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Bile Acids and Bariatric Surgery

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Abstract

Bariatric surgery, specifically Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG), are the most effective and durable treatments for morbid obesity and potentially a viable treatment for type 2 diabetes (T2D). The resolution rate of T2D following these procedures is between 40-80% and far surpasses that achieved by medical management alone. The molecular basis for this improvement is not entirely understood, but has been attributed in part to the altered enterohepatic circulation of bile acids. In this review we highlight how bile acids potentially contribute to improved lipid and glucose homeostasis, insulin sensitivity and energy expenditure after these procedures. The impact of altered bile acid levels in enterohepatic circulation is also associated with changes in gut microflora, which may further contribute to some of these beneficial effects. We highlight the beneficial effects of experimental surgical procedures in rodents that alter bile secretory flow without gastric restriction or altering nutrient flow. This information suggests a role for bile acids beyond dietary fat emulsification in altering whole body glucose and lipid metabolism strongly, and also suggests emerging roles for the activation of the bile acid receptors farnesoid x receptor (FXR) and G-protein coupled bile acid receptor (TGR5) in these improvements. The limitations of rodent studies and the current state of our understanding is reviewed and the potential effects of bile acids mediating the short-and long-term metabolic improvements after bariatric surgery is critically examined.

Keywords

Bariatric surgery; metabolic surgery; bile acids; metabolism; obesity; Roux-en-Y gastric bypass (RYGB); vertical sleeve gastrectomy (VSG)

1. Introduction – The Obesity Epidemic

The prevalence of obesity has continued to increase over the past 30 years and is associated with increased risk of numerous comorbid medical conditions, including insulin resistance,

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type 2 diabetes (T2D), and cardiovascular disease. Obesity and these associated conditions contribute to increased all-cause mortality (Flegal et al., 2013). In 2008, an estimated 1.46 billion adults globally were overweight (BMI > 25 kg/m²) and 502 million adults were obese (BMI >30 kg/m²). The economic costs associated with obesity are staggering, with healthcare costs alone in the United States at that time being an estimated at \$147 billion (Finkelstein et al., 2009). Given current trends, approximately 50% of American adults will be obese by 2030 (Swinburn et al., 2011) and the economic burden will be unsustainable (Trogdon et al., 2008).

2. Bariatric Surgery is the Most Effective and Durable Treatment for Obesity

Numerous studies have demonstrated that intensive lifestyle intervention consisting of rigorous exercise and dietary restriction can be effective, but result in only modest weight loss (~5-6% of baseline body weight) (Ikramuddin and Livingston, 2013). Importantly, this weight loss is not sustained long-term (The Look AHEAD Research Group, 2014) despite a few individuals losing significant excess body weight (Blackburn, 1995). Even this small degree of weight loss has been shown to be associated with decreased cardiovascular risk, but over time these improvements are lost with weight regain (Wing et al., 2011).

Unlike intensive lifestyle intervention, metabolic and bariatric surgery is the most effective and durable treatment for class III obesity (BMI ≥ 40 kg/m²) with and without diabetes (Pories et al., 1995). In fact, revised guidelines for the management of T2D from the 2nd Diabetes Surgery Summit (2015), endorsed by numerous professional organizations, including the International Diabetes Federation and American Diabetes Association, recommends metabolic and bariatric surgery for the treatment of T2D in individuals with a BMI >35 kg/m². Moreover, these new guidelines stress that individuals with difficult to control diabetes who are obese but with a BMI <35 kg/m² should also be evaluated for metabolic surgery (Cefalu et al., 2016; Rubino et al., 2016).

The long-term efficacy of bariatric surgery is demonstrated by more significant weight loss compared to intensive medical therapy (Dixon et al., 2008; Mingrone et al., 2012; O'Brien et al., 2006; Schauer et al., 2012) in patients with T2D, resulting in decreased overall mortality (Sjöström et al., 2004; 2007). In particular, RYGB is associated with durable remission of T2D, achieving target HbA1C (glycated hemoglobin levels of <6.5%) in ~70% of subjects beyond 3 years (Arterburn et al., 2012; Schauer et al., 2014).

The benefits of metabolic and bariatric surgery are not limited to improved insulin and glucose handling. Cardiovascular disease (Lavie et al., 2009; Sjöström et al., 2004; 2012), cancer risk (Adams and Hunt, 2009; Ashrafian et al., 2011; Sjöström et al., 2009), nonalcoholic fatty liver disease (de Almeida et al., 2006; Lassailly et al., 2013; Vernon et al., 2011) and even pulmonary hypertension (Mathier et al., 2008; Pugh et al., 2013; Sheu et al., 2015) are all markedly improved after these procedures. While many of these improvements are undoubtedly attributable to long-term weight loss, additional data support a weight-independent role for other hormonal or metabolic mediators of the early effects of these operations.

Currently, the two most popular bariatric procedures in the United States are Roux-en-Y gastric bypass (RYGB; Figure 1) and vertical sleeve gastrectomy (VSG; Figure 2). Both operations are effective in promoting weight loss, and data suggest that RYGB may be slightly superior in the long-term. Longitudinal cohorts have demonstrated an average weight loss with RYGB of 10% at 1 month (Dunn et al., 2012), 27% at 6 months, 34% at 1 year (Fabbrini et al., 2010), 33% at 2 years (Tamboli et al., 2014) and 27% at 5 years. The weight loss in these studies was characterized by improved insulin sensitivity and glycemic control, findings consistent with previous reports (Buchwald et al., 2004; 2009). Interestingly, the metabolic improvements occur as early as one week postoperatively, at a time when weight loss is minimal to none; we attribute at least some of these improvements to caloric restriction (E. N. Hansen et al., 2011; Isbell et al., 2010), suggesting the involvement of other additional factors involved in driving the metabolic improvements after bariatric procedures.

3. What are the Mechanisms behind the Effectiveness of Bariatric Surgery?

3.1 Malabsorptive and Restrictive

While the terms “malabsorptive” and “restrictive” have continued to fall out of favor as the field of metabolic and bariatric surgery has matured over the last two decades, it is important to understand the historical context in which these terms originally developed. As surgical and medical management of abdominal trauma improved after the Second World War, survival increased following traumatic bowel resection, despite associated significant weight loss. Specific macronutrient and micronutrient malabsorption were well-documented sequelae of extensive bowel resections (Kremen et al., 1954). From these case series it became obvious that the small bowel was not merely a “uniform tube” and that different regions (e.g. duodenum, jejunum, ileum) had different absorptive capacities and selectivity for nutrients and other molecules (Weckesser et al., 1949). These findings led to the development of deliberate intestinal bypasses (e.g. jejuno-ileal bypass) and resections to promote weight loss in obese subjects. Interestingly, it was documented that bypassing a particular length of small bowel could reliably lead to weight loss; however, operative reversal led to weight regain almost to the exact body weight preoperatively (Payne et al., 1963) – an early example of body weight set-point theory (Harris, 1990). Thus, originally the term ‘malabsorptive’ described the apparent mechanisms of early bariatric operations, in which patients did indeed have significant macro- and micronutrient malabsorption. Even though the weight loss was marked, the morbidity associated with these intentionally malabsorptive procedures was intolerable. Novel operations were developed that focused on restricting the size of the stomach, by partitioning either with an externally restrictive device (e.g. vertical gastric partitioning) or without (e.g. gastric partitioning) (Nguyen et al., 2014). Early operations that were completely restrictive in design failed in terms of weight loss, however, further innovations led to the development of the current operative procedures currently performed, namely, RYGB, VSG and biliopancreatic diversion.

From a clinical perspective it is important to note that patients do indeed exhibit apparent micronutrient malabsorption following bariatric operations, most notably the biliopancreatic diversion (Risstad et al., 2015). However, most clinical studies have not found evidence of

malabsorption in bariatric surgical patients (Carswell et al., 2014; G. Wang et al., 2012). Indeed, the mechanisms leading to the metabolic improvements of these bariatric operations involve far more complex physiologic processes than can be explained by restriction and malabsorption alone (Frikke-Schmidt and Seeley, 2016; Mahawar, 2016; Melissas et al., 2007; Stefater et al., 2012).

3.2 Weight-Dependent vs. Weight Independent

Numerous investigators have examined the short- and long-term changes after bariatric surgery. Typical weight loss following bariatric surgery (Figure 3) has been described by multiple groups and consists of a gradual decline in body mass; however, improvements in glucose homeostasis are apparent within hours to few days following the operative procedures (Knop and R. Taylor, 2013; Pories et al., 1995). As with any treatment that produces weight loss over time, insulin sensitivity and glucose tolerance improve, however, the early observed effects on insulin sensitivity (Figure 3) do not parallel the gradual changes in body weight. These early effects were reported over twenty years ago (Pories et al., 1995), and have assumed more prominence when the same procedures were performed via laparoscopic approaches that minimize the inflammatory responses previously observed with open procedures (Abumrad et al., 2012). One of most challenging aspects of research in bariatric surgery – clinical or animal studies – is identifying the changes driving the metabolic improvements seen postoperatively from those that are merely temporally associated with the decreases in body weight, adiposity, and caloric intake.

3.3 Novel Developments and Insights

Controversy exists regarding the mechanisms of metabolic benefits of bariatric surgery with some attributing most of the improvements to the associated weight loss (Bradley et al., 2012; Fabbrini et al., 2010). Others reported mechanisms include: increased intestinal gluconeogenesis (Saeidi et al., 2013), decreased hepatic glucose production (Dunn et al., 2012), improved β cell function (Isbell et al., 2010; Jørgensen et al., 2012), improved hepatic insulin sensitivity (Fabbrini et al., 2010), improved peripheral insulin sensitivity (Fabbrini et al., 2010; Tamboli et al., 2011) and altered incretin release (D. E. Cummings et al., 2002; E. N. Hansen et al., 2011; Isbell et al., 2010), with the latter derived from entero-endocrine cells (EECs) and proposed as a major contributor to overall metabolic improvements.

We have recently shown that moderate caloric restriction, similar to what is observed in the first days after RYGB (~600-800 kcal/day for 3-10 days), replicate many of the early post-RYGB improvements in glucose homeostasis without elevated GLP-1 levels (Isbell et al., 2010). Severe caloric restriction improves glycemic control and insulin sensitivity without weight loss (Williams et al., 1998). The beneficial effects of caloric restriction appear to be primarily due to reduced fasting and post-prandial hepatic glucose production (Christiansen et al., 2000; Henry et al., 1985; Jazet et al., 2005), and post-prandial (Kelley et al., 1993) or insulin-mediated (Markovic et al., 1998) suppression of hepatic glycogenolysis (Christiansen et al., 2000). Taken together, these studies support a role for caloric restriction immediately after RYGB as one of the underlying anti-diabetic mechanisms improving hepatic glucose production (Gumbs et al., 2005), while the long-term improvements are due

to weight loss resulting in sustained improvements in hepatic glucose production associated with enhanced peripheral (skeletal muscle) insulin sensitivity (Tamboli et al., 2011).

In general, two hypotheses attempting to explain the effects after bariatric surgery are the foregut and hindgut hypotheses. In the foregut hypothesis, exclusion of duodenal nutrient exposure is proposed to inhibit release of an unknown diabetogenic factor. This hypothesis is supported by several studies that have focused on duodenal bypass as being responsible for the weight loss-independent benefits immediately after RYGB (Korner et al., 2005; Laferrère et al., 2007; Morínigo et al., 2006a; Roux et al., 2006); although this has been challenged (Kindel et al., 2011). On the other hand, the hindgut hypothesis posits that rapid delivery of nutrients to the distal intestine causes greater stimulation of L-cells and GLP-1 release, augmenting meal-stimulated insulin secretion and lowering prandial blood glucose. We (Isbell et al., 2010) and others (Kashyap et al., 2010; Laferrère et al., 2007; le Roux et al., 2007; Morínigo et al., 2006a) have described large increases in postprandial GLP-1 immediately after RYGB that are sustained in the long-term (Bose et al., 2010; Morínigo et al., 2006a; 2006b; Vidal et al., 2009). Intriguingly, the increased GLP-1 at one month post-operative coincides with significant increases in total bile acids (Albaugh et al., 2015). As the complex physiology of metabolism and body weight regulation is increasingly appreciated, contributions of both the foregut and hindgut hypotheses are likely at work in these patients and experimental models, though the search for a particular factor linking each of these hypotheses continues to be sought. In this regard, bile acids appear to be uniquely suited to mediate a number of other metabolic changes in animals and humans that have been described following bariatric surgery.

4. Bile Acids

In recent years, bile acids have been implicated as potential mediators of the weight-independent effects of bariatric surgery with respect to glucose homeostasis and insulin sensitivity. The mechanisms leading to these effects are currently of great interest and thus it is important to understand how bile acid metabolism and the enterohepatic circulation may be affected by bariatric operations.

4.1 Synthesis and Metabolism

Bile acid synthesis occurs primarily in the liver through two distinct biochemical pathways referred to as the classic (neutral) and alternate (acidic) pathways, with the classic pathway being responsible for the majority (75%) of bile acid pool size in humans (Thomas et al., 2008). Both of these pathways include combinations of enzymatic conversions that modify a sterol backbone as well as the hydrocarbon side chain of cholesterol. Hepatic cholesterol-7 α -hydroxylase (CYP7A1) is the rate limiting enzyme for the classic bile acid biosynthetic pathway, converting cholesterol to 7 α -hydroxycholesterol and committing it to bile acid production. Alternatively, cholesterol can be acted upon by sterol-27 hydroxylase (CYP27A1) that catalyzes the first committed reaction in the alternate pathway, which is highly expressed in peripheral tissues and macrophages (Schwarz et al., 2001). Both the classic and alternate pathways funnel into the two major precursors of human bile acid synthesis. These precursors can potentially be substrates for sterol 12 α -hydroxylase

(CYP8B1), which hydroxylates the 12 position of the steroid molecule, effectively generating cholic acid (CA). Without 12 α -hydroxylation the resulting bile acid produced is chenodeoxycholic acid (CDCA).

The composition of the bile acid pool as well as the major primary bile acid species, can vary greatly among animal species. This is particularly important when studying the effects of animal models of bariatric operations and attempting to translate those results back to clinical medicine. In humans, CA and CDCA are the most abundant primary bile acids, with the overall bile acid pool being derived from approximately 40% CA, 40% CDCA and 20% deoxycholic acid (DCA) (Chiang, 2013). In rodents this differs significantly, with the major primary bile acid species derived from ~25% CA, ~50% β -muricholic acid (β -MCA), and smaller amounts of α -muricholic acid (α -MCA) as well as other minor species (de Aguiar Vallim et al., 2013). The muricholic bile acids, which do not exist in humans, result from CDCA being additionally hydroxylated on the 6-position of the sterol backbone. Aside from marked difference in primary bile acids, it is also noteworthy that the alternate pathway contributes to a much larger portion of the bile acid biosynthesis in rodents compared to humans (Russell, 2003). Moreover, in many studies examining changes in bile acids following bariatric surgery, bile acids are lumped into broad categories (e.g. primary, secondary, conjugated and unconjugated bile acids), and changes in individual bile acid species may be overlooked. Newly synthesized bile acids are referred to as primary bile acids, while those same primary bile acids can be conjugated with either glycine or taurine in humans and can be referred to collectively as conjugated bile acids. Bile acids that have been chemically transformed by bacteria are referred to as secondary bile acids.

Differences in bile acid chemical structures can also lead to variation in the biologic effects that are intrinsic to each bile acid. The number and position of hydroxyl groups predominately determines the hydrophilic index of bile acids and this index differs greatly among individuals depending on disease phenotype (Haeusler et al., 2013). Presence of hydroxyl groups above and below the sterol backbone ring (α and β orientations, respectively) confers increased hydrophilicity compared to hydroxyl groups in only one orientation. For example, the presence of 6 α - and 7 β -oriented hydroxyl groups in MCA and 7 β -orientation of the hydroxyl group in ursodeoxycholic acid (UCDA) confer more hydrophilic properties than most other species. Hydrophobic bile acids (e.g. LCA) have been shown to be cytotoxic and have been linked to a number of GI tract malignancies (Ajouz et al., 2014), suggesting that they contribute to inflammation and potentially increase epithelial permeability (Stenman et al., 2013). On the other hand, hydrophilic bile acids have been shown to have cytoprotective properties (Amaral et al., 2009; Barrasa et al., 2013).

Gut microbiota metabolize nutrients and bile acids within the gastrointestinal tract, significantly affecting the intestinal environment. and diversity of secondary bile acid species (Kübeck et al., 2016). Bacterial transformation of bile acids is another factor that may be altered by bariatric surgery. This chemical transformation has been proposed to serve at least two purposes. The first being detoxification of the intraluminal bile acids that can be bactericidal and the second is to liberate the glycine/taurine conjugate that can subsequently be used for bacterial metabolic needs (Ridlon et al., 2006). Bile acids also have intrinsic antimicrobial properties. Typically, bacteria can chemically transform the bacterially-toxic

hydrophobic bile acids to less toxic species by a number of reactions. These reactions include deconjugation, oxidation, sulfation, and dehydroxylation generating secondary bile acids: deoxycholic acid (DCA) and lithocholic acid (LCA) (Staels and Fonseca, 2009). Sulfation is the major detoxification pathway for hydrophobic bile acids (Chiang, 2013). Without bacterial transformation there is a lack of bile acid diversity, as has been demonstrated in germ free mice (Midtvedt, 1974; Ridlon et al., 2006; Sayin et al., 2013). Thus, it is clear that, microbiome-induced changes in bile acid diversity represent potential mechanisms linking bariatric surgery, bile acids, and metabolic improvements (Kaska et al., 2016; F. Li et al., 2013; Seeley et al., 2015) but further studies directly testing these mechanisms are needed to demonstrate their importance and verify that they are not merely changes secondary to metabolic improvements due to other unrecognized pathways.

4.2 Endocrine and Hormonal Functions

The discovery that bile acids could act as receptor ligands opened up a completely new field of biochemistry and biologic regulation (Makishima et al., 1999; H. Wang et al., 1999). In the years since, the potential biologic roles of bile acids have greatly expanded, with the majority of the major metabolic effects being signaled through the farnesoid X receptor (FXR) and the G-protein coupled Bile Acid Receptor (GPBAR, TGR5).

Bile acids play significant roles in lipid and glucose homeostasis (Cariou and Staels, 2007; Jiao et al., 2015; Ma et al., 2006a; Sinal et al., 2000; Y. Zhang et al., 2006) and regulation of energy expenditure (Thomas et al., 2009; Watanabe et al., 2006). These metabolic effects have been linked to the primary bile acid receptor FXR (Caudel et al., 2005; Jiao et al., 2015; Pang et al., 2015; Tu et al., 2000). FXR regulates bile acid synthesis (Fu et al., 2015) by modulating CYP7A1, but FXR also directly influences glucose and lipid metabolism (Cariou et al., 2005; Duran-Sandoval et al., 2005; Sinal et al., 2000; van Dijk et al., 2009; Watanabe et al., 2004). Bile acid-FXR activation stimulates glycogen synthesis (Li et al., 2010), decreases gluconeogenesis (Cipriani et al., 2010; Ma et al., 2006b; Y. Zhang et al., 2006) and increases glycolysis, leading to improved glucose tolerance and insulin sensitivity. In fact, transgenic mice overexpressing CYP7A1 in the liver were found to be resistant to high-fat diet (HFD)-induced obesity and to the development of fatty liver and insulin resistance (T. Li et al., 2010). Interestingly, the use of bile acid sequestrants (e.g. resins) have glucose lowering ability in type 2 diabetic patients, while simultaneously acting as lipid lowering agents (Bays et al., 2008; Fonseca et al., 2008; Garg and Grundy, 1994; Goldberg et al., 2008; Hansen et al., 2014; Staels et al., 2010; Zieve et al., 2007).

TGR5 is not expressed in hepatocytes, but is localized to sinusoidal endothelial cells (Keitel et al., 2008), monocytes (Kawamata et al., 2003), EECs (Habib et al., 2013; Thomas et al., 2009), adipose tissue (Svensson et al., 2013; Watanabe et al., 2006), smooth muscle (Rajagopal et al., 2013), skeletal muscle (Watanabe et al., 2006), pancreas (Kumar et al., 2012) as well as the central nervous system (Poole et al., 2010). Through kinase signaling pathways, TGR5 activation stimulates gallbladder filling (T. Li et al., 2011), modulates energy expenditure (Watanabe et al., 2006), stimulates GLP-1 release from intestinal L cells (Habib et al., 2013; Katsuma et al., 2005; Thomas et al., 2009), suppresses hepatic glycogenolysis (Potthoff et al., 2013) reduces inflammation (Frikke Schmidt et al., 2016)

and inflammatory macrophage activation (Kawamata et al., 2003; Keitel et al., 2008; Lou et al., 2014; Maruyama et al., 2002; Y. D. Wang et al., 2008), improves pancreatic function (Kumar et al., 2016; Vettorazzi et al., 2016) and improves non-alcoholic fatty liver disease (Ding et al., 2016). TGR5 knockout mice have mildly reduced BA pools (Maruyama et al., 2006; Vassileva et al., 2006), impaired glucose tolerance (Thomas et al., 2009) and exacerbated inflammatory responses (Péan et al., 2013).

Metabolic activation of specific bile acid receptors, particularly involving FXR, vary with bile acid species. For example, UDCA has been shown to be antagonistic to FXR and leads to increased bile acid synthesis through decreasing intestinal expression of FGF19 (Mueller et al., 2015); selective FXR inhibitors (i.e. glyco- β -tauro-muricholic acid) have been effective in reversing obesity and improving associated metabolic parameters (Jiang et al., 2015). In contrast, FXR agonists decrease energy expenditure (EE) and induce obesity and insulin resistance in mice (Watanabe et al., 2011). FXR is highly expressed in the liver and intestine and when bound to bile acids, activates complex transcription program to inhibit expression of Cyp7A1 and epithelial transport proteins that control the enterohepatic bile circulation (Chiang, 2013, 2009; Stroeve et al., 2010).

4.3 Digestive Physiology and the Enterohepatic Circulation

After bile acids are synthesized within the liver they are secreted into the biliary circulation, subsequently stored in gallbladder, and then eventually released into the duodenal lumen of the intestine in response to dietary intake (Thomas et al., 2008). Bile is an electrolyte fluid enriched in bile acids, phospholipids (lecithin), bilirubin and cholesterol, which facilitates the emulsification of dietary fat. Bile acids are absorbed through both passive and active mechanisms in the small intestine (Dawson et al., 2003; 2009). Passive bile acid absorption occurs throughout the length of intestinal lumen, but active transport of bile acids exclusively occurs in the ileum (Einar Krag, 1974; Schiff et al., 1972). Most bile acids are reabsorbed actively in the distal ileum by brush border apical sodium-dependent bile acid transporter (ASBT) and multi-drug resistance-associated protein 3 (MRP3) (Dawson et al., 2009). Bile acids are shuttled through the enterocyte to the basolateral membrane by the ileum bile acid binding protein (IABP) and are ultimately exported across the basolateral membrane into portal circulation by the heteromeric organic solute transporter, OST α /OST β (Ballatori et al., 2005; Dawson et al., 2009; 2005). Bile acids that escape ileal uptake enter the colon, where commensal gut bacteria deconjugate, oxidize, and dehydroxylate primary bile acids into secondary bile acids. The net daily turnover of the bile acid pool in humans is about 5%, with the entire pool being approximately 3 grams (Chiang, 2013). In the enterocytes, once the bile acids are transported to the basolateral membrane, they are secreted into portal circulation by organic solute transporter and heterodimer (OST α /OST β). In liver sinusoids, bile acids are taken up by Na⁺-dependent taurocholate cotransport peptide (NTCP) into hepatocytes (Kosters and Dawson, 2015).

Several studies have examined how bile acid chemical species diversity and pool size vary across species, however, differences that specifically result from bariatric surgery or other intestinal manipulation have not been well studied. Regardless, significant decreases in bile acid pool size likely exist among animal species, especially in mammals that lack a

gallbladder (e.g. the rat). Surgical removal of the gallbladder (cholecystectomy) in humans does not change the overall bile acid pool composition, but pool size is decreased (Berr et al., 1989). The decrease in pool size is attributed to the lack of the gallbladder, which is the major storage site in human and also due feedback inhibition of bile acid synthesis mediated through FXR-mediated inhibition of CYP7A1 in the classic synthetic pathway (Kullak Ublick et al., 1995). Additionally, intestinal transit time may also affect the enterohepatic circulation and subsequently bile acid composition (Duane, 1978; Duane et al., 1976; Duane and Hanson, 1978). Further, the changes in transit time may also influence the gut microbiome that accompany bariatric operations and alter bile acid diversity (Fiorucci and Distrutti, 2015; Furet et al., 2010; Ridlon et al., 2006; Swann et al., 2011).

5. Bile Acids and Obesity

The links among bile acids, energy expenditure (Broeders et al., 2015; Watanabe et al., 2006), and GI hormone signaling (Knop, 2010; Thomas et al., 2009), represent attractive targets for induction of various the metabolic changes associated with bariatric surgery. Several factors related to obesity, insulin sensitivity, diet and diet composition may impact bile acid homeostasis independent of bariatric surgery, and those factors are not currently well understood. It is clear from the literature that there are fundamental differences in bile acid metabolism regulated by total body adiposity between lean and obese individuals independent of insulin resistance. Several groups have shown decreased circulating concentrations of bile acids in obesity relative to leans (Albaugh et al., 2015; Cariou et al., 2011), though others suggest that insulin resistance drives increased bile acid synthesis and circulating bile acids (Haeusler et al., 2015; Sun et al., 2016). In addition to increasing synthesis and pool size, insulin resistance is associated with altered bile acid composition, specifically increased abundance of 12 α -hydroxylated bile acid species which may be important negative regulators of insulin action (Haeusler et al., 2013). Given that obesity and insulin resistance are generally highly correlated, this apparent disconnect between bile acid concentrations and body mass is paradoxical. Further complicating the study of these phenomena in obesity are the confounders of age and sex (Prinz et al., 2015; Xie et al., 2015), both of which appear to influence circulating bile acid concentrations and lead to significant inter-individual variability (Frommherz et al., 2016). Moreover, longitudinal data has actually showed that weight loss leads to lower bile acid concentrations in the plasma. Thus, it is clear that the metabolic abnormalities associated with obesity, insulin resistance and T2D exist on a spectrum and are not necessarily independent of one another, and may be a function of altered enterohepatic bile acid circulation (Haeusler et al., 2015). Better understanding of the molecular basis for these improvements is an area of intense research (Wewalka et al., 2014).

A clear understanding of the contribution of bile acids to metabolic improvements after bariatric procedures is confounded by concurrent improvements in insulin sensitivity secondary to weight loss (Andersén et al., 1988). It is well-known from animal studies that high concentrations of glucose and insulin stimulate the expression of CYP7A1, the rate-limiting step of bile acid synthesis, to increase the bile acid pool (T. Li et al., 2012). Consistent with elevations in glucose, urinary bile acids that represent spill-over from the enterohepatic circulation to the periphery are associated with higher HgbA1c (D. R. Taylor

et al., 2014). Consistent with this hypothesis, reductions of 12 α -hydroxylated species appear to be beneficial in diabetes and obesity (Haeusler et al., 2012; Qi et al., 2014). Hepatic expression of the bile salt export pump (BSEP) as well as the sodium-taurocholate co-transporting polypeptide is also decreased in obese relative to lean subjects, (Haeusler et al., 2015) potentially introducing another confounder.

Caloric restriction and altered dietary composition are two factors that contribute to at least some of the metabolic improvements following bariatric surgery. While caloric restriction does not appear to affect bile acid pool size or composition in man (Duane et al., 1976; Jahansouz et al., 2016; van Nierop et al., 2016), the few studies that have examined the effect of altering dietary fat source and fat composition, commonly occurring in the postoperative period, have yielded inconsistent effects (Andersén and Hellström, 1980; Lindstedt et al., 1965). Diet is known to induce changes in bile acid species and total bile acid pool (Bisschop et al., 2004; M. Zhang and Yang, 2016), and these are likely intricately related to the gut microbiome (Kübeck et al., 2016). Finally, it is important to take into consideration the species differences while extrapolating differences between humans and rodents where changes in bile acid composition and concentration have been reported (Ferland et al., 1989; Fu and Klaassen, 2013).

The identification of bile acids as metabolic mediators has motivated some to pursue interventional studies examining potential off-target effects, but the number of those studies has been few. One interventional study showed that 6 weeks of oral tauro-ursodeoxycholic acid, a bile acid that has been shown to be elevated early after RYGB (Albaugh et al., 2015), improves hepatic and skeletal muscle insulin sensitivity in obese, insulin resistant subjects without frank diabetes (Kars et al., 2010). Animal models have suggested numerous off-target effects of ursodeoxycholic acid (UDCA), including alleviation of endoplasmic reticulum stress (Özcan et al., 2006; Roma et al., 2011), augmented glucose-stimulated insulin secretion (Düfer et al., 2012) and augmentation of the incretin effect through GLP-1 and potentially other incretin hormones (Rafferty et al., 2011), though data in humans are limited (Murakami et al., 2013).

5.1 Bile Acids and Bariatric Surgery – Clinical Experience

There are a number of bariatric procedures performed around the world, but as mentioned the most prevalent worldwide are RYGB (Figure 3) and VSG (Figure 4). Over the last decade numerous clinical studies have reported changes in bile acids associated with bariatric surgery procedures (Table 1). In large part, human studies have confirmed that fasting or postprandial total bile acid concentrations are increased following RYGB (Ahmad et al., 2013; Albaugh et al., 2015; De Giorgi et al., 2015; Ferrannini et al., 2015; Gerhard et al., 2013; Jahansouz et al., 2016; Jørgensen et al., 2015; Nakatani et al., 2009; Pournaras et al., 2012; Simonen et al., 2012; Steinert et al., 2013; Werling et al., 2013b) and BPD (Ferrannini et al., 2015; Nakatani et al., 2009). The effects of VSG on bile acid levels is mixed with some showing increased plasma concentrations (Jahansouz et al., 2016; Khan et al., 2016; Steinert et al., 2013), but others detecting no change (Belgaumkar et al., 2016; Escalona et al., 2016; Nakatani et al., 2009). As expected, studies examining adjustable gastric banding, known to be an exclusively restrictive procedure, show no changes in

circulating bile acids (Kohli et al., 2013a; Pournaras et al., 2012). While most studies report a preoperative and then a single postoperative time point for comparison (Coupaye et al., 2013; Ferrannini et al., 2015; Pournaras et al., 2012; Simonen et al., 2012; Werling et al., 2013b), only a few have reported longitudinal observations with multiple measurements (Albaugh et al., 2015; Jørgensen et al., 2015; Steinert et al., 2013). These longitudinal studies, with repeated measures over time, have demonstrated that there are considerable fluctuations in plasma bile acids that may have biologic effects, the mechanisms of which have not yet been determined.

Given the increased appreciation for the endocrine effects of bile acids, much research over the last decade has focused on describing the potential mechanism involved in the influence of bile acids on the overall metabolic improvements associated with bariatric surgical operations. Early studies demonstrated that GI rearrangement or diversion of GI secretions was associated with changes in glucose homeostasis (Ermini et al., 1991; Leriche and Joung, 1939; Manfredini et al., 1985; Takahashi et al., 1996). Subsequent studies also noted that increased exposure of the distal intestine to proximal GI secretions enhanced bile acid absorption (Tsuchiya et al., 1996). The enhanced and more rapid delivery of pancreatic and gallbladder secretions to the distal bowel is a central feature in RYGB and BPD operations, but also occurs in VSG. As mentioned above, the relevance of bile acids to the metabolic improvements after bariatric procedures was not fully appreciated until bile acids were recognized as endogenous hormones. Subsequently, a cross-sectional study demonstrated that individuals who had previously had RYGB had increased circulating concentrations of bile acids compared to weight-matched individuals (Patti et al., 2009). Regardless of what has been demonstrated clinically, no studies to date have shown unequivocally that changes in bile acid metabolism are necessary or sufficient for the metabolic benefits of bariatric surgery.

5.2 Bile Acids and Bariatric Surgery – Experimental Models

Experimental models of metabolic and bariatric operations that have been developed over the last decade have provided a wealth of data on the mechanisms of these operations (Table 2). The VSG and ileal interposition procedures have been most studied in rats and mice, given that they are technically simpler than the RYGB and bile diversion operations. Similar to what is observed clinically, VSG increases total bile acids in rats (B. P. Cummings et al., 2012) and mice (Ding et al., 2016; Myronovych et al., 2014), with apparent increases in conjugated as well as unconjugated species. Studies of RYGB have also demonstrated increased bile acids in rat studies (Bhutta et al., 2015; Spinelli et al., 2016).

One of the advantages of rodent models is the ability to isolate a particular portion of the bariatric operation in order to ask focused, hypothesis-driven questions. For example, the duodenal-jejunal bypass isolates the ‘bypass’ portion of RYGB in the absence of gastric restriction and has metabolic effects in obese and lean rodents (Habegger et al., 2014; Kindel et al., 2011; 2009; B. Li et al., 2013; Rubino and Marescaux, 2004; Wu et al., 2016; X. Zhang et al., 2015). Moreover, similar to the RYGB and BPD operations, ileal interposition isolates the effects of intestinal rearrangement that permit high concentrations of bile from the upper GI tract to reach the ileum and/or large intestine. Ileal transposition, a procedure

that interposes a segment of the distal ileum in a more proximal jejunal position, has been shown to improve insulin sensitivity and glucose tolerance (Culnan et al., 2010; B. P. Cummings et al., 2010; Ikezawa et al., 2012; Strader et al., 2009) in a number of genetic and diet-induced obesity/diabetic rodent models. Similar to the observed findings with ileal interposition, bile diversion operations (Flynn et al., 2015; Kohli et al., 2013b; Pierre et al., 2016; X. Zhang et al., 2015) result in complete diversion of bile from the upper GI tract to either the mid-jejunum (Goncalves et al., 2015; Kohli et al., 2013b) or ileum (Flynn et al., 2015); both of which are associated with not only significant elevations in circulating plasma bile acids but also improved glucose tolerance, insulin sensitivity, hypophagia, weight loss and resolution of hepatic steatosis. It is clear that the major common theme amongst these exploratory procedures – bile diversion, ileal interposition, and duodenal-jejunal bypass – is a paradoxical elevation of plasma bile acids.

The mechanisms of why these animal models increase plasma bile acids remains unclear. Based on the current known mechanisms controlling bile acid homeostasis, the observed increases in circulating bile acids following bariatric procedures should negatively regulate synthetic machinery through direct (FXR transcriptional control) and/or indirect bile acid-mediated (FGF19/FGFR4) mechanisms (Chiang, 2009; S. Li et al., 2014; Staels and Fonseca, 2009). In our recent publication (Flynn et al., 2015), we observed that diversion of bile from the gall bladder to the terminal ileum did not result in suppression of CYP7A1 activity, suggesting that CYP7A1 must be under the influence of additional pathways that are not considered part of the classic (neutral) and alternate (acidic) pathways involved in bile acid synthesis. This area requires intense investigation, and may require examination of the various pathways involved in bile acid clearance, or even examining the involvement of the microbiome in influencing bile acid homeostasis. In this regard, fecal bile acids have been reported as either decreased (Kohli et al., 2010) or unchanged (Kohli et al., 2013b; Pierre et al., 2016) after ileal interposition or bile diversion, respectively, while similar data in RYGB has shown conflicting results (Bhutta et al., 2015; J. V. Li et al., 2011).

Numerous studies have examined the kinetics of bile acid homeostasis, including the contributions of hepatic synthesis and clearance through fecal and urinary losses. Isotopic dilution techniques have been described *in vivo* (Everson, 1987; Hulzebos et al., 2001; Stellaard et al., 1984) as well as *in vitro* (Robins and Brunengraber, 1982). As bile acids have become recognized as receptor ligands, however, few studies have examined the impact of tissue accumulation of bile acids on the ensuing metabolic effects (Swann et al., 2011). Tissue specific changes in both receptors, FXR (Ryan et al., 2014) and TGR5 (Ding et al., 2016; McGavigan et al., 2017) are expected to drive a significant component of the overall metabolic effects after bariatric surgery. However, receptor-knock out studies have failed to completely abrogate all the beneficial metabolic effects of bariatric surgery. Further studies of tissue-specific and whole-body knockout mice are necessary to understand which receptors drive specific metabolic effects on food intake, taste preference, glucose and lipid metabolism. As mentioned above, though, confirmatory human studies are necessary in any of these cases as rodent and human physiology differ significantly.

6. Observations and Caveats from Experimental Models

There are a number of caveats to the experimental models of bariatric surgery that must be considered when attempting to translate the findings to humans. One of the most disputed areas relates to the discrepancies between the observed increased energy expenditure (EE) with RYGB in rodents (Bueter et al., 2010; Nestoridi et al., 2012; Stylopoulos et al., 2009) and mice (Flynn et al., 2015) versus the decreased EE observed in humans (Carey et al., 2006; Knuth et al., 2014; Tamboli et al., 2010), though this is still disputable depending on the techniques used to analyze the data (Dirksen et al., 2013; Werling et al., 2013a). Our recent findings of similar observed increases in EE in mice following bile diversion (Flynn et al., 2015) implicate a role for bile acids in modulating EE. The bile acid-induced increases in EE in mice are mediated by activation of brown adipose tissue deiodinase enzyme expression in both rodents (Watanabe et al., 2006) and humans (Broeders et al., 2015), but the effects in humans appear to be less robust. Exogenous administration of chenodeoxycholic acid (CDCA) to 12 healthy female subjects for two days resulted in increased oxygen consumption and EE (Broeders et al., 2015). Regardless, the bile acid induced changes in EE do not appear to play a significant role following bariatric surgical procedures in humans (Carey et al., 2006; Knuth et al., 2014; Tamboli et al., 2010) and this is an area that requires further investigation.

A second factor that differs substantially between rodents and humans post-bariatric procedures relates to the degree of segmental intestinal partitioning of nutrient handling and their involvement in the metabolic improvements associated with bariatric surgery. The separation of bile and pancreatic secretions from enteral nutrient flow is associated with significant changes in intestinal reprogramming of nutrient handling. Stylopoulos et al. demonstrated that RYGB is associated with reprogramming of intestinal glucose metabolism in the Roux limb of RYGB-treated rats, resulting in increased intestinal glucose metabolism in that segment (Saeidi et al., 2013). Interestingly, recent studies by Baud et al. demonstrated negligible glucose absorption in the bile-deprived alimentary limb (AL); glucose uptake in the AL was restored by the addition of bile (Baud et al., 2016). Despite these observations, there is concordance of observations demonstrating significant macronutrient malabsorption, primarily involving lipids, with RYGB and bile diversion in mice (Flynn et al., 2015; Hao et al., 2013) and rats (Shin et al., 2013; Stylopoulos et al., 2009). No studies have yet addressed the effects of specific intestinal segment specific re-organization on fatty acid absorption in RYGB.

Intestinal nutrient sensing, mediated by the enteroendocrine cells (EEC) and/or intestinal neuronal pathways, plays a key role in intestinal response to nutrient absorption and handling (Breen et al., 2012; Lam et al., 2010; Pal et al., 2015; Zadeh-Tahmasebi et al., 2016). Numerous investigators posit that bile acids target apically-expressed TGR5 on EEC along the GI tract (Engelstoft et al., 2008; Reimann et al., 2012). This may help explain the apparent bile acid-mediated stimulation of GLP-1 secretion in humans and rodents, when increasing the luminal bile acid concentration with bile acid sequestrants (Beysen et al., 2011; Shang et al., 2010); however this has not been reproduced by all human studies (Garg et al., 2011; Marina et al., 2012; Smushkin et al., 2013). Once believed to be apically-expressed, the location of TGR5 within the intestine has been disputed and has been

suggested to be present on the basolateral membrane (Brighton et al., 2015); if proven correct, this finding would significantly change the physiological understanding of how bile acids couple to incretin secretion.

Another important factor relates to intestinal villous hypertrophy, commonly observed in numerous rodent models of RYGB (le Roux et al., 2010) and ileal interposition (C. F. Hansen et al., 2014; Kohli et al., 2010). Similar findings of hypertrophy in the small intestines were previously described in bariatric patients (Dudrick et al., 1977; Spak et al., 2010). While the mechanisms underlying these changes remain unknown, several studies have suggested a role for exposure to undigested food as a potential mechanism that is associated with increased EEC cell function (le Roux et al., 2010) affecting the whole intestinal mucosa. Thus, it is possible that the lack of bile or other GI secretions within the Roux limb of a RYGB or bile diversion may result in excessive intraluminal ‘indigestible’ nutrients that signal enterocytes to hypertrophy/proliferate (B. P. Cummings et al., 2010; Kohli et al., 2010; Saeidi et al., 2013; Spak et al., 2010).

7. Summary and Future Directions

Metabolic and bariatric surgery is a field that has made significant advances in the last decade at elucidating the mechanisms of these highly effective operations for treating obesity as well as the related comorbid conditions like diabetes/insulin resistance. There are a number of physiologic and molecular processes that are altered by bariatric surgery that are associated with concomitant significant elevations of circulating bile acids. Whether all these processes are being driven, or potentially modified, by bile acids is unknown, but this area of study remains ripe for identifying novel and better therapies for obesity and diabetes.

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References

- Abumrad, NN., Breitman, I., Wattacheril, J., Hubbard, WJ., Chaudry, IH. Fischers Mastery of Surgery. Lippincott Williams & Wilkins; 2012. Metabolic and Inflammatory Responses to Trauma and Infection; p. 1-49.
- Adams TD, Hunt SC. Cancer and Obesity: Effect of Bariatric Surgery. World Journal of Surgery. 2009; 33:2028–2033. DOI: 10.1007/s00268-009-0169-1 [PubMed: 19672652]
- Ahmad NN, Pfalzer A, Kaplan LM. Roux-en-Y gastric bypass normalizes the blunted postprandial bile acid excursion associated with obesity. Int J Obes (Lond). 2013; 37:1553–1559. DOI: 10.1038/ijo.2013.38 [PubMed: 23567924]
- Ajouz H, Mukherji D, Shamseddine A. Secondary bile acids: an underrecognized cause of colon cancer. World Journal of Surgical Oncology. 2014; 12:164.doi: 10.1186/1477-7819-12-164 [PubMed: 24884764]
- Albaugh VL, Flynn CR, Cai S, Xiao Y, Tamboli RA, Abumrad NN. Early Increases in Bile Acids Post Roux-en-Y Gastric Bypass Are Driven by Insulin-Sensitizing, Secondary Bile Acids. J Clin Endocrinol Metab. 2015; 100:E1225–33. DOI: 10.1210/jc.2015-2467 [PubMed: 26196952]

- Amaral JD, Viana RJS, Ramalho RM, Steer CJ, Rodrigues CMP. Bile acids: regulation of apoptosis by ursodeoxycholic acid. *J Lipid Res.* 2009; 50:1721–1734. DOI: 10.1194/jlr.R900011-JLR200 [PubMed: 19417220]
- Andersén E, Hellström K. Influence of fat-rich versus carbohydrate-rich diets on bile acid kinetics, biliary lipids, and net steroid balance in hyperlipidemic subjects. *Metabolism.* 1980; 29:400–409. DOI: 10.1016/0026-0495(80)90163-8 [PubMed: 6990177]
- Andersén E, Karlaganis G, Sjövall J. Altered bile acid profiles in duodenal bile and urine in diabetic subjects. *Eur J Clin Invest.* 1988; 18:166–172. DOI: 10.1111/j.1365-2362.1988.tb02408.x [PubMed: 3133222]
- Arterburn DE, Bogart A, Sherwood NE, Sidney S, Coleman KJ, Haneuse S, O'Connor PJ, Theis MK, Campos GM, McCulloch D, Selby J. A Multisite Study of Long-term Remission and Relapse of Type 2 Diabetes Mellitus Following Gastric Bypass. *Obes Surg.* 2012; 23:93–102. DOI: 10.1007/s11695-012-0802-1
- Ashrafian H, Ahmed K, Rowland SP, Patel VM, Gooderham NJ, Holmes E, Darzi A, Athanasiou T. Metabolic surgery and cancer. *Cancer.* 2011; 117:1788–1799. DOI: 10.1002/cncr.25738 [PubMed: 21509756]
- Ballatori N, Christian WV, Lee JY, Dawson PA, Soroka CJ, Boyer JL, Madejczyk MS, Li N. OSTα-OSTβ: A major basolateral bile acid and steroid transporter in human intestinal, renal, and biliary epithelia. *Hepatology.* 2005; 42:1270–1279. DOI: 10.1002/hep.20961 [PubMed: 16317684]
- Barrasa JI, Olmo N, Lizarbe MA, Turnay J. Bile acids in the colon, from healthy to cytotoxic molecules. *Toxicol In Vitro.* 2013; 27:964–977. DOI: 10.1016/j.tiv.2012.12.020 [PubMed: 23274766]
- Baud G, Daoudi M, Hubert T, Raverdy V, Pigeyre M, Hervieux E, Devienne M, Ghunaim M, Bonner C, Quenon A, Pigny P, Klein A, Kerr-Conte J, Gmyr V, Caiazzo R, Pattou F. Bile Diversion in Roux-en-Y Gastric Bypass Modulates Sodium-Dependent Glucose Intestinal Uptake. *Cell Metabolism.* 2016; :1–14. DOI: 10.1016/j.cmet.2016.01.018
- Belgaumkar AP, Vincent RP, Carswell KA, Hughes RD, Alaghband-Zadeh J, Mitry RR, le Roux CW, Patel AG. Changes in Bile Acid Profile After Laparoscopic Sleeve Gastrectomy are Associated with Improvements in Metabolic Profile and Fatty Liver Disease. *Obes Surg.* 2016; 26:1195–1202. DOI: 10.1007/s11695-015-1878-1 [PubMed: 26337697]
- Berr F, Stellaard F, Pratschke E, Paumgartner G. Effects of cholecystectomy on the kinetics of primary and secondary bile acids. *J Clin Invest.* 1989; 83:1541–1550. DOI: 10.1172/JCI114050 [PubMed: 2708522]
- Beysen C, Murphy EJ, Deines K, Chan M, Tsang E, Glass A, Turner SM, Protasio J, Riiff T, Hellerstein MK. Effect of bile acid sequestrants on glucose metabolism, hepatic de novo lipogenesis, and cholesterol and bile acid kinetics in type 2 diabetes: a randomised controlled study. *Diabetologia.* 2011; 55:432–442. DOI: 10.1007/s00125-011-2382-3 [PubMed: 22134839]
- Bhutta HY, Rajpal N, White W, Freudenberg JM, Liu Y, Way J, Rajpal D, Cooper DC, Young A, Tavakkoli A, Chen L. Effect of Roux-en-Y gastric bypass surgery on bile acid metabolism in normal and obese diabetic rats. *PLoS ONE.* 2015; 10:e0122273.doi: 10.1371/journal.pone.0122273 [PubMed: 25798945]
- Bisschop PH, Bandsma R, Stellaard F, Harmsel ter A, Meijer AJ, Sauerwein HP, Kuipers F, Romijn JA. Low-fat, high-carbohydrate and high-fat, low-carbohydrate diets decrease primary bile acid synthesis in humans. *Am J Clin Nutr.* 2004; 79:570–576. [PubMed: 15051599]
- Blackburn G. Effect of degree of weight loss on health benefits. *Obes Res.* 1995; 3(2):211s–216s. [PubMed: 8581779]
- Bose M, Teixeira J, Olivan B, Bawa B, Arias S, Machineni S, Pi Sunyer FX, Scherer PE, Laferrère B. Weight loss and incretin responsiveness improve glucose control independently after gastric bypass surgery. *Journal of Diabetes.* 2010; 2:47–55. DOI: 10.1111/j.1753-0407.2009.00064.x [PubMed: 20676394]
- Bradley D, Conte C, Mittendorfer B, Eagon JC, Varela JE, Fabbrini E, Gastaldelli A, Chambers KT, Su X, Okunade A, Patterson BW, Klein S. Gastric bypass and banding equally improve insulin sensitivity and β cell function. *J Clin Invest.* 2012; 122:4667–4674. DOI: 10.1172/JCI64895 [PubMed: 23187122]

- Breen DM, Rasmussen BA, Kokorovic A, Wang R, Cheung GWC, Lam TKT. Jejunal nutrient sensing is required for duodenal-jejunal bypass surgery to rapidly lower glucose concentrations in uncontrolled diabetes. *Nat Med.* 2012; 18:950–955. DOI: 10.1038/nm.2745 [PubMed: 22610279]
- Brighton CA, Rievaj J, Kuhre RE, Glass LL, Schoonjans K, Holst JJ, Gribble FM, Reimann F. Bile Acids Trigger GLP-1 Release Predominantly by Accessing Basolaterally Located G Protein–Coupled Bile Acid Receptors. *Endocrinology.* 2015; 156:3961–3970. DOI: 10.1210/en.2015-1321 [PubMed: 26280129]
- Broeders EPM, Nascimento EBM, Havekes B, Brans B, Roumans KHM, Tailleux A, Schaart G, Kouach M, Charton J, Deprez B, Bouvy ND, Mottaghy F, Staels B, van Marken Lichtenbelt WD, Schrauwen P. The Bile Acid Chenodeoxycholic Acid Increases Human Brown Adipose Tissue Activity. *Cell Metabolism.* 2015; doi: 10.1016/j.cmet.2015.07.002
- Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories WJ, Fahrback K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. *JAMA.* 2004; 292:1724–1737. DOI: 10.1001/jama.292.14.1724 [PubMed: 15479938]
- Buchwald H, Estok R, Fahrback K, Banel D, Jensen MD, Pories WJ, Bantle JP, Sledge I. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *The American Journal of Medicine.* 2009; 122:248–256.e5. DOI: 10.1016/j.amjmed.2008.09.041 [PubMed: 19272486]
- Bueter M, Löwenstein C, Olbers T, Wang M, Cluny NL, Bloom SR, Sharkey KA, Lutz TA, le Roux CW. Gastric Bypass Increases Energy Expenditure in Rats. *Gastroenterology.* 2010; 138:1845–1853.e1. DOI: 10.1053/j.gastro.2009.11.012 [PubMed: 19931268]
- Carey DG, Pliego GJ, Raymond RL. Body composition and metabolic changes following bariatric surgery: effects on fat mass, lean mass and basal metabolic rate: six months to one-year follow-up. *Obes Surg.* 2006; 16:1602–1608. DOI: 10.1381/096089206779319347 [PubMed: 17217636]
- Cariou B, Chetiveaux M, Zaïr Y. Fasting plasma chenodeoxycholic acid and cholic acid concentrations are inversely correlated with insulin sensitivity in adults. *Nutrition &* 2011; doi: 10.1186/s12986-015-0029-y
- Cariou B, Staels B. FXR: a promising target for the metabolic syndrome? *Trends in Pharmacological Sciences.* 2007; 28:236–243. [PubMed: 17412431]
- Carswell KA, Vincent RP, Belgaumkar AP, Sherwood RA, Amiel SA, Patel AG, le Roux CW. The effect of bariatric surgery on intestinal absorption and transit time. *Obes Surg.* 2014; 24:796–805. DOI: 10.1007/s11695-013-1166-x [PubMed: 24374942]
- Cefalu WT, Rubino F, Cummings DE. Metabolic Surgery for Type 2 Diabetes: Changing the Landscape of Diabetes Care. *Diabetes Care.* 2016; 39:857–860. DOI: 10.2337/dc16-0686 [PubMed: 27222543]
- Chiang JYL. Bile acid metabolism and signaling. *Compr Physiol.* 2013; 3:1191–1212. DOI: 10.1002/cphy.c120023 [PubMed: 23897684]
- Chiang JYL. Bile acids: regulation of synthesis. *The Journal of Lipid Research.* 2009; 50:1955–1966. DOI: 10.1194/jlr.R900010-JLR200 [PubMed: 19346330]
- Christiansen MP, Linfoot PA, Neese RA, Hellerstein MK. Effect of dietary energy restriction on glucose production and substrate utilization in type 2 diabetes. *Diabetes.* 2000; 49:1691–1699. DOI: 10.2337/diabetes.49.10.1691 [PubMed: 11016453]
- Cipriani S, Mencarelli A, Palladino G, Fiorucci S. FXR activation reverses insulin resistance and lipid abnormalities and protects against liver steatosis in Zucker (fa/fa) obese rats. *J Lipid Res.* 2010; 51:771–784. DOI: 10.1194/jlr.M001602 [PubMed: 19783811]
- Coupaye M, Rivière P, Breuil MC, Castel B, Bogard C, Dupré T, Flamant M, Msika S, Ledoux S. Comparison of Nutritional Status During the First Year After Sleeve Gastrectomy and Roux-en-Y Gastric Bypass. *Obes Surg.* 2013; 24:276–283. DOI: 10.1007/s11695-013-1089-6
- Culnan DM, Albaugh VL, Sun M, Lynch CJ, Lang CH, Cooney RN. Ileal interposition improves glucose tolerance and insulin sensitivity in the obese Zucker rat. *Am J Physiol Gastrointest Liver Physiol.* 2010; 299:G751–60. DOI: 10.1152/ajpgi.00525.2009 [PubMed: 20634437]
- Cummings BP, Bettaieb A, Graham JL, Stanhope KL, Kowala M, Haj FG, Chouinard ML, Havel PJ. Vertical Sleeve Gastrectomy Improves Glucose and Lipid Metabolism and Delays Diabetes Onset in UCD-T2DM Rats. *Endocrinology.* 2012; 153:3620–3632. DOI: 10.1210/en.2012-1131 [PubMed: 22719048]

- Cummings BP, Strader AD, Stanhope KL, Graham JL, Lee J, Raybould HE, Baskin DG, Havel PJ. Ileal interposition surgery improves glucose and lipid metabolism and delays diabetes onset in the UCD-T2DM rat. *Gastroenterology*. 2010; 138:2437–46–2446.e1. DOI: 10.1053/j.gastro.2010.03.005 [PubMed: 20226188]
- Cummings DE, Weigle DS, Frayo RS, Breen PA, Ma MK, Dellinger EP, Purnell JQ. Plasma Ghrelin Levels after Diet-Induced Weight Loss or Gastric Bypass Surgery. *N Engl J Med*. 2002; 346:1623–1630. DOI: 10.1056/NEJMoa012908 [PubMed: 12023994]
- Dawson PA, Haywood J, Craddock AL, Wilson M, Tietjen M, Kluckman K, Maeda N, Parks JS. Targeted deletion of the ileal bile acid transporter eliminates enterohepatic cycling of bile acids in mice. *Journal of Biological Chemistry*. 2003; 278:33920–33927. DOI: 10.1074/jbc.M306370200 [PubMed: 12819193]
- Dawson PA, Hubbert M, Haywood J, Craddock AL, Zerangue N, Christian WV, Ballatori N. The heteromeric organic solute transporter alpha-beta, Ostalpha-Ostbeta, is an ileal basolateral bile acid transporter. *Journal of Biological Chemistry*. 2005; 280:6960–6968. DOI: 10.1074/jbc.M412752200 [PubMed: 15563450]
- Dawson PA, Lan T, Rao A. Bile acid transporters. *The Journal of Lipid Research*. 2009; 50:2340–2357. DOI: 10.1194/jlr.R900012-JLR200 [PubMed: 19498215]
- de Aguiar Vallim TQ, Tarling EJ, Edwards PA. Pleiotropic Roles of Bile Acids in Metabolism. *Cell Metabolism*. 2013; 17:657–669. DOI: 10.1016/j.cmet.2013.03.013 [PubMed: 23602448]
- de Almeida SR, Rocha PRS, Sanches MD, Leite VHR, da Silva RAP, Diniz MTC, de Fátima Haueisen Sander Diniz M, Rocha ALS. Roux-en-Y Gastric Bypass Improves the Nonalcoholic Steatohepatitis (NASH) of Morbid Obesity. *Obes Surg*. 2006; 16:270–278. DOI: 10.1381/096089206776116462 [PubMed: 16545157]
- De Giorgi S, Campos V, Egli L, Toepel U, Carrel G, Cariou B, Rainteau D, Schneiter P, Tappy L, Giusti V. Long-term effects of Roux-en-Y gastric bypass on postprandial plasma lipid and bile acids kinetics in female non diabetic subjects: A cross-sectional pilot study. *Clin Nutr*. 2015; 34:911–917. DOI: 10.1016/j.clnu.2014.09.018 [PubMed: 25306425]
- Ding L, Sousa KM, Jin L, Dong B, Kim BW, Ramirez R, Xiao Z, Gu Y, Yang Q, Wang J, Yu D, Pigazzi A, Schones D, Yang L, Moore D, Wang Z, Huang W. Vertical sleeve gastrectomy activates GPBAR-1/TGR5 to sustain weight loss, improve fatty liver, and remit insulin resistance in mice. *Hepatology*. 2016; 64:760–773. DOI: 10.1002/hep.28689 [PubMed: 27312543]
- Dirksen C, Jørgensen NB, Bojsen-Møller KN, Kielgast U, Jacobsen SH, Clausen TR, Worm D, Hartmann B, Rehfeld JF, Damgaard M, Madsen JL, Madsbad S, Holst JJ, Hansen DL. Gut hormones, early dumping and resting energy expenditure in patients with good and poor weight loss response after Roux-en-Y gastric bypass. *Int J Obes (Lond)*. 2013; 37:1452–1459. DOI: 10.1038/ijo.2013.15 [PubMed: 23419600]
- Dixon JB, O'Brien PE, Playfair J, Chapman L, Schachter LM, Skinner S, Proietto J, Bailey M, Anderson M. Adjustable Gastric Banding and Conventional Therapy for Type 2 Diabetes: A Randomized Controlled Trial. *JAMA*. 2008; 299:316–323. DOI: 10.1001/jama.299.3.316 [PubMed: 18212316]
- Duane WC. Simulation of the defect of bile acid metabolism associated with cholesterol cholelithiasis by sorbitol ingestion in man. *J Lab Clin Med*. 1978; 91:969–978. [PubMed: 650061]
- Duane WC, Ginsberg RL, Bennion LJ. Effects of fasting on bile acid metabolism and biliary lipid composition in man. *The Journal of Lipid Research*. 1976; 17:211–219. [PubMed: 932555]
- Duane WC, Hanson KC. Role of Gallbladder Emptying and Small Bowel Transit in Regulation of Bile-Acid Pool Size in Man. *J Lab Clin Med*. 1978; 92:858–872. [PubMed: 739167]
- Dudrick SJ, Daly JM, Castro G, Akhtar M. Gastrointestinal adaptation following small bowel bypass for obesity. *Ann Surg*. 1977; 185:642–648. [PubMed: 871220]
- Dunn JP, Abumrad NN, Breitman I, Marks-Shulman PA, Flynn CR, Jabbour K, Feurer ID, Tamboli RA. Hepatic and peripheral insulin sensitivity and diabetes remission at 1 month after Roux-en-Y gastric bypass surgery in patients randomized to omentectomy. *Diabetes Care*. 2012; 35:137–142. DOI: 10.2337/dc11-1383 [PubMed: 22040841]
- Düfer M, Hörth K, Wagner R, Schittenhelm B, Prowald S, Wagner TFJ, Oberwinkler J, Lukowski R, Gonzalez FJ, Krippeit-Drews P, Drews G. Bile acids acutely stimulate insulin secretion of mouse

- β -cells via farnesoid X receptor activation and K(ATP) channel inhibition. *Diabetes*. 2012; 61:1479–1489. DOI: 10.2337/db11-0815 [PubMed: 22492528]
- Einar Krag SFP. Active and Passive Bile Acid Absorption in Man Perfusion studies of the Ileum and Jejunum. *Journal of Clinical Investigation*. 1974; 53:1686–1694. DOI: 10.1172/JCI107720 [PubMed: 4830231]
- Engelstoft MS, Egerod KL, Holst B, Schwartz TW. A Gut Feeling for Obesity: 7TM Sensors on Enteroendocrine Cells. *Cell Metabolism*. 2008; 8:447–449. DOI: 10.1016/j.cmet.2008.11.004 [PubMed: 19041758]
- Ermini M, Iaconis E, Mori A. The effects of bilio-jejunal diversion on streptozotocin diabetes in the rat. *Acta Diabetol Lat*. 1991; 28:79–89. [PubMed: 1862694]
- Escalona A, Muñoz R, Iribarra V, Solari S, Allende F, Francisco Miquel J. Bile acids synthesis decreases after laparoscopic sleeve gastrectomy. *Surgery for Obesity and Related Diseases*. 2016; 12:763–769. DOI: 10.1016/j.soard.2015.11.015 [PubMed: 26948941]
- Everson GT. Steady-state kinetics of serum bile acids in healthy human subjects: single and dual isotope techniques using stable isotopes and mass spectrometry. *The Journal of Lipid Research*. 1987; 28:238–252. [PubMed: 3553403]
- Fabbrini E, Tamboli RA, Magkos F, Marks-Shulman PA, Eckhauser AW, Richards WO, Klein S, Abumrad NN. Surgical removal of omental fat does not improve insulin sensitivity and cardiovascular risk factors in obese adults. *Gastroenterology*. 2010; 139:448–455. DOI: 10.1053/j.gastro.2010.04.056 [PubMed: 20457158]
- Ferland G, Tuchweber B, Perea A, Yousef IM. Effect of aging and dietary restriction on bile acid metabolism in rats. *Lipids*. 1989; 24:842–848. DOI: 10.1007/BF02535757 [PubMed: 2811607]
- Ferrannini E, Camastra S, Astiarraga B, Nannipieri M, Castro-Perez J, Xie D, Wang L, Chakravarthy M, Haeusler RA. Increased Bile Acid Synthesis and Deconjugation After Biliopancreatic Diversion. *Diabetes*. 2015; 64:3377–3385. DOI: 10.2337/db15-0214 [PubMed: 26015549]
- Finkelstein EA, Trogon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer- and service-specific estimates. *Health Aff (Millwood)*. 2009; 28:w822–31. DOI: 10.1377/hlthaff.28.5.w822 [PubMed: 19635784]
- Fiorucci S, Distrutti E. Bile Acid-Activated Receptors, Intestinal Microbiota, and the Treatment of Metabolic Disorders. *Trends in Molecular Medicine*. 2015; 21:702–714. [PubMed: 26481828]
- Flegal KM, Kit BK, Orpana H, Graubard BI. Association of All-Cause Mortality With Overweight and Obesity Using Standard Body Mass Index Categories: A Systematic Review and Meta-analysis. *JAMA*. 2013; 309:71–82. DOI: 10.1001/jama.2012.113905 [PubMed: 23280227]
- Flynn CR, Albaugh VL, Cai S, Cheung-Flynn J, Williams PE, Brucker RM, Bordenstein SR, Guo Y, Wasserman DH, Abumrad NN. Bile diversion to the distal small intestine has comparable metabolic benefits to bariatric surgery. *Nat Commun*. 2015; 6:7715.doi: 10.1038/ncomms8715 [PubMed: 26197299]
- Frikke Schmidt H, O'Rourke RW, Lumeng CN, Sandoval DA, Seeley RJ. Does bariatric surgery improve adipose tissue function? *Obes Rev*. 2016; 17:795–809. DOI: 10.1111/obr.12429 [PubMed: 27272117]
- Frikke-Schmidt, H., Seeley, RJ. Obesity (Silver Spring). 2016. Defending a new hypothesis of how bariatric surgery works; p. n/a-n/a.
- Frommherz L, Bub A, Hummel E, Rist MJ, Roth A, Watzl B, Kulling SE. Age-Related Changes of Plasma Bile Acid Concentrations in Healthy Adults—Results from the Cross-Sectional KarMeN Study. *PLoS ONE*. 2016; 11:e0153959.doi: 10.1371/journal.pone.0153959 [PubMed: 27092559]
- Fu ZD, Klaassen CD. Increased bile acids in enterohepatic circulation by short-term calorie restriction in male mice. *Toxicology and Applied Pharmacology*. 2013; 273:680–690. DOI: 10.1016/j.taap.2013.10.020 [PubMed: 24183703]
- Furet JP, Kong LC, Tap J, Poitou C, Basdevant A, Bouillot JL, Mariat D, Corthier G, Doré J, Henegar C, Rizkalla S, Clement K. Differential adaptation of human gut microbiota to bariatric surgery-induced weight loss: links with metabolic and low-grade inflammation markers. *Diabetes*. 2010; 59:3049–3057. DOI: 10.2337/db10-0253 [PubMed: 20876719]
- Garg SK, Ritchie PJ, Moser EG, Snell Bergeon JK, Freson BJ, Hazenfield RM. Effects of colessevelam on LDL-C, A1c and GLP-1 levels in patients with type 1 diabetes: a pilot randomized double-blind

- trial. *Diabetes Obes Metab.* 2011; 13:137–143. DOI: 10.1111/j.1463-1326.2010.01320.x [PubMed: 21199265]
- Gerhard GS, Styer AM, Wood GC, Roesch SL, Petrick AT, Gabrielsen J, Strodel WE, Still CD, Argyropoulos G. A role for fibroblast growth factor 19 and bile acids in diabetes remission after Roux-en-Y gastric bypass. *Diabetes Care.* 2013; 36:1859–1864. DOI: 10.2337/dc12-2255 [PubMed: 23801799]
- Goncalves D, Barataud A, De Vadder F, Vinera J, Zitoun C, Duchampt A, Mithieux G. Bile Routing Modification Reproduces Key Features of Gastric Bypass in Rat. *Ann Surg.* 2015; 262:1006–1015. DOI: 10.1097/SLA.0000000000001121 [PubMed: 25575265]
- Gumbs AA, Modlin IM, Ballantyne GH. Changes in Insulin Resistance Following Bariatric Surgery: Role of Caloric Restriction and Weight Loss. *Obes Surg.* 2005; 15:462–473. DOI: 10.1381/0960892053723367 [PubMed: 15946423]
- Habegger KM, Al-Massadi O, Heppner KM, Myronovych A, Holland J, Berger J, Yi CX, Gao Y, Lehti M, Ottaway N, Amburgy S, Raver C, Müller TD, Pfluger PT, Kohli R, Perez-Tilve D, Seeley RJ, Tschöp MH. Duodenal nutrient exclusion improves metabolic syndrome and stimulates villus hyperplasia. *Gut.* 2014; 63:1238–1246. DOI: 10.1136/gutjnl-2013-304583 [PubMed: 24107591]
- Habib AM, Richards P, Rogers GJ, Reimann F, Gribble FM. Co-localisation and secretion of glucagon-like peptide 1 and peptide YY from primary cultured human L cells. *Diabetologia.* 2013; 56:1413–1416. DOI: 10.1007/s00125-013-2887-z [PubMed: 23519462]
- Haeusler RA, Astiarraga B, Camastra S, Accili D, Ferrannini E. Human insulin resistance is associated with increased plasma levels of 12 α -hydroxylated bile acids. *Diabetes.* 2013; 62:4184–4191. DOI: 10.2337/db13-0639 [PubMed: 23884887]
- Haeusler RA, Camastra S, Nannipieri M, Astiarraga B, Castro-Perez J, Xie D, Wang L, Chakravarthy M, Ferrannini E. Increased bile acid synthesis and impaired bile acid transport in human obesity. *J Clin Endocrinol Metab.* 2015; :2015–2583. DOI: 10.1210/jc.2015-2583
- Haeusler RA, Pratt-Hyatt M, Welch CL, Klaassen CD, Accili D. Impaired Generation of 12-Hydroxylated Bile Acids Links Hepatic Insulin Signaling with Dyslipidemia. *Cell Metabolism.* 2012; 15:65–74. DOI: 10.1016/j.cmet.2011.11.010 [PubMed: 22197325]
- Hansen CF, Vassiliadis E, Vrang N, Sangild PT, Cummings BP, Havel P, Jelsing J. The effect of ileal interposition surgery on enteroendocrine cell numbers in the UC Davis type 2 diabetes mellitus rat. *Regulatory Peptides.* 2014; 189:31–39. [PubMed: 24512816]
- Hansen EN, Tamboli RA, Isbell JM, Saliba J, Dunn JP, Marks-Shulman PA, Abumrad NN. Role of the foregut in the early improvement in glucose tolerance and insulin sensitivity following Roux-en-Y gastric bypass surgery. *Am J Physiol Gastrointest Liver Physiol.* 2011; 300:G795–802. DOI: 10.1152/ajpgi.00019.2011 [PubMed: 21372167]
- Hao Z, Zhao Z, Berthoud HR, Ye J. Development and Verification of a Mouse Model for Roux-en-Y Gastric Bypass Surgery with a Small Gastric Pouch. *PLoS ONE.* 2013; 8:e52922.doi: 10.1371/journal.pone.0052922 [PubMed: 23326365]
- Harris RB. Role of set-point theory in regulation of body weight. *The FASEB Journal.* 1990; 4:3310–3318. [PubMed: 2253845]
- Henry RR, Schaeffer L, Olefsky JM. Glycemic effects of intensive caloric restriction and isocaloric refeeding in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab.* 1985; 61:917–925. DOI: 10.1210/jcem-61-5-917 [PubMed: 4044780]
- Hulzebos CV, Renfurm L, Bandsma RH, Verkade HJ, Boer T, Boverhof R, Tanaka H, Mierau I, Sauer PJ, Kuipers F, Stellaard F. Measurement of parameters of cholic acid kinetics in plasma using a microscale stable isotope dilution technique: application to rodents and humans. *The Journal of Lipid Research.* 2001; 42:1923–1929. [PubMed: 11714862]
- Ikezawa F, Shibata C, Kikuchi D, Imoto H, Miura K, Naitoh T, Ogawa H, Sasaki I, Tsuchiya T. Effects of ileal interposition on glucose metabolism in obese rats with diabetes. *Surgery.* 2012; 151:822–830. DOI: 10.1016/j.surg.2011.12.026 [PubMed: 22316438]
- Ikramuddin S, Livingston EH. New Insights on Bariatric Surgery Outcomes. *JAMA.* 2013; 310:2401–2402. DOI: 10.1001/jama.2013.280927 [PubMed: 24189645]
- Isbell JM, Tamboli RA, Hansen EN, Saliba J, Dunn JP, Phillips SE, Marks-Shulman PA, Abumrad NN. The importance of caloric restriction in the early improvements in insulin sensitivity after Roux-

en-Y gastric bypass surgery. *Diabetes Care*. 2010; 33:1438–1442. DOI: 10.2337/dc09-2107 [PubMed: 20368410]

- Jahansouz C, Xu H, Hertzel AV, Serrot FJ, Kvalheim N, Cole A, Abraham A, Luthra G, Ewing K, Leslie DB, Bernlohr DA, Ikramuddin S. Bile Acids Increase Independently From Hypocaloric Restriction After Bariatric Surgery. *Ann Surg*. 2016; 264:1022–1028. DOI: 10.1097/SLA.0000000000001552 [PubMed: 26655924]
- Jansen PLM, van Werven J, Aarts E, Berends F, Janssen I, Stoker J, Schaap FG. Alterations of hormonally active fibroblast growth factors after Roux-en-Y gastric bypass surgery. *Dig Dis*. 2011; 29:48–51. DOI: 10.1159/000324128 [PubMed: 21691104]
- Jazet IM, Pijl H, Frölich M, Romijn JA, Meinders AE. Two days of a very low calorie diet reduces endogenous glucose production in obese type 2 diabetic patients despite the withdrawal of blood glucose-lowering therapies including insulin. *Metabolism*. 2005; 54:705–712. DOI: 10.1016/j.metabol.2004.12.015 [PubMed: 15931603]
- Jiang C, Xie C, Lv Y, Li J, Krausz KW, Shi J, Brocker CN, Desai D, Amin SG, Bisson WH, Liu Y, Gavrilova O, Patterson AD, Gonzalez FJ. Intestine-selective farnesoid X receptor inhibition improves obesity-related metabolic dysfunction. *Nat Commun*. 2015; 6:10166.doi: 10.1038/ncomms10166 [PubMed: 26670557]
- Jiao Y, Lu Y, Li XY. Farnesoid X receptor: a master regulator of hepatic triglyceride and glucose homeostasis. *Acta Pharmacologica Sinica*. 2015; 36:44–50. DOI: 10.1038/aps.2014.116 [PubMed: 25500875]
- Jørgensen NB, Dirksen C, Bojsen-Møller KN, Kristiansen VB, Wulff BS, Rainteau D, Humbert L, Rehfeld JF, Holst JJ, Madsbad S, Clausen TR. Improvements in glucose metabolism early after gastric bypass surgery are not explained by increases in total bile acids and fibroblast growth factor 19 concentrations. *J Clin Endocrinol Metab*. 2015; 100:E396–406. DOI: 10.1210/jc.2014-1658 [PubMed: 25536209]
- Jørgensen NB, Jacobsen SH, Dirksen C, Bojsen-Møller KN, Naver L, Hvolris L, Clausen TR, Wulff BS, Worm D, Lindqvist Hansen D, Madsbad S, Holst JJ. Acute and long-term effects of Roux-en-Y gastric bypass on glucose metabolism in subjects with Type 2 diabetes and normal glucose tolerance. *Am J Physiol Endocrinol Metab*. 2012; 303:E122–31. DOI: 10.1152/ajpendo.00073.2012 [PubMed: 22535748]
- Kars M, Yang L, Gregor MF, Mohammed BS, Pietka TA, Finck BN, Patterson BW, Horton JD, Mittendorfer B, Hotamisligil GS, Klein S. Tauroursodeoxycholic Acid may improve liver and muscle but not adipose tissue insulin sensitivity in obese men and women. *Diabetes*. 2010; 59:1899–1905. DOI: 10.2337/db10-0308 [PubMed: 20522594]
- Kashyap SR, Daud S, Kelly KR, Gastaldelli A, Win H, Brethauer S, Kirwan JP, Schauer PR. Acute effects of gastric bypass versus gastric restrictive surgery on β -cell function and insulinotropic hormones in severely obese patients with type 2 diabetes. *Int J Obes Relat Metab Disord*. 2010; 34:462–471. DOI: 10.1038/ijo.2009.254
- Kaska L, Sledzinski T, Chomiczewska A, Dettlaff-Pokora A, Swierczynski J. Improved glucose metabolism following bariatric surgery is associated with increased circulating bile acid concentrations and remodeling of the gut microbiome. *WJG*. 2016; 22:8698–8719. DOI: 10.3748/wjg.v22.i39.8698 [PubMed: 27818587]
- Katsuma S, Hirasawa A, Tsujimoto G. Bile acids promote glucagon-like peptide-1 secretion through TGR5 in a murine enteroendocrine cell line STC-1. *Biochemical and Biophysical Research Communications*. 2005; 329:386–390. DOI: 10.1016/j.bbrc.2005.01.139 [PubMed: 15721318]
- Kawamata Y, Fujii R, Hosoya M, Harada M, Yoshida H, Miwa M, Fukusumi S, Habata Y, Itoh T, Shintani Y, Hinuma S, Fujisawa Y, Fujino M. A G protein-coupled receptor responsive to bile acids. *Journal of Biological Chemistry*. 2003; 278:9435–9440. DOI: 10.1074/jbc.M209706200 [PubMed: 12524422]
- Keitel V, Donner M, Winandy S, Kubitz R, Häussinger D. Expression and function of the bile acid receptor TGR5 in Kupffer cells. *Biochemical and Biophysical Research Communications*. 2008; 372:78–84. DOI: 10.1016/j.bbrc.2008.04.171 [PubMed: 18468513]
- Kelley DE, Wing R, Buonocore C, Sturis J, Polonsky K, Fitzsimmons M. Relative effects of calorie restriction and weight loss in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab*. 1993; 77:1287–1293. DOI: 10.1210/jcem.77.5.8077323 [PubMed: 8077323]

- Khan FH, Shaw L, Zhang W, Salazar-Gonzalez RM, Mowery S, Oehrle M, Zhao X, Jenkins T, Setchell KDR, Inge TH, Kohli R. Fibroblast growth factor 21 correlates with weight loss after vertical sleeve gastrectomy in adolescents. *Obesity (Silver Spring)*. 2016; 24:2377–2383. DOI: 10.1002/oby.21658 [PubMed: 27615057]
- Kindel TL, Martins PJF, Yoder SM, Jandacek RJ, Seeley RJ, D'Alessio DA, Obici S, Tso P. Bypassing the duodenum does not improve insulin resistance associated with diet-induced obesity in rodents. *Obesity (Silver Spring)*. 2011; 19:380–387. DOI: 10.1038/oby.2010.263 [PubMed: 21030948]
- Kindel TL, Yoder SM, Seeley RJ, D'Alessio DA, Tso P. Duodenal-jejunal exclusion improves glucose tolerance in the diabetic, Goto-Kakizaki rat by a GLP-1 receptor-mediated mechanism. *J Gastrointest Surg*. 2009; 13:1762–1772. DOI: 10.1007/s11605-009-0912-9 [PubMed: 19488823]
- Knop FK. Bile-induced secretion of glucagon-like peptide-1: pathophysiological implications in type 2 diabetes? *Am J Physiol Endocrinol Metab*. 2010; 299:E10–3. DOI: 10.1152/ajpendo.00137.2010 [PubMed: 20424139]
- Knop FK, Taylor R. Mechanism of metabolic advantages after bariatric surgery: it's all gastrointestinal factors versus it's all food restriction. *Diabetes Care*. 2013; 36(2):S287–91. DOI: 10.2337/dcS13-2032 [PubMed: 23882061]
- Knuth ND, Johannsen DL, Tamboli RA, Marks-Shulman PA, Huizenga R, Chen KY, Abumrad NN, Ravussin E, Hall KD. Metabolic adaptation following massive weight loss is related to the degree of energy imbalance and changes in circulating leptin. *Obesity (Silver Spring)*. 2014; 22:2563–2569. DOI: 10.1002/oby.20900 [PubMed: 25236175]
- Kohli R, Bradley D, Setchell KD, Eagon JC, Abumrad NA, Klein S. Weight Loss Induced by Roux-en-Y Gastric Bypass But Not Laparoscopic Adjustable Gastric Banding Increases Circulating Bile Acids. *Journal of Clinical Endocrinology & Metabolism*. 2013a; 98:E708–E712. DOI: 10.1210/jc.2012-3736 [PubMed: 23457410]
- Kohli R, Kirby M, Setchell KDR, Jha P, Klustaitis K, Woollett LA, Pfluger PT, Balistreri WF, Tso P, Jandacek RJ, Woods SC, Heubi JE, Tschoep MH, D'Alessio DA, Shroyer NF, Seeley RJ. Intestinal adaptation after ileal interposition surgery increases bile acid recycling and protects against obesity-related comorbidities. *Am J Physiol Gastrointest Liver Physiol*. 2010; 299:G652–60. DOI: 10.1152/ajpgi.00221.2010 [PubMed: 20595624]
- Kohli R, Setchell KD, Kirby M, Myronovych A, Ryan KK, Ibrahim SH, Berger J, Smith K, Toure M, Woods SC, Seeley RJ. A surgical model in male obese rats uncovers protective effects of bile acids post-bariatric surgery. *Endocrinology*. 2013b; 154:2341–2351. DOI: 10.1210/en.2012-2069 [PubMed: 23592746]
- Korner J, Bessler M, Cirilo LJ, Conwell IM, Daud A, Restuccia NL, Wardlaw SL. Effects of Roux-en-Y Gastric Bypass Surgery on Fasting and Postprandial Concentrations of Plasma Ghrelin, Peptide YY, and Insulin. *J Clin Endocrinol Metab*. 2005; 90:359–365. DOI: 10.1210/jc.2004-1076 [PubMed: 15483088]
- Kosters A, Dawson PA. The Na⁺-taurocholate cotransporting polypeptide knockout mouse: A new tool for study of bile acids and hepatitis B virus biology. *Hepatology*. 2015; 62:19–21. DOI: 10.1002/hep.27780 [PubMed: 25761948]
- Kremen AJ, Linner JH, Nelson CH. An experimental evaluation of the nutritional importance of proximal and distal small intestine. *Ann Surg*. 1954; 140:439–448. [PubMed: 13198079]
- Kullak Ublick GA, Paumgartner G, Berr F. Long-term effects of cholecystectomy on bile acid metabolism. *Hepatology*. 1995; 21:41–45. DOI: 10.1002/hep.1840210109 [PubMed: 7806167]
- Kumar DP, Asgharpour A, Mirshahi F, Park SH, Liu S, Imai Y, Nadler JL, Grider JR, Murthy KS, Sanyal AJ. Activation of Transmembrane Bile Acid Receptor TGR5 Modulates Pancreatic Islet α Cells to Promote Glucose Homeostasis. *J Biol Chem*. 2016; 291:6626–6640. DOI: 10.1074/jbc.M115.699504 [PubMed: 26757816]
- Kumar DP, Rajagopal S, Mahavadi S, Mirshahi F, Grider JR, Murthy KS, Sanyal AJ. Activation of transmembrane bile acid receptor TGR5 stimulates insulin secretion in pancreatic beta cells. *Biochemical and Biophysical Research Communications*. 2012; 427:600–605. DOI: 10.1016/j.bbrc.2012.09.104 [PubMed: 23022524]
- Kübeck R, Bonet-Ripoll C, Hoffmann C, Walker A, Müller VM, Schüppel VL, Lagkouvardos I, Scholz B, Engel KH, Daniel H, Schmitt-Kopplin P, Haller D, Clavel T, Klingenspor M. Dietary

- fat and gut microbiota interactions determine diet-induced obesity in mice. *Molecular Metabolism*. 2016; 5:1162–1174. DOI: 10.1016/j.molmet.2016.10.001 [PubMed: 27900259]
- Laferrière B, Heshka S, Wang K, Khan Y, McGinty J, Teixeira J, Hart AB, Olivan B. Incretin Levels and Effect Are Markedly Enhanced 1 Month After Roux-en-Y Gastric Bypass Surgery in Obese Patients With Type 2 Diabetes. *Diabetes Care*. 2007; 30:1709–1716. DOI: 10.2337/dc06-1549 [PubMed: 17416796]
- Lam CKL, Chari M, Rutter GA, Lam TKT. Hypothalamic Nutrient Sensing Activates a Forebrain-Hindbrain Neuronal Circuit to Regulate Glucose Production In Vivo. *Diabetes*. 2010; 60:107–113. DOI: 10.2337/db10-0994 [PubMed: 20870971]
- Lassailly G, Caiazzo R, Pattou F, Mathurin P. Bariatric surgery for curing NASH in the morbidly obese? *Journal of Hepatology*. 2013; 58:1249–1251. DOI: 10.1016/j.jhep.2012.12.026 [PubMed: 23333451]
- Lavie CJ, Milani RV, Ventura HO. Obesity and Cardiovascular Disease. *Journal of the American College of Cardiology*. 2009; 53:1925–1932. [PubMed: 19460605]
- le Roux CW, Borg C, Wallis K, Vincent RP, Bueter M, Goodlad R, Ghatti MA, Patel A, Bloom SR, Aylwin SJB. Gut Hypertrophy After Gastric Bypass Is Associated With Increased Glucagon-Like Peptide 2 and Intestinal Crypt Cell Proliferation. *Ann Surg*. 2010; 252:50–56. DOI: 10.1097/SLA.0b013e3181d3d21f [PubMed: 20562614]
- le Roux CW, Welbourn R, Werling M, Osborne A, Kokkinos A, Laurenus A, Lönnroth H, Fändriks L, Ghatti MA, Bloom SR, Olbers T. Gut hormones as mediators of appetite and weight loss after Roux-en-Y gastric bypass. *Ann Surg*. 2007; 246:780–785. DOI: 10.1097/SLA.0b013e3180caa3e3 [PubMed: 17968169]
- Leriche R, Joung A. Essai sur le traitement chirurgical du diabète par la dérivation biliaire: documents expérimentaux et cliniques. *Annales d'Endocrinologie*. 1939; 1:3–10.
- Li B, Lu Y, Srikant CB, Gao ZH, Liu JL. Intestinal adaptation and Reg gene expression induced by antidiabetic duodenal-jejunal bypass surgery in Zucker fatty rats. *Am J Physiol Gastrointest Liver Physiol*. 2013; 304:G635–45. DOI: 10.1152/ajpgi.00275.2012 [PubMed: 23370676]
- Li F, Jiang C, Krausz KW, Li Y, Albert I, Hao H, Fabre KM, Mitchell JB, Patterson AD, Gonzalez FJ. Microbiome remodelling leads to inhibition of intestinal farnesoid X receptor signalling and decreased obesity. *Nat Commun*. 2013; 4:2384.doi: 10.1038/ncomms3384 [PubMed: 24064762]
- Li JV, Ashrafian H, Bueter M, Kinross J, Sands C, le Roux CW, Bloom SR, Darzi A, Athanasiou T, Marchesi JR, Nicholson JK, Holmes E. Metabolic surgery profoundly influences gut microbial-host metabolic cross-talk. *Gut*. 2011; 60:1214–1223. DOI: 10.1136/gut.2010.234708 [PubMed: 21572120]
- Li S, Hsu DDF, Li B, Luo X, Alderson N, Qiao L, Ma L, Zhu HH, He Z, Suino-Powell K, Ji K, Li J, Shao J, Xu HE, Li T, Feng GS. Cytoplasmic tyrosine phosphatase Shp2 coordinates hepatic regulation of bile acid and FGF15/19 signaling to repress bile acid synthesis. *Cell Metab*. 2014; 20:320–332. DOI: 10.1016/j.cmet.2014.05.020 [PubMed: 24981838]
- Li T, Franci JM, Boehme S, Ochoa A, Zhang Y, Klaassen CD, Erickson SK, Chiang JYL. Glucose and insulin induction of bile acid synthesis: mechanisms and implication in diabetes and obesity. *J Biol Chem*. 2012; 287:1861–1873. DOI: 10.1074/jbc.M111.305789 [PubMed: 22144677]
- Li T, Holmstrom SR, Kir S, Umetani M, Schmidt DR, Klier SA, Mangelsdorf DJ. The G protein-coupled bile acid receptor, TGR5, stimulates gallbladder filling. *Molecular Endocrinology*. 2011; 25:1066–1071. DOI: 10.1210/me.2010-0460 [PubMed: 21454404]
- Li T, Owsley E, Matozel M, Hsu P, Novak CM, Chiang JYL. Transgenic expression of cholesterol 7 α -hydroxylase in the liver prevents high-fat diet-induced obesity and insulin resistance in mice. *Hepatology*. 2010; 52:678–690. DOI: 10.1002/hep.23721 [PubMed: 20623580]
- Lindstedt S, Avigan J, Goodman DS, Sjövall J, Steinberg D. The effect of dietary fat on the turnover of cholic acid and on the composition of the biliary bile acids in man. *Journal of Clinical Investigation*. 1965; 44:1754–1765. DOI: 10.1172/JCI105283 [PubMed: 5843709]
- Lou G, Ma X, Fu X, Meng Z, Zhang W, Wang YD, Van Ness C, Yu D, Xu R, Huang W. GPBAR1/TGR5 Mediates Bile Acid-Induced Cytokine Expression in Murine Kupffer Cells. *PLoS ONE*. 2014; 9:e93567.doi: 10.1371/journal.pone.0093567 [PubMed: 24755711]

- Ma K, Saha PK, Chan L, Moore DD. Farnesoid X receptor is essential for normal glucose homeostasis. *J Clin Invest*. 2006a; 116:1102–1109. DOI: 10.1172/JCI25604 [PubMed: 16557297]
- Ma K, Saha PK, Chan L, Moore DD. Farnesoid X receptor is essential for normal glucose homeostasis. *J Clin Invest*. 2006b; 116:1102–1109. DOI: 10.1172/JCI25604 [PubMed: 16557297]
- Mahawar KK. Gastric Bypass Is not a “Restrictive and Malabsorptive” Procedure. *Obes Surg*. 2016; : 1–2. DOI: 10.1007/s11695-016-2270-5
- Makishima M, Okamoto AY, Repa JJ, Tu H, Learned RM, Luk A, Hull MV, Lustig KD, Mangelsdorf DJ, Shan B. Identification of a nuclear receptor for bile acids. *Science*. 1999; 284:1362–1365. DOI: 10.1126/science.284.5418.1362 [PubMed: 10334992]
- Manfredini G, Ermini M, Scopsi L, Bonaguidi F, Ferrannini E. Internal biliary diversion improves glucose tolerance in the rat. *AJP: Gastrointestinal and Liver Physiology*. 1985; 249:G519–G527.
- Marina AL, Utzschneider KM, Wright LA, Montgomery BK, Marcovina SM, Kahn SE. Colesevelam Improves Oral but Not Intravenous Glucose Tolerance by a Mechanism Independent of Insulin Sensitivity and β -Cell Function. *Diabetes Care*. 2012; 35:1119–1125. DOI: 10.2337/dc11-2050 [PubMed: 22446171]
- Markovic TP, Jenkins AB, Campbell LV, Furler SM, Kraegen EW, Chisholm DJ. The Determinants of Glycemic Responses to Diet Restriction and Weight Loss in Obesity and NIDDM. *Diabetes Care*. 1998; 21:687–694. DOI: 10.2337/diacare.21.5.687 [PubMed: 9589225]
- Maruyama T, Miyamoto Y, Nakamura T, Tamai Y, Okada H, Sugiyama E, Nakamura T, Itadani H, Tanaka K. Identification of membrane-type receptor for bile acids (M-BAR). *Biochemical and Biophysical Research Communications*. 2002; 298:714–719. DOI: 10.1016/S0006-291X(02)02550-0 [PubMed: 12419312]
- Maruyama T, Tanaka K, Suzuki J, Miyoshi H, Harada N, Nakamura T, Miyamoto Y, Kanatani A, Tamai Y. Targeted disruption of G protein-coupled bile acid receptor 1 (Gpbar1/M-Bar) in mice. *J Endocrinol*. 2006; 191:197–205. DOI: 10.1677/joe.1.06546 [PubMed: 17065403]
- Mathier MA, Zhang J, Ramanathan RC. Dramatic Functional Improvement Following Bariatric Surgery in a Patient With Pulmonary Arterial Hypertension and Morbid Obesity. *Chest*. 2008; 133:789–792. DOI: 10.1378/chest.07-0815 [PubMed: 18321907]
- McGavigan AK, Garibay D, Henseler ZM, Chen J, Bettaieb A, Haj FG, Ley RE, Chouinard ML, Cummings BP. TGR5 contributes to glucoregulatory improvements after vertical sleeve gastrectomy in mice. *Gut*. 2017; 66:226–234. DOI: 10.1136/gutjnl-2015-309871 [PubMed: 26511794]
- Melissas J, Koukouraki S, Askoxylakis J, Stathaki M, Daskalakis M, Perisinakis K, Karkavitsas N. Sleeve Gastrectomy — A Restrictive Procedure? *Obes Surg*. 2007; 17:57–62. DOI: 10.1007/s11695-007-9006-5 [PubMed: 17355769]
- Mencarelli A, Renga B, D'Amore C, Santorelli C, Graziosi L, Bruno A, Monti MC, Distrutti E, Cipriani S, Donini A, Fiorucci S. Dissociation of intestinal and hepatic activities of FXR and LXRA supports metabolic effects of terminal ileum interposition in rodents. *Diabetes*. 2013; 62:3384–3393. DOI: 10.2337/db13-0299 [PubMed: 23835330]
- Midtvedt T. Microbial bile acid transformation. *Am J Clin Nutr*. 1974; 27:1341–1347. [PubMed: 4217103]
- Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, Nanni G, Pomp A, Castagneto M, Ghirlanda G, Rubino F. Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes. *N Engl J Med*. 2012; 366:1577–1585. DOI: 10.1056/NEJMoa1200111 [PubMed: 22449317]
- Morínigo R, Lacy AM, Casamitjana R, Delgado S, Gomis R, Vidal J. GLP-1 and Changes in Glucose Tolerance following Gastric Bypass Surgery in Morbidly Obese Subjects. *Obes Surg*. 2006a; 16:1594–1601. DOI: 10.1381/096089206779319338 [PubMed: 17217635]
- Morínigo R, Moizé V, Musri M, Lacy AM, Navarro S, Marín JL, Delgado S, Casamitjana R, Vidal J. Glucagon-Like Peptide-1, Peptide YY, Hunger, and Satiety after Gastric Bypass Surgery in Morbidly Obese Subjects. *J Clin Endocrinol Metab*. 2006b; 91:1735–1740. DOI: 10.1210/jc.2005-0904 [PubMed: 16478824]

- Mueller M, Thorell A, Claudel T, Jha P, Koefeler H, Lackner C, Hoesel B, Fauler G, Stojakovic T, Einarsson C, Marschall HU, Trauner M. Ursodeoxycholic acid exerts farnesoid X receptor-antagonistic effects on bile acid and lipid metabolism in morbid obesity. *Journal of Hepatology*. 2015; 62:1398–1404. DOI: 10.1016/j.jhep.2014.12.034 [PubMed: 25617503]
- Murakami M, Une N, Nishizawa M, Suzuki S, Ito H, Horiuchi T. Incretin secretion stimulated by ursodeoxycholic acid in healthy subjects. *Springerplus*. 2013; 2:20.doi: 10.1186/2193-1801-2-20 [PubMed: 23450079]
- Myronovych A, Kirby M, Ryan KK, Zhang W, Jha P, Setchell KD, Dexheimer PJ, Aronow B, Seeley RJ, Kohli R. Vertical sleeve gastrectomy reduces hepatic steatosis while increasing serum bile acids in a weight-loss-independent manner. *Obesity (Silver Spring)*. 2014; 22:390–400. DOI: 10.1002/oby.20548 [PubMed: 23804416]
- Nakatani H, Kasama K, Oshiro T, Watanabe M, Hirose H, Itoh H. Serum bile acid along with plasma incretins and serum high-molecular weight adiponectin levels are increased after bariatric surgery. *Metabolism*. 2009; 58:1400–1407. DOI: 10.1016/j.metabol.2009.05.006 [PubMed: 19570554]
- Nestoridi E, Kvas S, Kucharczyk J, Stylopoulos N. Resting energy expenditure and energetic cost of feeding are augmented after Roux-en-Y gastric bypass in obese mice. *Endocrinology*. 2012; 153:2234–2244. DOI: 10.1210/en.2011-2041 [PubMed: 22416083]
- Nguyen, NT., Blackstone, RP., Morton, JM., Ponce, J., Rosenthal, RJ. *The ASMBS Textbook of Bariatric Surgery*. Springer; New York, NY: 2014.
- Özcan U, Yilmaz E, Özcan L, Furuhashi M, Vaillancourt E, Smith RO, Görgün CZ, Hotamisligil GS. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. *Science*. 2006; 313:1137–1140. DOI: 10.1126/science.1128294 [PubMed: 16931765]
- O'Brien PE, McPhail T, Chaston TB, Dixon JB. Systematic Review of Medium-Term Weight Loss after Bariatric Operations. *Obes Surg*. 2006; 16:1032–1040. DOI: 10.1381/096089206778026316 [PubMed: 16901357]
- Pal A, Rhoads DB, Tavakkoli A. Foregut exclusion disrupts intestinal glucose sensing and alters portal nutrient and hormonal milieu. *Diabetes*. 2015; 64:1941–1950. DOI: 10.2337/db14-1578 [PubMed: 25576062]
- Patti ME, Houten SM, Bianco AC, Bernier R, Larsen PR, Holst JJ, Badman MK, Maratos-Flier E, Mun EC, Pihlajamäki J, Auwerx J, Goldfine AB. Serum bile acids are higher in humans with prior gastric bypass: potential contribution to improved glucose and lipid metabolism. *Obesity*. 2009; 17:1671–1677. DOI: 10.1038/oby.2009.102 [PubMed: 19360006]
- Payne JH, DeWind LT, Commons RR. Metabolic observations in patients with jejunoileal shunts. *The American Journal of Surgery*. 1963; 106:273–289. DOI: 10.1016/0002-9610(63)90017-5 [PubMed: 14042557]
- Péan N, Doignon I, Garcin I, Besnard A, Julien B, Liu B, Branchereau S, Spraul A, Guettier C, Humbert L, Schoonjans K, Rainteau D, Tordjmann T. The receptor TGR5 protects the liver from bile acid overload during liver regeneration in mice. *Hepatology*. 2013; 58:1451–1460. DOI: 10.1002/hep.26463 [PubMed: 23686672]
- Pierre JF, Martinez KB, Ye H, Nadimpalli A, Morton TC, Yang J, Wang Q, Patno N, Chang EB, Yin DP. Activation of bile acid signaling improves metabolic phenotypes in high-fat diet-induced obese mice. *AJP: Gastrointestinal and Liver Physiology*. 2016; 311:G286–G304. DOI: 10.1152/ajpgi.00202.2016
- Poole DP, Godfrey C, Cattaruzza F, Cottrell GS, Kirkland JG, Pelayo JC, Bunnett NW, Corvera CU. Expression and function of the bile acid receptor GpBAR1 (TGR5) in the murine enteric nervous system. *Neurogastroenterology & Motility*. 2010; 22:814–e228. - PubMed - NCBI. [PubMed: 20236244]
- Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, Barakat HA, deRamon RA, Israel G, Dolezal JM. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Ann Surg*. 1995; 222:339–50. discussion 350–2. [PubMed: 7677463]
- Pothoff MJ, Potts A, He T, Duarte JA, Taussig R, Mangelsdorf DJ, Kliewer SA, Burgess SC. Colesevelam suppresses hepatic glycogenolysis by TGR5-mediated induction of GLP-1 action in

- DIO mice. *Am J Physiol Gastrointest Liver Physiol.* 2013; 304:G371–80. DOI: 10.1152/ajpgi.00400.2012 [PubMed: 23257920]
- Pournaras DJ, Glicksman C, Vincent RP, Kuganlipava S, Alaghband-Zadeh J, Mahon D, Bekker JHR, Gbatei MA, Bloom SR, Walters JRF, Welbourn R, le Roux CW. The role of bile after Roux-en-Y gastric bypass in promoting weight loss and improving glycaemic control. *Endocrinology.* 2012; 153:3613–3619. DOI: 10.1210/en.2011-2145 [PubMed: 22673227]
- Prinz P, Hofmann T, Ahnis A, Elbelt U, Goebel-Stengel M, Klapp BF, Rose M, Stengel A. Plasma bile acids show a positive correlation with body mass index and are negatively associated with cognitive restraint of eating in obese patients. *Front Neurosci.* 2015; 9:S498.doi: 10.3389/fnins.2015.00199
- Pugh ME, Newman JH, Williams DB, Brittain E, Robbins IM, Hemnes AR. Hemodynamic Improvement of Pulmonary Arterial Hypertension After Bariatric Surgery: Potential Role for Metabolic Regulation. *Diabetes Care.* 2013; 36:e32–e33. DOI: 10.2337/dc12-1650 [PubMed: 23431096]
- Qi Y, Jiang C, Cheng J, Krausz KW, Li T, Ferrell JM, Gonzalez FJ, Chiang JYL. Bile acid signaling in lipid metabolism: Metabolomic and lipidomic analysis of lipid and bile acid markers linked to anti-obesity and anti-diabetes in mice. *Biochim Biophys Acta.* 2014; 1851:19–29. DOI: 10.1016/j.bbali.2014.04.008 [PubMed: 24796972]
- Rafferty EP, Wylie AR, Hand KH, Elliott CE, Grieve DJ, Green BD. Investigating the effects of physiological bile acids on GLP-1 secretion and glucose tolerance in normal and GLP-1R(-/-) mice. *Biol Chem.* 2011; 392:539–546. DOI: 10.1515/BC.2011.050 [PubMed: 21521075]
- Rajagopal S, Kumar DP, Mahavadi S, Bhattacharya S, Zhou R, Corvera CU, Bunnnett NW, Grider JR, Murthy KS. Activation of G protein-coupled bile acid receptor, TGR5, induces smooth muscle relaxation via both Epac- and PKA-mediated inhibition of RhoA/Rho kinase pathway. *Am J Physiol Gastrointest Liver Physiol.* 2013; 304:G527–35. DOI: 10.1152/ajpgi.00388.2012 [PubMed: 23275618]
- Reimann F, Tolhurst G, Gribble FM. G-protein-coupled receptors in intestinal chemosensation. *Cell Metabolism.* 2012; 15:421–431. DOI: 10.1016/j.cmet.2011.12.019 [PubMed: 22482725]
- Ridlon JM, Kang DJ, Hylemon PB. Bile salt biotransformations by human intestinal bacteria. *The Journal of Lipid Research.* 2006; 47:241–259. DOI: 10.1194/jlr.R500013-JLR200 [PubMed: 16299351]
- Risstad H, Søvik TT, Engström M, Aasheim ET, Fagerland MW, Olsén MF, Kristinsson JA, le Roux CW, Bøhmer T, Birkeland KI, Mala T, Olbers T. Five-Year Outcomes After Laparoscopic Gastric Bypass and Laparoscopic Duodenal Switch in Patients With Body Mass Index of 50 to 60: A Randomized Clinical Trial. *JAMA Surg.* 2015; 150:352–361. DOI: 10.1001/jamasurg.2014.3579 [PubMed: 25650964]
- Robins SJ, Brunengraber H. Origin of biliary cholesterol and lecithin in the rat: contribution of new synthesis and preformed hepatic stores. *The Journal of Lipid Research.* 1982; 23:604–608. [PubMed: 7097125]
- Roma MG, Toledo FD, Boaglio AC, Basiglio CL, Crocenzi FA, Sánchez Pozzi EJ. Ursodeoxycholic acid in cholestasis: linking action mechanisms to therapeutic applications. *Clin Sci.* 2011; 121:523–544. DOI: 10.1042/CS20110184 [PubMed: 21854363]
- Roux CWL, Aylwin SJB, Batterham RL, Borg CM, Coyle F, Prasad V, Shurey S, Gbatei MA, Patel AG, Bloom SR. Gut Hormone Profiles Following Bariatric Surgery Favor an Anorectic State, Facilitate Weight Loss, and Improve Metabolic Parameters. *Ann Surg.* 2006; 243:108–114. DOI: 10.1097/01.sla.0000183349.16877.84 [PubMed: 16371744]
- Rubino F, Marescaux J. Effect of duodenal-jejunal exclusion in a non-obese animal model of type 2 diabetes: a new perspective for an old disease. *Ann Surg.* 2004; 239:1–11. DOI: 10.1097/01.sla.0000102989.54824.fc [PubMed: 14685093]
- Rubino F, Nathan DM, Eckel RH, Schauer PR, Alberti KGMM, Zimmet PZ, Del Prato S, Ji L, Sadikot SM, Herman WH, Amiel SA, Kaplan LM, Taroncher-Oldenburg G, Cummings DE, Albache N, Batterham RL, Bhatt DL, Boza C, Cefalu WT, Cohen RV, Courcoulas AP, Dinneen SF, Dixon JB, Ferrannini E, Fioretto P, Frühbeck G, Gagner M, Grant RW, Ikramuddin S, Johnston DG, Kashyap SR, Kelly T, Klupa T, Korner J, Laferrère B, Lebovitz HE, Lee WJ, le Roux CW, Mechanick JI, Mingrone G, Morton JM, Pories WJ, Ratner RE, Rayman G, Sugerman HJ, Van

- Gaal L, Vidal J, Weng J, Wolfe BM. Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: A Joint Statement by International Diabetes Organizations. *Diabetes Care*. 2016; 39:861–877. DOI: 10.2337/dc16-0236 [PubMed: 27222544]
- Russell DW. The Enzymes, Regulation, and Genetics of Bile Acid Synthesis. *Annu Rev Biochem*. 2003; 72:137–174. DOI: 10.1146/annurev.biochem.72.121801.161712 [PubMed: 12543708]
- Ryan KK, Tremaroli V, Clemmensen C, Kovatcheva-Datchary P, Myronovych A, Karns R, Wilson-Perez HE, Sandoval DA, Kohli R, Bäckhed F, Seeley RJ. FXR is a molecular target for the effects of vertical sleeve gastrectomy. *Nature*. 2014; 509:183–188. DOI: 10.1038/nature13135 [PubMed: 24670636]
- Saeidi N, Meoli L, Nestoridi E, Gupta NK, Kvas S, Kucharczyk J, Bonab AA, Fischman AJ, Yarmush ML, Stylopoulos N. Reprogramming of intestinal glucose metabolism and glycemic control in rats after gastric bypass. *Science*. 2013; 341:406–410. DOI: 10.1126/science.1235103 [PubMed: 23888041]
- Sayin SI, Wahlström A, Felin J, Jäntti S, Marschall HU, Bamberg K, Angelin B, Hyötyläinen T, Oreši M, Bäckhed F. Gut Microbiota Regulates Bile Acid Metabolism by Reducing the Levels of Tauro-beta-muricholic Acid, a Naturally Occurring FXR Antagonist. *Cell Metabolism*. 2013; 17:225–235. DOI: 10.1016/j.cmet.2013.01.003 [PubMed: 23395169]
- Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Brethauer SA, Navaneethan SD, Aminian A, Pothier CE, Kim ESH, Nissen SE, Kashyap SR. STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes--3-year outcomes. *N Engl J Med*. 2014; 370:2002–2013. DOI: 10.1056/NEJMoa1401329 [PubMed: 24679060]
- Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, Thomas S, Abood B, Nissen SE, Bhatt DL. Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes. *N Engl J Med*. 2012; 366:1567–1576. DOI: 10.1056/NEJMoa1200225 [PubMed: 22449319]
- Schiff ER, Small NC, Dietschy JM. Characterization of the kinetics of the passive and active transport mechanisms for bile acid absorption in the small intestine and colon of the rat. *Journal of Clinical Investigation*. 1972; 51:1351–1362. DOI: 10.1172/JCI106931 [PubMed: 5024036]
- Schmidt JB, Pedersen SD, Gregersen NT, Vestergaard L, Nielsen MS, Ritz C, Madsbad S, Worm D, Hansen DL, Clausen TR, Rehfeld JF, Astrup A, Holst JJ, Sjödin A. Effects of RYGB on energy expenditure, appetite and glycemic control: a randomized controlled clinical trial. *Int J Obes (Lond)*. 2015; doi: 10.1038/ijo.2015.162
- Schwarz M, Russell DW, Dietschy JM, Turley SD. Alternate pathways of bile acid synthesis in the cholesterol 7 α -hydroxylase knockout mouse are not upregulated by either cholesterol or cholestyramine feeding. *The Journal of Lipid Research*. 2001; 42:1594–1603. DOI: 10.1146/annurev.cellbio.16.1.459 [PubMed: 11590215]
- Seeley RJ, Chambers AP, Sandoval DA. The role of gut adaptation in the potent effects of multiple bariatric surgeries on obesity and diabetes. *Cell Metabolism*. 2015; 21:369–378. DOI: 10.1016/j.cmet.2015.01.001 [PubMed: 25662404]
- Shang Q, Saumoy M, Holst JJ, Salen G, Xu G. Colesevelam improves insulin resistance in a diet-induced obesity (F-DIO) rat model by increasing the release of GLP-1. *AJP: Gastrointestinal and Liver Physiology*. 2010; 298:G419–G424. DOI: 10.1152/ajpgi.00362.2009
- Sheu EG, Channick R, Gee DW. Improvement in severe pulmonary hypertension in obese patients after laparoscopic gastric bypass or sleeve gastrectomy. *Surg Endosc*. 2015; 30:633–637. DOI: 10.1007/s00464-015-4251-5 [PubMed: 26091991]
- Shin AC, Zheng H, Townsend RL, Patterson LM, Holmes GM, Berthoud HR. Longitudinal assessment of food intake, fecal energy loss, and energy expenditure after Roux-en-Y gastric bypass surgery in high-fat-fed obese rats. *Obes Surg*. 2013; 23:531–540. DOI: 10.1007/s11695-012-0846-2 [PubMed: 23269513]
- Simonen M, Dali-Youcef N, Kaminska D, Venesmaa S, Käkälä P, Pääkkönen M, Hallikainen M, Kolehmainen M, Uusitupa M, Moilanen L, Laakso M, Gylling H, Patti ME, Auwerx J, Pihlajamäki J. Conjugated bile acids associate with altered rates of glucose and lipid oxidation after Roux-en-Y gastric bypass. *Obes Surg*. 2012; 22:1473–1480. DOI: 10.1007/s11695-012-0673-5 [PubMed: 22638681]

- Sinal CJ, Tohkin M, Miyata M, Ward JM, Lambert G, Gonzalez FJ. Targeted disruption of the nuclear receptor FXR/BAR impairs bile acid and lipid homeostasis. *Cell*. 2000; 102:731–744. [PubMed: 11030617]
- Sjöström L, Gummesson A, Sjöström CD, Narbro K, Peltonen M, Wedel H, Bengtsson C, Bouchard C, Carlsson B, Dahlgren S, Jacobson P, Karason K, Karlsson J, Larsson B, Lindroos AK, Lönroth H, Näslund I, Olbers T, Stenlöf K, Torgerson J, Carlsson LM. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. *Lancet Oncol*. 2009; 10:653–662. DOI: 10.1016/S1470-2045(09)70159-7 [PubMed: 19556163]
- Sjöström L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjöström CD, Sullivan M, Wedel H. Lifestyle, Diabetes, and Cardiovascular Risk Factors 10 Years after Bariatric Surgery. *N Engl J Med*. 2004; 351:2683–2693. DOI: 10.1056/NEJMoa035622 [PubMed: 15616203]
- Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard C, Carlsson B, Bengtsson C, Dahlgren S, Gummesson A, Jacobson P, Karlsson J, Lindroos AK, Lönroth H, Näslund I, Olbers T, Stenlöf K, Torgerson J, Ågren G, Carlsson LMS. Effects of Bariatric Surgery on Mortality in Swedish Obese Subjects. *N Engl J Med*. 2007; 357:741–752. DOI: 10.1056/NEJMoa066254 [PubMed: 17715408]
- Sjöström L, Peltonen M, Jacobson P, Sjöström CD, Karason K, Wedel H, Ahlin S, Anveden Å, Bengtsson C, Bergmark G, Bouchard C, Carlsson B, Dahlgren S, Karlsson J, Lindroos AK, Lönroth H, Narbro K, Näslund I, Olbers T, Svensson PA, Carlsson LMS. Bariatric Surgery and Long-term Cardiovascular Events. *JAMA*. 2012; 307:56–65. DOI: 10.1001/jama.2011.1914 [PubMed: 22215166]
- Smushkin G, Sathananthan M, Piccinini F, Man CD, Law JH, Cobelli C, Zinsmeister AR, Rizza RA, Vella A. The Effect of a Bile Acid Sequestrant on Glucose Metabolism in Subjects With Type 2 Diabetes. *Diabetes*. 2013; 62:1094–1101. DOI: 10.2337/db12-0923 [PubMed: 23250357]
- Spak E, Björklund P, Helander HF, Vieth M, Olbers T, Casselbrant A, Lönroth H, Fändriks L. Changes in the mucosa of the Roux-limb after gastric bypass surgery. *Histopathology*. 2010; 57:680–688. DOI: 10.1111/j.1365-2559.2010.03677.x [PubMed: 21054493]
- Spinelli V, Lalloyer F, Baud G, Osto E, Kouach M, Daoudi M, Vallez E, Raverdy V, Goossens JF, Descat A, Doytcheva P, Hubert T, Lutz TA, Lestavel S, Staels B, Pattou F, Tailleux A. Influence of Roux-en-Y gastric bypass on plasma bile acid profiles: a comparative study between rats, pigs and humans. *Int J Obes (Lond)*. 2016; 40:1260–1267. DOI: 10.1038/ijo.2016.46 [PubMed: 27089995]
- Staels B, Fonseca VA. Bile acids and metabolic regulation: mechanisms and clinical responses to bile acid sequestration. *Diabetes Care*. 2009; 32(2):S237–45. DOI: 10.2337/dc09-S355 [PubMed: 19875558]
- Stefater MA, Wilson-Pérez HE, Chambers AP. All bariatric surgeries are not created equal: insights from mechanistic comparisons. *Endocrine*. 2012; 33:595–622. DOI: 10.1210/er.2011-1044
- Steinert RE, Peterli R, Keller S, Meyer-Gerspach AC, Drewe J, Peters T, Beglinger C. Bile acids and gut peptide secretion after bariatric surgery: a 1-year prospective randomized pilot trial. *Obesity (Silver Spring)*. 2013; 21:E660–8. DOI: 10.1002/oby.20522 [PubMed: 23804517]
- Stellaard F, Sackmann M, Sauerbruch T, Paumgartner G. Simultaneous determination of cholic acid and chenodeoxycholic acid pool sizes and fractional turnover rates in human serum using ¹³C-labeled bile acids. *The Journal of Lipid Research*. 1984; 25:1313–1319. [PubMed: 6530587]
- Stenman LK, Holma R, Eggert A, Korpela R. A novel mechanism for gut barrier dysfunction by dietary fat: epithelial disruption by hydrophobic bile acids. *AJP: Gastrointestinal and Liver Physiology*. 2013; 304:G227–G234. DOI: 10.1152/ajpgi.00267.2012
- Strader AD, Clausen TR, Goodin SZ, Wendt D. Ileal interposition improves glucose tolerance in low dose streptozotocin-treated diabetic and euglycemic rats. *Obes Surg*. 2009; 19:96–104. DOI: 10.1007/s11695-008-9754-x [PubMed: 18989728]
- Stylopoulos N, Hoppin AG, Kaplan LM. Roux-en-Y gastric bypass enhances energy expenditure and extends lifespan in diet-induced obese rats. *Obesity*. 2009; 17:1839–1847. DOI: 10.1038/oby.2009.207 [PubMed: 19556976]

- Sun W, Zhang D, Wang Z, Sun J, Xu B, Chen Y, Ding L, Huang X, Lv X, Lu J, Bi Y, Xu Q. Insulin Resistance is Associated With Total Bile Acid Level in Type 2 Diabetic and Nondiabetic Population. *Medicine (Baltimore)*. 2016; 95:e2778.doi: 10.1097/MD.0000000000002778 [PubMed: 26962776]
- Svensson PA, Olsson M, Andersson-Assarsson JC, Taube M, Pereira MJ, Froguel P, Jacobson P. The TGR5 gene is expressed in human subcutaneous adipose tissue and is associated with obesity, weight loss and resting metabolic rate. *Biochemical and Biophysical Research Communications*. 2013; 433:563–566. DOI: 10.1016/j.bbrc.2013.03.031 [PubMed: 23523790]
- Swann JR, Want EJ, Geier FM, Spagou K, Wilson ID, Sidaway JE, Nicholson JK, Holmes E. Systemic gut microbial modulation of bile acid metabolism in host tissue compartments. *Proc Natl Acad Sci USA*. 2011; 108(1):4523–4530. DOI: 10.1073/pnas.1006734107 [PubMed: 20837534]
- Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, Gortmaker SL. The global obesity pandemic: shaped by global drivers and local environments. *The Lancet*. 2011; 378:804–814. DOI: 10.1016/S0140-6736(11)60813-1
- Takahashi M, Sasaki I, Naito H, Funayama Y. Chronic bile diversion to the urinary bladder enhances cholecystokinin release and suppresses gastric inhibitory polypeptide release in dogs. *The Tohoku journal of* 1996
- Tamboli RA, Breitman I, Marks-Shulman PA, Jabbour K, Melvin W, Williams B, Clements RH, Feurer ID, Abumrad NN. Early weight regain after gastric bypass does not affect insulin sensitivity but is associated with elevated ghrelin. *Obesity (Silver Spring)*. 2014; 22:1617–1622. DOI: 10.1002/oby.20776 [PubMed: 24777992]
- Tamboli RA, Hajri T, Jiang A, Marks-Shulman PA, Williams DB, Clements RH, Melvin W, Bowen BP, Shyr Y, Abumrad NN, Flynn CR. Reduction in Inflammatory Gene Expression in Skeletal Muscle from Roux-en-Y Gastric Bypass Patients Randomized to Omentectomy. *PLoS ONE*. 2011; 6:e28577.doi: 10.1371/journal.pone.0028577 [PubMed: 22194858]
- Tamboli RA, Hossain HA, Marks PA, Eckhauser AW, Rathmacher JA, Phillips SE, Buchowski MS, Chen KY, Abumrad NN. Body composition and energy metabolism following Roux-en-Y gastric bypass surgery. *Obesity (Silver Spring)*. 2010; 18:1718–1724. DOI: 10.1038/oby.2010.89 [PubMed: 20414197]
- Taylor DR, Alaghband-Zadeh J, Cross GF, Omar S, le Roux CW, Vincent RP. Urine Bile Acids Relate to Glucose Control in Patients with Type 2 Diabetes Mellitus and a Body Mass Index Below 30 kg/m². *PLoS ONE*. 2014; 9:e93540.doi: 10.1371/journal.pone.0093540 [PubMed: 24736330]
- The Look AHEAD Research Group. Eight-year weight losses with an intensive lifestyle intervention: The look AHEAD study. *Obesity (Silver Spring)*. 2014; 22:5–13. DOI: 10.1002/oby.20662 [PubMed: 24307184]
- Thomas C, Gioiello A, Noriega L, Strehle A, Oury J, Rizzo G, Macchiarulo A, Yamamoto H, Matak C, Pruzanski M, Pellicciari R, Auwerx J, Schoonjans K. TGR5-mediated bile acid sensing controls glucose homeostasis. *Cell Metabolism*. 2009; 10:167–177. DOI: 10.1016/j.cmet.2009.08.001 [PubMed: 19723493]
- Thomas C, Pellicciari R, Pruzanski M, Auwerx J, Schoonjans K. Targeting bile-acid signalling for metabolic diseases. *Nat Rev Drug Discov*. 2008; 7:678–693. DOI: 10.1038/nrd2619 [PubMed: 18670431]
- Trogdon JG, Finkelstein EA, Hylands T, Dellea PS, Kamal Bahl SJ. Indirect costs of obesity: a review of the current literature. *Obes Rev*. 2008; 9:489–500. DOI: 10.1111/j.1467-789X.2008.00472.x [PubMed: 18331420]
- Tsuchiya T, Kalogeris TJ, Tso P. Ileal transposition into the upper jejunum affects lipid and bile salt absorption in rats. *Am J Physiol*. 1996; 271:G681–91. [PubMed: 8897889]
- van Nierop FS, Kulik W, Endert E, Schaap FG, Olde Damink SW, Romijn JA, Soeters MR. Effects of acute dietary weight loss on postprandial plasma bile acid responses in obese insulin resistant subjects. *Clinical Nutrition*. 2016; doi: 10.1016/j.clnu.2016.10.006
- Vassileva G, Golovko A, Markowitz L, Abbondanzo SJ, Zeng M, Yang S, Hoos L, Tetzloff G, Levitan D, Murgolo NJ, Keane K, Davis HR, Hedrick J, Gustafson EL. Targeted deletion of Gpbar1 protects mice from cholesterol gallstone formation. *Biochem J*. 2006; 398:423–430. DOI: 10.1042/BJ20060537 [PubMed: 16724960]

- Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther.* 2011; 34:274–285. DOI: 10.1111/j.1365-2036.2011.04724.x [PubMed: 21623852]
- Vettorazzi JF, Ribeiro RA, Borck PC, Branco RCS, Soriano S, Merino B, Boschero AC, Nadal A, Quesada I, Carneiro EM. The bile acid TUDCA increases glucose-induced insulin secretion via the cAMP/PKA pathway in pancreatic beta cells. *Metabolism.* 2016; 65:54–63. DOI: 10.1016/j.metabol.2015.10.021
- Vidal J, Nicolau J, Romero F, Casamitjana R, Momblan D, Conget I, Morínigo R, Lacy AM. Long-Term Effects of Roux-en-Y Gastric Bypass Surgery on Plasma Glucagon-Like Peptide-1 and Islet Function in Morbidly Obese Subjects. *J Clin Endocrinol Metab.* 2009; 94:884–891. DOI: 10.1210/jc.2008-1620 [PubMed: 19106269]
- Wang G, Agenor K, Pizot J, Kotler DP, Harel Y, Van Der Schueren BJ, Quercia I, McGinty J, Laferrière B. Accelerated Gastric Emptying but No Carbohydrate Malabsorption 1 Year After Gastric Bypass Surgery (GBP). *Obes Surg.* 2012; 22:1263–1267. DOI: 10.1007/s11695-012-0656-6 [PubMed: 22527599]
- Wang H, Chen J, Hollister K, Sowers LC, Forman BM. Endogenous Bile Acids Are Ligands for the Nuclear Receptor FXR/BAR. *Mol Cell.* 1999; 3:543–553. DOI: 10.1016/S1097-2765(00)80348-2 [PubMed: 10360171]
- Wang YD, Chen WD, Wang M, Yu D, Forman BM, Huang W. Farnesoid X receptor antagonizes nuclear factor kappaB in hepatic inflammatory response. *Hepatology.* 2008; 48:1632–1643. DOI: 10.1002/hep.22519 [PubMed: 18972444]
- Watanabe M, Horai Y, Houten SM, Morimoto K, Sugizaki T, Arita E, Matakaki C, Sato H, Tanigawara Y, Schoonjans K, Itoh H, Auwerx J. Lowering bile acid pool size with a synthetic farnesoid X receptor (FXR) agonist induces obesity and diabetes through reduced energy expenditure. *J Biol Chem.* 2011; 286:26913–26920. DOI: 10.1074/jbc.M111.248203 [PubMed: 21632533]
- Watanabe M, Houten SM, Matakaki C, Christoffolete MA, Kim BW, Sato H, Messaddeq N, Harney JW, Ezaki O, Kodama T, Schoonjans K, Bianco AC, Auwerx J. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature.* 2006; 439:484–489. DOI: 10.1038/nature04330 [PubMed: 16400329]
- Weckesser EC, Chinn AB, Scott MW Jr, Price JW. Extensive resection of the small intestine. *The American Journal of Surgery.* 1949; 78:706–714. DOI: 10.1016/0002-9610(49)90312-8 [PubMed: 15391181]
- Werling M, Olbers T, Fändriks L, Bueter M, Lönroth H, Stenlöf K, le Roux CW. Increased Postprandial Energy Expenditure May Explain Superior Long Term Weight Loss after Roux-en-Y Gastric Bypass Compared to Vertical Banded Gastroplasty. *PLoS ONE.* 2013a; 8:e60280.doi: 10.1371/journal.pone.0060280 [PubMed: 23573244]
- Werling M, Vincent RP, Cross GF, Marschall HU, Fändriks L, Lönroth H, Taylor DR, Alaghband-Zadeh J, Olbers T, le Roux CW. Enhanced fasting and postprandial plasma bile acid responses after Roux-en-Y gastric bypass surgery. *Scand J Gastroenterol.* 2013b; 48:1257–1264. DOI: 10.3109/00365521.2013.833647 [PubMed: 24044585]
- Wewalka M, Patti ME, Barbato C, Houten SM, Goldfine AB. Fasting Serum Taurine-Conjugated Bile Acids Are Elevated in Type 2 Diabetes and Do Not Change With Intensification of Insulin. *J Clin Endocrinol Metab.* 2014; 99:1442–1451. DOI: 10.1210/jc.2013-3367 [PubMed: 24432996]
- Williams KV, Mullen ML, Kelley DE, Wing RR. The effect of short periods of caloric restriction on weight loss and glycemic control in type 2 diabetes. *Diabetes Care.* 1998; 21:2–8. [PubMed: 9538962]
- Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, Hill JO, Brancati FL, Peters A, Wagenknecht L. Look AHEAD Research Group. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care.* 2011; 34:1481–1486. DOI: 10.2337/dc10-2415 [PubMed: 21593294]
- Wu Q, Zhang X, Zhong M, Han H, Liu S, Liu T, Wei M, Guo W, Xie H, Hu S, Zhang G. Effects of Bariatric Surgery on Serum Bile Acid Composition and Conjugation in a Diabetic Rat Model. *Obes Surg.* 2016; 26:2384–2392. DOI: 10.1007/s11695-016-2087-2 [PubMed: 26843082]

- Xie G, Wang Y, Wang X, Zhao A, Chen T, Ni Y, Wong L, Zhang H, Zhang J, Liu C, Liu P, Jia W. Profiling of Serum Bile Acids in a Healthy Chinese Population Using UPLC–MS/MS. *J Proteome Res.* 2015; 14:850–859. DOI: 10.1021/pr500920q [PubMed: 25581415]
- Zadeh-Tahmasebi M, Duca FA, Rasmussen BA, Bauer PV, Côté CD, Filippi BM, Lam TKT. Activation of short and long chain fatty acid sensing machinery in the ileum lowers glucose production in vivo. *J Biol Chem.* 2016; 291:8816–8824. DOI: 10.1074/jbc.M116.718460 [PubMed: 26896795]
- Zhang M, Yang XJ. Effects of a high fat diet on intestinal microbiota and gastrointestinal diseases. *WJG.* 2016; 22:8905.doi: 10.3748/wjg.v22.i40.8905 [PubMed: 27833381]
- Zhang X, Liu T, Wang Y, Zhong M, Zhang G, Liu S, Wu T, Rayner CK, Hu S. Comparative Effects of Bile Diversion and Duodenal-jejunal Bypass on Glucose and Lipid Metabolism in Male Diabetic Rats. *Obes Surg.* 2015; :1–11. DOI: 10.1007/s11695-015-1925-y [PubMed: 25052254]
- Zhang Y, Lee FY, Barrera G, Lee H, Vales C, Gonzalez FJ, Willson TM, Edwards PA. Activation of the nuclear receptor FXR improves hyperglycemia and hyperlipidemia in diabetic mice. *Proceedings of the National Academy of Sciences.* 2006; 103:1006–1011. DOI: 10.1073/pnas.0506982103

Figure 1. Roux-en-Y Gastric Bypass

The proximal stomach is divided creating a stomach pouch (~30ml) that continues to have nutrient flow and the remaining stomach, referred to as the gastric remnant, is removed from enteral nutrient contact. A portion of jejunum is transected and connected to the stomach pouch forming the Roux limb, the length of which can vary depending on patient and/or surgeon factors. Intestinal continuity is restored by attaching the biliopancreatic limb to the Roux limb downstream via a connection referred to as a jejunojejunostomy. The remaining bowel distal to this connection is referred to as the common channel.

Figure 2. Vertical Sleeve Gastrectomy

In this operation, approximately 70% of the stomach is removed (shaded) and a tube-like gastric 'sleeve' remains. There is no anatomical rearrangement of the small bowel in this operation, but the stomach volume is significantly decreased.

Figure 3. Body mass index and insulin resistance improve after bariatric surgery, but not at the same rate

Representative data from bariatric surgical patients that have undergone Roux-en-Y gastric bypass over time. Postoperatively patients have declines in both body mass index as well as insulin resistance via the surrogate marker HOMA after Roux-en-Y gastric bypass. These declines, however, do not parallel each other and are suggestive that early decreases in insulin sensitivity are independent of body weight loss (Fabbrini et al., 2010).

Figure 4. Changes in bile acid enterohepatic circulation and metabolism after bariatric procedures

In response to dietary fat, bile acids produced by the liver are released from the gallbladder into the lumen of the intestine. Commensal gut bacteria deconjugate bile acids which are reabsorbed in the terminal ileum. In obese subjects prior to surgery circulating bile acid levels and insulin sensitivity are reduced compared to lean controls. BA transport via enterocytes (ileocytes and colonocytes) is mediated by the apical bile acid transporter, ASBT, the cytosolic bile acid shuttle protein, Ibabp, and the basolateral transporter *Ostα/β* with the assistance of MRP3. In response to bile acid absorption and activation of the nuclear receptor FXR, fibroblast growth factor 19 (FGF19) is released into portal circulation where it acts on the liver to inhibit bile acid synthesis. Bile acids also stimulate the release of GLP-1 or GLP-2, hormones that act in an endocrine fashion to modulate insulin release and lipid absorption, respectively. The release of GLP-1 from endocrine L-cell is potentiated by the cell surface bile acid receptor TGR5. Early after surgery (< 1 month), hepatic bile acid production and enterohepatic circulation are increased. These changes are commensurate with increased FGF19 and GLP1 production and improved hepatic insulin sensitivity. The more rapid and enhanced delivery of bile acids to the terminal ileum is associated with improved glucose handling, enhanced energy expenditure in the periphery and altered gut microflora.

Table 1
Studies describing changes in plasma bile acids after bariatric procedures in humans

Sample Size / Operation	Time Postop	Fasted/Fed	BA changes	Reference
10 VSG	Preop, 1, 3 mo.	Fasting, Post-prandial	Increased fasting and augmented prandial response	(Khan et al., 2016)
12 VSG 13 RYGB 15 Hypocaloric	7 days	Fasting	Increase total, conjugated, relative to hypocaloric diet	(Jahansouz et al., 2016)
19 VSG	Preop, 1, 3, 6, 12 mo.	Fasting	Minimal to no changes in bile acids, but decreased synthesis via surrogate marker	(Escalona et al., 2016)
24 RYGB	Preop, 1, 2, 6, 12, 24 mo.	Fasting	Bimodal increase in total, UDCA and conjugates early, general increases by 1y	(Albaugh et al., 2015)
12 NGT 13 T2DM	1 wk., 13 wk. 1 year	Fasting, Post-prandial	Fasting decreased at 1 week in NGT but unchanged in T2DM, increased thereafter to 1 year; AUC total BA decreased after MM at 1 week, but increased thereafter	(Jørgensen et al., 2015)
18 VSG	Preop 6mo	Fasting	No total changes; decreased conjugated and increased UDCA	(Belgaumkar et al., 2016)
14 RYGB 14 Obese	11 wk.	Post-prandial	Increased rise in postprandial, only a trend for increased fasting	(Schmidt et al., 2015)
22 RYGB 15 BPD	2-10wks (early) 1-2yrs (late)	Fasting	Both procedures increased total	(Ferrannini et al., 2015)
11 RYGB	33.8 mo.	Post-prandial	Increased fasting, earlier postprandial rise	(De Giorgi et al., 2015)
>30 RYGB >30 Obese	>1 year	Fasting	Increased total with RYGB, larger % increase in diabetic>>non-diabetic	(Gerhard et al., 2013)
5 RYGB 7 Lean	1, 4, 40 wk.	Post-prandial	Increased prandial rise by RYGB	(Ahmad et al., 2013)
7 RYGB 7 VSG 6 Lean	1, 3, 12 mo.	Fasting, Post-prandial	Increased over one year, RYGB>>VSG	(Steinert et al., 2013)
63 RYGB	Preop and at 15 mo.	Fasting, Post-prandial	Increased fasting and postprandial responses in RYGB	(Werling et al., 2013b)
10AGB 8RYGB	Preop and 20% wt. loss	Fasting, Post-prandial	Doubled fasting + postprandial in RYGB, AGB No change or trend to decrease	(Kohlietal., 2013a)
30 RYGB	Preop and 12 mo.	Fasting	BA 2-fold increase after RYGB	(Simonen et al., 2012)
12 RYGB 6AGB	Day 4, 42	Fasting	Increased total in RYGB only, not AGB	(Pournaras et al., 2012)
35 RYGB	Preop, 3 mo.	Fasting	Total increased	(Jansen et al., 2011)
9VSG 6AGB 6 VSG/DS 13 RYGB	Preop, 1, 3 mo.	Fasting	Increased total and secondary by RYGB/DS, No increase in VSG, AGB	(Nakatani et al., 2009)
9 RYGB 5 Obese Match 10 Lean Match	2-4 yr. postop (cross-section)	Fasting	Increased total and conjugated species	(Parti et al., 2009)

Abbreviations: VSG, vertical sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass; AGB, adjustable gastric banding; DS, duodenal switch; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus; MM, mixed meal; AUC, area under the curve

Table 2
Studies describing changes in plasma bile acids after bariatric procedures in rodents

Species	Operation	Time Postop	Fasted/Fed	BA changes	Reference
Mouse	VSG	14 wk.	Fasting	Increased total, conjugated and unconjugated	(Ding et al., 2016)
Rat	DJB	12 wk.	Fasting	Increased total and conjugated	(Wu et al., 2016)
Rat	RYGB	8 d	Fasting	Increased total, conjugated and unconjugated	(Spinelli et al., 2016)
Mouse	BD	8 wk.	Fasting	Increased total	(Pierre et al., 2016)
Mouse	RYGB BD	8 wk.	Fasting	Increased total by BD, no change in RYGB	(Flynn et al., 2015)
Rat	DJB BD	2, 8 wk.	Fasting	Increased total in both operations	(X. Zhang et al., 2015)
Rat (SD and ZDF)	RYGB	Preop, 3-28d	Fasting	Increased total, no change in fecal BAs	(Bhutta et al., 2015)
Rat	DES	4wk	Fasting	Increased total BAs only in DES, not pair-fed or sham	(Habegger et al., 2014)
Rat	Ileal Interposition	7 mo.	Fasting	Increased total, and some conjugated, and unconjugated	(Mencarelli et al., 2013)
Mouse	VSG	2, 4, 6 wk.	Fasting + Fed	Increased total and conjugated	(Myronovych et al., 2014)
UCD-T2DM Rat	VSG	3 mo, 5 mo.	Fasting	Increased total and conjugated	(B. P. Cummings et al., 2012)
Rat	Ileal Interposition	10 wk.	Fasting	No change in total (trend for increase)	(Ikezawa et al., 2012)
Rat	Ileal Interposition	6 wk.	Fasting + Fed	Increased fasting and postprandial total – primary and secondary increased	(Kohli et al., 2010)
Rat	BD	4-5 wk.	Fasting	Increased total	(Kohli et al., 2013b)
UCD-T2DM Rat	Ileal Interposition	2 mo.	Fasting	Increased total	(B. P. Cummings et al., 2010)
Zucker Rat	Ileal Interposition	35 d	Fasting	Increased total (3-fold)	(Culhan et al., 2010)
Rats – Long Evans STZ Model	Ileal Interposition	12 wk.	Fasting	Increased total (3-fold elevation)	(Strader et al., 2009)

Abbreviations: VSG, vertical sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass; DJB, duodenojejunal bypass; DES, duodenoendoluminal sleeve; BD, bile diversion; BA, bile acids; ZDF, Zucker diabetic fatty rat; SD, Sprague-Dawley; UCD-T2DM, UC Davis Type 2 Diabetes Rat