAs. BAs are non-absorbable resins prescribed for

dyslipidemia and surprisingly showed favorable results on glucose homeostasis and insulin sensitivity in individuals with DM2 (41). Of the sequestrants BAs only colesevelam is approved by the US Food and Drug Administration, and by the European Medical Agency for treatment of DM2.

The mechanism of action of colesevelam in reducing plasma glucose levels has several hypotheses. However, it has been shown that colsevelam increases GLP-1 levels mediated by activation of TGR5, activates FRX which, as described above, increases peripheral glucose uptake and reduces gluconeogenesis, and reduces glucose uptake at the intestinal level (42). The guidelines from the American Diabetes Association American (ADA), American College of Endocrinology, and Association of Clinical Endocrinologists include colesevelam as therapies to aid in the management of DM2 (43, 44).

The clinical effectiveness of colesevalan as a complementary drug to the treatment of DM2 have already been evaluated in association with the various treatment options recommended for DM2 that include metformin, SGLT-2 inhibitors, DPP-IV inhibitors, GLP-1 receptor agonists, thiazolidinedione and insulin. However, the ADA mentions colesevelam as a drug to be prescribed in selected patients because of limiting side effects and modest efficacy (45).

CONCLUSION

The great discussions on the use of BAs in the treatment of DM2 would be to what extent their effects have clinical relevance, that is, to what extent the activation of TGR5 and FRX, although we already have the theoretical rationale, will promote glycemic control, what would be the potential adverse effects of this modulation, the use of selective drugs that will act on TGR5 or will act on FRX, or a drug that will modulate all these receptors. Therefore, the great difficulty is the production of a molecule that acts on the BAs signaling in a tissue-specific way that has the ability to significantly normalize glycemic homeostasis without significant side effects.

Competing interests: The authors disclose no conflict of interest.

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