Effects of incretin therapy and bariatric surgery on inflammation in obese patients

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ARTICLE INFO

ABSTRACT

Obesity is a major and rapidly growing global health concern and is known to be associated with significant morbidity and mortality. The obese state, irrespective of complication, is associated with chronic systemic inflammation, increasingly recognized as an important risk factor for the development of cardiovascular disease and insulin resistance. Several therapies used to treat obesity and associated comorbidities such as diabetes have been shown to attenuate inflammation and atherosclerotic factors. Data from experimental and clinical studies strongly support the beneficial effects of DPP-4 inhibitors, GLP-1 receptor agonists and bariatric surgery on inflammation as well as endothelial dysfunction and atherosclerosis.

1. Introduction

Obesity is a rapidly growing and significant problem worldwide, with approximately two-thirds of adults being overweight or obese in the United States (Ogden et al., 2014). Obesity has recently been classified by revered medical associations as a chronic disease state (Adopts New Polic, 2013; Garvey et al., 2014) and is known to be associated with significant morbidity and mortality (Clinical Guidelines, 1998), accounting for approximately 300,000 deaths annually in the USA (Kopelman, 2007). The goal of treating obesity is to prevent its associated complications including hypertension, type 2 diabetes mellitus, cardiovascular disease, renal disease, certain cancers, and many more (Clinical Guidelines, 1998). Moreover, the obese state, as a disease process itself, is associated with chronic systemic inflammation, irrespective of complication. Since inflammation is a quantifiable condition and represents a common denominator among obesity and its co-morbidities, its reduction could be a plausible therapeutic goal. Currently, the treatment of obesity consists of a combination of diet, exercise, behavior modification, weight loss medication and surgery. Anti-obesity medications, currently approved by the Food and Drug Administration (FDA) for long term use, include lorcaserin, phentermine, topiramate, naltrexone, bupropion and high dose liraglutide (Krentz

et al., 2016).

The purpose of this review article is to illustrate the mechanisms of inflammation in obesity, and emphasize the anti-inflammatory effects of current common therapies, specifically incretin agents and bariatric surgery.

2. Adipose tissue – active organ of inflammation

Obesity is the result of accumulated adiposity. Adipose tissue is derived from multipotent mesenchymal stem cells, which differentiate under the influence of diverse factors (Cornelius et al., 1994). Of particular importance is the Wnt signalling pathway. A study by Ross et al. demonstrates how Wnt signalling regulates adipogenesis through a molecular switch (Ross et al., 2000). When activated, Wnt signalling will maintain pre-adipocytes in their undifferentiated state. When this signalling pathway is inhibited, pre-adipocytes can then differentiate (Ross et al., 2000). Certain cytokines, such as IL-6 and TNF, impair the normal differentiation of preadipocytes by maintaining the previously mentioned Wnt signalling and promote an inflammatory phenotype of adipocytes (Gustafson and Smith, 2006).

There are different types of adipose tissue, some more active than others. Adipocytes are destined to become either white or brown fat

based on the presence of the surface myogenic factor Myf5 (Tsoukas et al., 2015). Brown adipose tissue is highly metabolically active and is involved in thermogenesis, as discussed in a review by Cannon et al. (Cannon and Nedergaard, 2004). Heat-producing adipocytes found in brown adipose tissue function to suppress weight gain and metabolic disease, thus are beneficial to cardiometabolic health (Harms and Seale, 2013). In contrast, white adipose tissue is less metabolically active and is not only increased by inflammatory states, but contributes to it (Makki et al., 2013). White adipose tissue under certain conditions may be induced into "brown-like" or beige adipose tissue, which has similar beneficial effects as brown adipose tissue. This conversion is usually under the control of a thermogenic stimulus (Harms and Seale, 2013; Giralt and Villarroya, 2013). In addition, it is well-known that intraabdominal/omental/visceral adipose tissue is more metabolically active and more inflammatory than subcutaneous adipose tissue and thus associated with greater cardiovascular risk (Lee et al., 2013; Neeland et al., 2013). Indeed, it has been shown that visceral adipose tissue releases more C-reactive protein (CRP), vascular endothelial growth factor (VEGF), plasminogen activator inhibitor 1 (PAI-1), monocyte chemoattractant protein-1 and two to three times more interleukin-6 (IL-6) (Fig. 1), than subcutaneous adipose tissue, as well as presenting greater numbers of CD4 and CD8 T-lymphocyte cells (Bruun et al., 2005; Fain et al., 2004; Fried et al., 1998; McLaughlin et al., 2014; Pou et al., 2007). Furthermore, there is a positive correlation between adiposity and the amount of inflammation measured by serum markers (CRP, fibrinogen, IL-6, IL-18, tumor necrosis factor alpha (TNF-α), vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin, endothelin-1 and von Willebrand factor), such that the more obese a person becomes, the more potent the inflammation observed (Fig. 1). This high grade inflammatory state has been reported to be potentially reversed by weight loss (Bastard et al., 2000; Bruun et al., 2003; Esposito et al., 2002, 2003; Ferri et al., 1999; Hotamisligil et al., 1995; Kern et al., 1995; Pontiroli et al., 2004; Schmidt et al., 2015; Christiansen et al., 2005). Moreover, confirming that visceral adipose tissue is more inflammatory than subcutaneous tissue, experiments consisting of visceral fat excision resulted in lower CRP levels, as opposed to abdominal liposuction (subcutaneous fat

excision), which did not result in significant improvement in glucose, insulin, homeostatic model assessment (HOMA) index, insulin sensitivity, IL-6, TNF-α, adiponectin and CRP (Klein et al., 2004; Lima et al., 2013; Ybarra et al., 2008). Thus, white adipose tissue, found viscerally, is an important inflammatory organ in the obese state.

3. Mechanisms of inflammation in obesity

Several potential mechanisms exist to explain how obesity generates a pro-inflammatory state (Fig. 2). As adipose tissue expands, a hypoxic state is created (Hummasti and Hotamisligil, 2010; Trayhurn, 2013; Trayhurn and WoodAdipokines, 2004; Netzer et al., 2015). Adiposity in the presence of hypoxia leads to a fed state whereby glycogen synthesis and accumulation in adipocytes and macrophages occur (Ceperuelo-Mallafre et al., 2016). The accumulation of glycogen in these uncommon stores has been shown in vitro to result in cytokine/adipokine activation and thus inflammation, and is known as adipocyte dysregulation (Ceperuelo-Mallafre et al., 2016). Adipokines are proteins secreted by adipocytes or adipose tissue (Trayhurn and WoodAdipokines, 2004). Numerous types of adipokines have been identified to date, including; several classic cytokines (adiponectin, adipsin, leptin, TNF-α, tumor growth factor-beta (TGF-β), IL-1β, IL-6, IL-8 and IL-10), acute-phase proteins (CRP, haptoglobin, PAI-1), chemokines (MCP-1), lymphokines (macrophage migration inhibitory factor), proteins of the complement system (acylation-stimulating protein), transport proteins (retinol-binding protein, cholesteryl ester transfer protein) and other growth factors (VEGF, nerve growth factor, hepatocyte growth factor) (Bruun et al., 2005; Fain et al., 2004; Hotamisligil et al., 1995; Kern et al., 1995; Christiansen et al., 2005; Trayhurn and WoodAdipokines, 2004; Yudkin et al., 1999). This inflammation attracts CD8^{+} effector T cells and, in turn, monocytes and other lymphocytes (Ceperuelo-Mallafre et al., 2016; Nishimura et al., 2009; Xu et al., 2003). These inflammatory cells then maintain the cycle of inflammation (Makki et al., 2013; Cildir et al., 2013; Weisberg et al., 2003). It is now well established that greater than 90% of adipokines produced by the adipose tissue (apart from adiponectin and leptin) is produced by non-fat cells (Fain et al., 2004; Fried et al., 1998). In fact, as adipose tissue
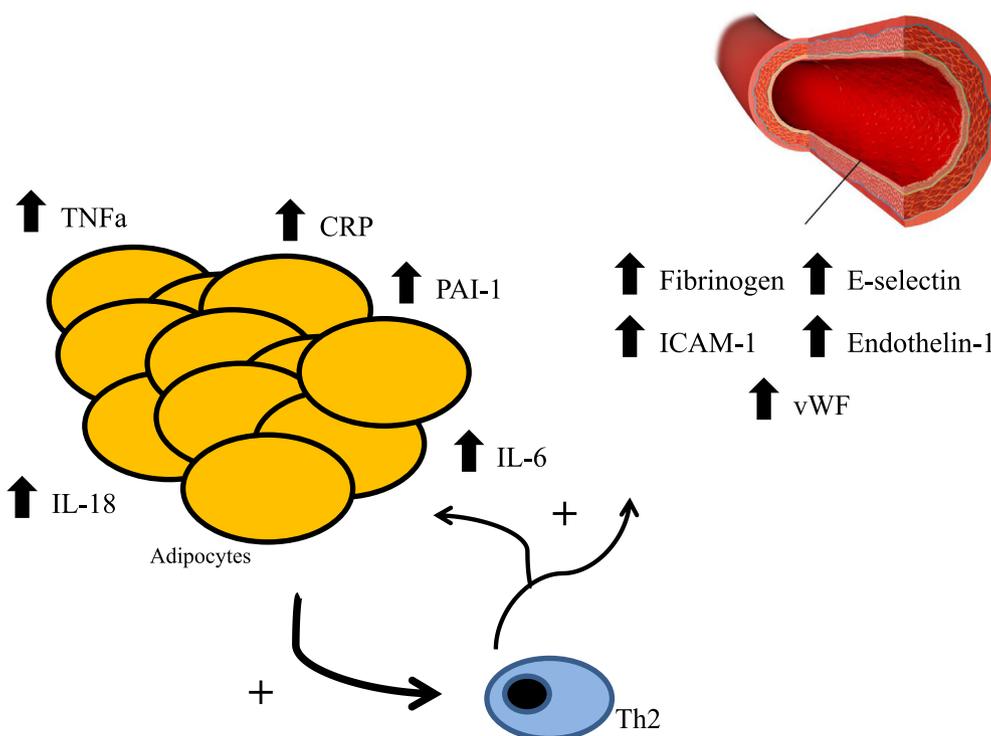
Fig. 1. Inflammation in adipose tissue There is a positive correlation between adiposity and inflammation. Visceral adipose tissue releases inflammatory markers such that as the level of adipose tissue increases, so does inflammation. CRP, C-reactive protein; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin-6; IL-18, interleukin 18; PAI-1, plasminogen activator inhibitor type 1; TNFα, tumor necrosis factor alpha; vWF, von Willebrand factor.
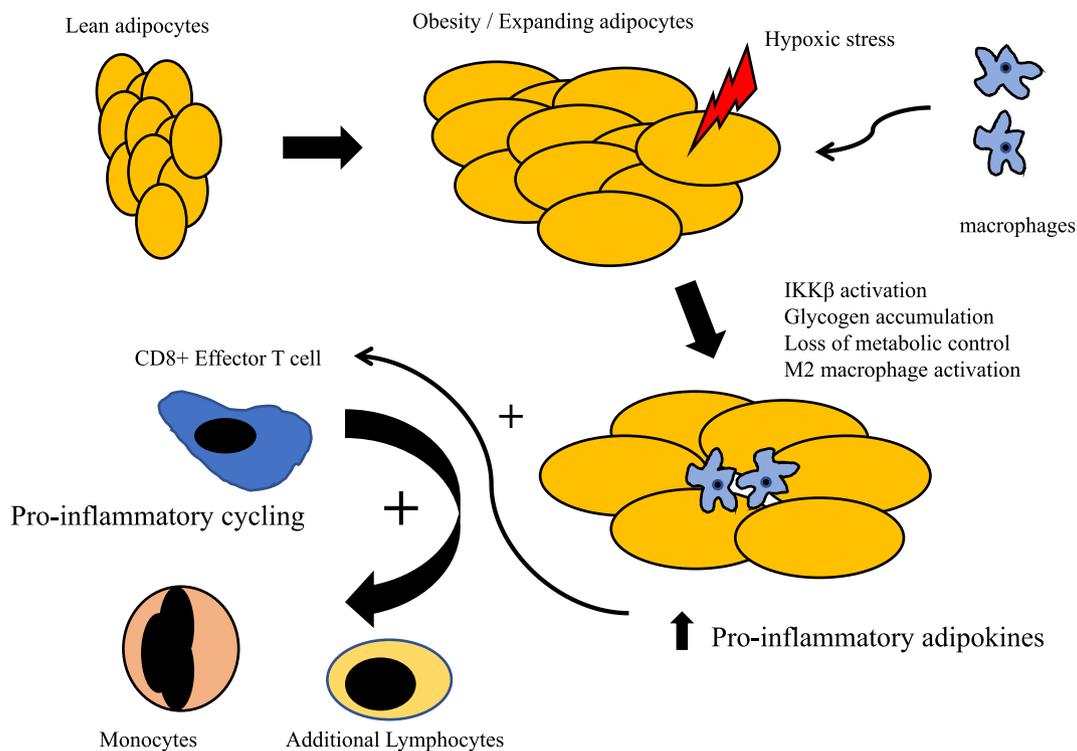
Fig. 2. Mechanism of pro-inflammation in obesity. Hypoxic stress on expanding adipocytes leads to glycogen synthesis within adipocytes and macrophages. This in turn results in adipocyte dysregulation with cytokine and adipokine activation. The cycle of inflammation is maintained by the attraction of CD8^{+} effector T cells, monocytes and other lymphocytes.

expands, there is increased infiltration of macrophages into the adipose tissue (Makki et al., 2013; Cildir et al., 2013; Weisberg et al., 2003). There are two broad categories of macrophages: M1 which are associated with an inflammatory state; and M2, associated with reduction of inflammation and healing (Mills et al., 2000). In conditions where elevated levels of glucose and fatty acids are present, M1 macrophages are favored (Chawla et al., 2011; Stevens et al., 1997). INF gamma is another potent stimulator of M1 macrophages. In turn, M1 macrophages amplify the inflammatory cascade by secreting cytokines and chemokines such as Il-6 and TNF-α (Castoldi et al., 2015).

This state of inflammation could then trigger the Ikkβ enzyme in myeloid cells as shown in animal studies and culminate in a state of insulin resistance (Ceperuelo-Mallafre et al., 2016; Arkan et al., 2005). Inflammation is also known to decrease adipocyte lipoprotein lipase activity in adipose tissue, reinforcing the notion of adipocyte dysregulation and unusual energy metabolism (Fried et al., 1998; Kern et al., 1995).

4. Effects of inflammation in obesity

Inflammation is increasingly recognized as an important risk factor for the development of cardiovascular disease and insulin resistance. Many inflammatory markers, such as IL-6, TNF-α, MCP-1 and CRP, have been shown to be independently related to risk of cardiovascular disease (Hotamisligil et al., 1995; Kern et al., 1995; Pontiroli et al., 2004; Schmidt et al., 2015; Christiansen et al., 2005; Klein et al., 2004; Lima et al., 2013). CRP is strongly associated with coronary heart disease and is used by some experts in assessing cardiovascular risk (Kern et al., 1995). Furthermore, in one study, men with abdominal obesity and serum CRP levels > 3.0 mg/L were shown to be 2.8-fold more likely to develop hypertension than those with a lower (< 1.0 mg/L) inflammatory marker detected (Niskanen et al., 2004). CRP, ICAM-1, TNF-α, and fibrinogen are elevated in the presence of traditional cardiovascular risk factors (total cholesterol, fasting glucose, insulin resistance, diabetes, blood pressure, BMI, high density lipoprotein

cholesterol, triglycerides and apolipoprotein A1) and are significantly more commonly elevated in obesity (Festa et al., 2001; Hak et al., 1999; Miller et al., 2005; Straczkowski et al., 2002). As expected, patients with a spectrum of dysglycemia from impaired fasting glucose to diabetes also have a corresponding spectrum of elevated CRP levels (Ford, 1999). The inflammatory process, through elevated CRP, does not require decades to establish in those with higher BMIs, and is even present in young adulthood, 17–39 years of age, before morbidity is identified (Visser et al., 1999). In obese teenagers, increased levels of IL-8 have been linked to insulin resistance (Kim et al., 2012).

For these reasons, it is important to efficiently treat inflammation early on in the course of obesity. Chronic low-grade inflammation produced by adipose tissue may lead to the development of non-communicable diseases such as diabetes and cardiovascular disease. Several therapies used to treat obesity and associated comorbidities such as diabetes have been shown to attenuate inflammation and atherosclerotic risk factors.

5. Incretin therapy

5.1. DPP4 inhibitors

The enzyme dipeptidyl peptidase 4 (DPP4) is mainly secreted by endothelial cells and regulates incretins (da Silva Junior et al., 2015). In addition, DPP4 plays a role in regulating cytokines, chemokines, and neuropeptides involved in inflammation and vascular function (da Silva Junior et al., 2015). Drugs inhibiting DPP-4 have been approved in the United States for the treatment of diabetes (Table 1).

5.1.1. Basic studies

There have been a number of experimental studies that evaluated the anti-inflammatory aspects of DPP-4 inhibition. In diabetic Zucker rats sitagliptin decreased CRP and IL-1β serum levels (Castoldi et al., 2015). Moreover, it has been shown to reduce macrophage infiltration of adipose tissue as well as the genetic transcription of MCP-1, IL-6 and

Table 1
List of FDA approved incretin-based drugs.

Drugs	Route of administration	Posology
DPP-4 inhibitors		
Alogliptin	Oral	Once daily
Linagliptin	Oral	Once daily
Saxagliptin	Oral	Once daily
Sitagliptin	Oral	Once daily
GLP-1 receptor agonists		
Human GLP-1 based		
Albiglutide	Subcutaneous	Once weekly
Dulaglutide	Subcutaneous	Once weekly
Liraglutide	Subcutaneous	Once daily
Semaglutide	Subcutaneous	Once weekly
Exendin-4 based		
Exenatide	Subcutaneous	Immediate release: Twice daily Extended release: Once weekly
Lixisenatide	Subcutaneous	Once daily

IL-12 in mouse models fed with a high fat diet (Dobrian et al., 2011). In agreement with these findings, vildagliptin has also significantly lowered cholesterol, triglycerides, total leukocyte count, CRP and TNF-α levels in streptozotocin diabetic rats (Khan et al., 2015).

Interestingly, DPP4 inhibitors have exerted anti-inflammatory effects in the atherosclerotic plaque itself. Alogliptin treatment induced a significant reduction of atherosclerotic lesions, IL-6, IL-1β, intraplaque macrophages and the expression of pro-inflammatory genes in mouse models (Shah et al., 2011; Ta et al., 2011). Furthermore, sitagliptin significantly reduced atherosclerotic plaque load in the aorta by priming monocytes into M2 anti-inflammatory macrophages in an ApoE−/− mouse model on a high cholesterol diet (Brenner et al., 2015). In another study involving ApoE−/− mouse models, teneligliptin (a DPP-4 inhibitor approved in Japan) inhibited atherogenesis by suppressing the pro-inflammatory phenotype of perivascular adipose tissue, particularly around the aortic arch (Salim et al., 2017).

Additionally, in vitro studies of human vascular endothelial cells treated with sitagliptin showed inhibition of TNF-α-induced plasminogen activator inhibitor type-1 (PAI-1), intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) mRNA and protein expression (Hu et al., 2013).

5.1.2. Clinical studies

Several clinical trials have studied the effects of DPP-4 inhibition in T2DM patients on inflammatory and cardiovascular biomarkers (Hattori, 2011; Makdissi et al., 2012; Rizzo et al., 2012; Satoh-Asahara et al., 2013; van Genugten et al., 2013). In a 12 week open-label study, sitagliptin and vildagliptin both decreased serum levels of pro-inflammatory cytokines IL-6 and IL-18 (Rizzo et al., 2012). In addition, in two open-label studies, treatment with sitagliptin showed significant reductions in serum levels of CRP (Hattori, 2011; Satoh-Asahara et al., 2013), VCAM-1 (Hattori, 2011) and TNF-α (Satoh-Asahara et al., 2013). Moreover, a randomized double-blinded study of 22 obese T2DM patients demonstrated a significant impact of 3 months of sitagliptin treatment on inflammatory pathways with lower serum levels of IL-6 and CRP as well as lower levels of monocyte mRNA expression of TNF-α, CCR-2, TLR-4, TLR-2, JNK-1 and IKKβ (Makdissi et al., 2012).

Thus, data from experimental and clinical studies strongly support the beneficial effects of DPP-4 inhibition on inflammation as well as endothelial dysfunction and atherosclerosis (Fig. 3).

5.2. GLP-1 receptor agonist

GLP-1 receptor (GLP-1R) agonists mimic the action of GLP-1, an incretin released in response to meal intake, and are rapidly metabolized and inactivated by the enzyme DPP4. In T2DM patients, GLP-1R agonists regulate blood sugar levels by stimulating the release of insulin, reducing glucagon, slowing gastric emptying, and inducing satiety (Abu-Hamdah et al., 2009; Baggio and Drucker, 2007; Cernea and Raz, 2011; Drucker, 2006; Sesti, 2011; Farr et al., 2016a). Beneficial effects have also been observed on blood pressure (Robinson et al., 2013), lipids (Sun et al., 2015), and weight (Robinson et al., 2013; Vilsboll et al., 2012; Farr et al., 2016b). Currently, there are seven GLP-1R agonists approved for the treatment of T2DM in the United States (Table 1) (FDA, 2014a; Trujillo et al., 2015; FDA, 2017). In addition, high dose liraglutide is approved for weight management in North America (Canada, 2016; FDA, 2014b). GLP-1R agonists have been shown to have anti-inflammatory (Fig. 3) and anti-atherosclerotic effects in both experimental and clinical studies.

5.2.1. Basic studies

In animal and in vitro models, GLP-1R agonists have been shown to have anti-inflammatory effects in many different cells and tissues; endothelial cells (Liu et al., 2009; Di Tomo et al., 2017), glomerular endothelial cells, adipocytes, monocytes, macrophages (Arakawa et al., 2010; Kodera et al., 2011; Guo et al., 2016), liver (Chen et al., 2014), brain (Parthsarathy and Holscher, 2013) and adipose tissue (Lee et al., 2012).
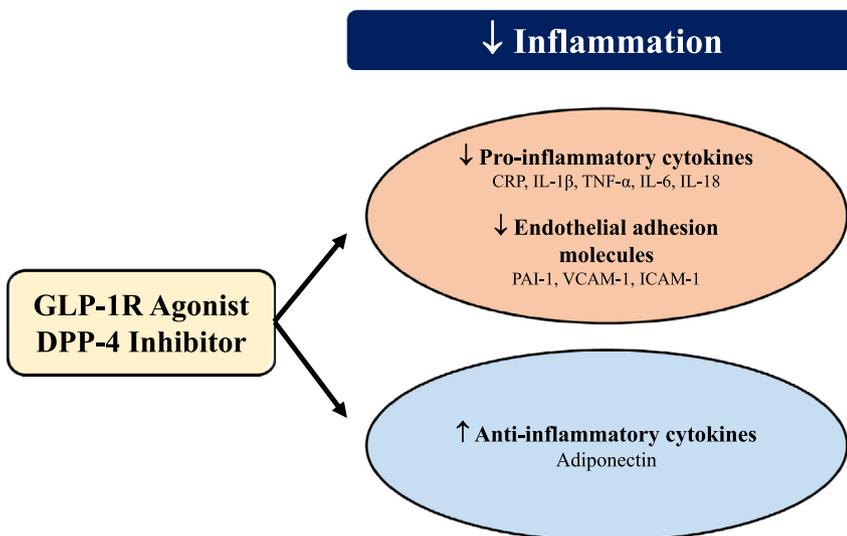
Exendin-4, which has been synthetically derived into the drug exenatide, is a GLP-1 analog which has been shown to decrease the mRNA expression of IL-6 and MCP-1 in adipose cells (Kim Chung le et al., 2009). It was also able to block apoptosis of human β-islet cells by interfering with the IL-1β-induced activation of the JNK pathway (Ferdaoussi et al., 2008). Moreover, in mice models, exposition to exendin-4 was associated with beneficial effects on inflammation and atherosclerosis (Chen et al., 2014; Ojima et al., 2013). It inhibited the NF-κB pathway and the secretion of TNF-β, IL-6 and IL-1β in macrophages (Guo et al., 2016), reduced IL-6 and TNF-α mRNA expression in liver tissue (Chen et al., 2014) as well as MCP-1 and ICAM expression in addition to macrophage infiltration in glomeruli (Ojima et al., 2013). Interestingly, continuous infusion of exendin-4 decreased monocyte endothelial adhesion and development of atherosclerosis in the thoracic aorta of both wild-type and atherosclerosis-prone apo E-deficient normoglycaemic mice (Arakawa et al., 2010).

Liraglutide, for its part, was demonstrated to have beneficial effects on endothelial dysfunction by blunting the TNF-α-induced (Liu et al., 2009; Krasner et al., 2014) and hyperglycemia-induced (Liu et al., 2009) expression of cell adhesion molecules such as PAI-1 (Liu et al., 2009), ICAM-1 (Liu et al., 2009), VCAM-1 (Liu et al., 2009; Krasner et al., 2014) and e-selectin (Krasner et al., 2014) as well as monocyte adhesion (Krasner et al., 2014) in human vascular endothelial cells (Aronis et al., 2014). Liraglutide has also been shown to reduce expression of TNF-α and NF-κB in hypoadiponectin mouse liver cells (Zhang et al., 2013). Additionally, it reduced oxidative stress and suppressed NF-κB signalling in human umbilical vein endothelial cells (Shiraki et al., 2012).

5.2.2. Clinical studies

In T2DM patients, GLP-1R agonists are associated with beneficial effects on a number of established inflammatory mediators and CVD biomarkers (Tsoukas et al., 2013). Exenatide, the synthetic form of exendin-4, and liraglutide are both shown to reduce hs-CRP (Mazidi et al., 2017). With exenatide, this effect was maintained at 1 year while under treatment (Bunck et al., 2010), but seemed to be lost 6 months after drug cessation in another study (FDA, 2014a).

GLP-1 treatment is also shown to have beneficial effects on the cytokine profile of T2DM patients. Liraglutide treatment is reported to decrease levels of pro-inflammatory TNF-α and IL-6 as well as macrophage activation while increasing levels of the anti-inflammatory adiponectin (Hogan et al., 2014). Moreover, a 12-week treatment with exenatide significantly suppressed the production of reactive oxygen species, NF-κB signalling and the mRNA expression of TNF-α, IL-1β,

↓ **Inflammation**

↓ **Pro-inflammatory cytokines**
CRP, IL-1β, TNF-α, IL-6, IL-18

↓ **Endothelial adhesion molecules**
PAI-1, VCAM-1, ICAM-1

↑ **Anti-inflammatory cytokines**
Adiponectin

GLP-1R Agonist DPP-4 Inhibitor

Fig. 3. Effects of incretin therapy on inflammation. Incretin therapy overall attenuates inflammation and promotes anti-inflammatory cytokines. CRP, C-reactive protein; ICAM-1, intercellular adhesion molecule-1; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-18, interleukin-18; PAI-1, plasminogen activator inhibitor type 1; TNFα, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion molecule-1.

TLR-2, TLR-4 and JNK-1 as well as the circulating levels of MCP-1, MMP-9, SAA and IL-6 (Chaudhuri et al., 2012). The reduction in IL-6 levels with GLP-1 agonists was also demonstrated in another study (Daousi et al., 2013). Additionally, exenatide has been associated with higher adiponectin and lower leptin levels (Bunck et al., 2010).

There are currently 4 published CV outcome trials for GLP-1 agonists studied in diabetic patients at high risk for CV events or with established cardiovascular disease; liraglutide (LEADER) (Ferdaoussi et al., 2008), lixisenatide (ELIXA) (Ojima et al., 2013), semaglutide (SUSTAIN-6) (Krasner et al., 2014) and albiglutide (HARMONY) (Hernandez et al., 2018). Both LEADER and SUSTAIN reported a significant decrease in 3-point MACE (CV mortality, non-fatal MI, non-fatal stroke) in patients receiving a GLP-1RA. Beneficial effects on the vascular endothelium through decreased inflammation may explain the improvement in CV outcomes in these trials, however exact mechanisms are not yet clear. GLP-1 treatment is demonstrated to have favorable effects on inflammation and other risk factors of atherosclerosis in different types of population, including non-diabetic patients. Indeed, in a large, 56-week, double-blind trial involving non-diabetic obese patients, liraglutide is significantly associated with improvements in hs-CRP, PAI-1, and adiponectin as well as weight loss compared to placebo (Pi-Sunyer et al., 2015). Similarly, six-month treatment with liraglutide significantly decreases hs-CRP and serum markers of endothelial function P-selectin, ICAM and VCAM in young obese women with or without PCOS (Kahal et al., 2015). However, in another study in overweight or obese prediabetic patients, there is no difference in inflammatory markers between the liraglutide and placebo groups (Kim et al., 2013). Finally, in T1DM patients, GLP-1 infusion significantly attenuated both hypoglycemia and hyperglycemia induced endothelial dysfunction, IL-6 production and oxidative stress (Ceriello et al., 2013).
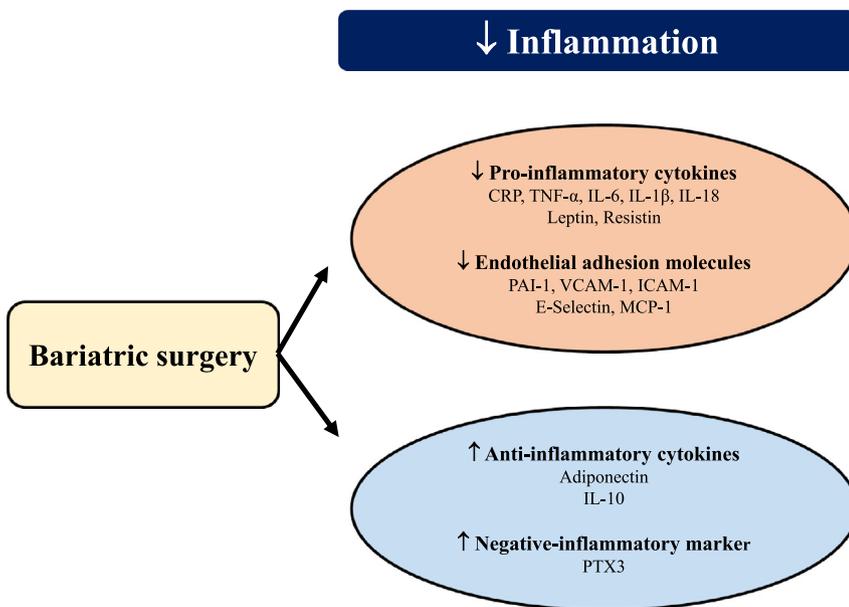
6. Bariatric surgery

Bariatric surgery is currently the most effective treatment for morbid obesity, involving significant reductions in weight and related comorbidities. The two main principles of bariatric surgery are restriction and malabsorption, either alone or in combination, with the Roux-en-Y gastric bypass (RYGB) being the most common procedure in the United States (Bult et al., 2008). Weight reduction surgery has been extensively associated with improvement in the inflammatory profile (Fig. 4). Additionally, bariatric surgery has been shown to have effects on the enteroinsular axis. Notably, malabsorptive bypass procedures increase incretin levels, while restrictive procedures do not (Vetter et al., 2009).

Notably, several studies demonstrated that bariatric surgery reduces

CRP, including restrictive (laparoscopic sleeve gastrectomy) (Gumbau et al., 2014; Hakeam et al., 2009; Mallipedhi et al., 2014; Morshed and Fathy, 2016; Wong et al., 2011), malabsorptive (biliopancreatic diversion) (Manco et al., 2007), and combination (Roux-en-Y) (Agrawal et al., 2009; Brethauer et al., 2011; Chen et al., 2009; Emery et al., 2007; Gletsu et al., 2005; Habib et al., 2009; Holdstock et al., 2005; Illan-Gomez et al., 2012; Joao Cabrera et al., 2010; Lin et al., 2007; Miller et al., 2011; Netto et al., 2015; Vazquez et al., 2005; Vilarrasa et al., 2007; Zagorski et al., 2005) procedures. In some of these studies, the reduction in CRP is correlated with the extent of weight loss (Manco et al., 2007; Agrawal et al., 2009). However, other findings show a lack of association (Holdstock et al., 2005; Miller et al., 2011; Zagorski et al., 2005), raising the possibility that factors beyond absolute weight loss may play a role in the anti-inflammatory effects of bariatric surgery, such as insulin sensitivity and adipokine levels (Holdstock et al., 2005; Illan-Gomez et al., 2012; Joao Cabrera et al., 2010; Miller et al., 2011; Vazquez et al., 2005).

In addition, many investigators report a reduction in several other mediators of inflammation and endothelial dysfunction after combination surgery; including IL-1β (Barazzoni et al., 2016), IL-6 (Emery et al., 2007; Gletsu et al., 2005; Holdstock et al., 2005; Illan-Gomez et al., 2012; Lin et al., 2007; Barazzoni et al., 2016), IL-18 (Vilarrasa et al., 2007; Schernthaner et al., 2006), TNFα (Barazzoni et al., 2016), MCP-1 (Schernthaner et al., 2006), soluble E-selectin (Vazquez et al., 2005) and PAI-1 (Brethauer et al., 2011; Vazquez et al., 2005). Particularly, in a recent study looking specifically at the improvement in the pro-atherosclerotic milieu 6 months after RYGB, a reduction in CRP, PAI-1, ICAM-1, leptin, resistin and TNF-α as well as an increase in adiponectin and IL-10 is noticed (Netto et al., 2015). This favorable adipokine profile is also supported by other studies that show lower CRP (Brethauer et al., 2011; Illan-Gomez et al., 2012; Miller et al., 2011) and leptin (Brethauer et al., 2011; Miller et al., 2011) in addition to higher adiponectin (Brethauer et al., 2011; Illan-Gomez et al., 2012; Miller et al., 2011; Schmatz et al., 2017) after weight loss surgery. Interestingly, long pentraxin-3 (PTX3), a novel negative inflammatory marker that might exert anti-atherosclerotic actions (Norata et al., 2009) is also found to increase post-RYGB (Barazzoni et al., 2016).

The effects of sleeve gastrectomy and (SG) and biliopancreatic diversion (BPD) on inflammatory cytokines have been less extensively studied. Nevertheless, a reduction in several inflammatory mediators, including IL-6 (Gumbau et al., 2014; Mallipedhi et al., 2014), MCP-1 (Gumbau et al., 2014), PAI-1 (Gumbau et al., 2014), and leptin (Gumbau et al., 2014; Mallipedhi et al., 2014), has been observed after SG. The data regarding BPD is scarce; some studies showing beneficial effects on adipokines, namely lower leptin (Murri et al., 2010) and

Fig. 4. Effects of bariatric surgery on inflammation. Bariatric surgery overall attenuates inflammation and promotes anti-inflammatory cytokines. CRP, C-reactive protein; ICAM-1, intercellular adhesion molecule-1; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-10, interleukin-10; IL-18, interleukin-18; MCP-1, monocyte chemotactic protein-1; PAI-1, plasminogen activator inhibitor type 1; PTX3, pentraxin-3; TNFα, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion molecule-1.

higher adiponectin (Manco et al., 2007; Murri et al., 2010), while another failed to show any link between pro-inflammatory cytokines, except for IP-10, and BPD surgery (Ballesteros-Pomar et al., 2014). However, some differences in lymphocyte subpopulations, namely decreased total and CD8 T Lymphocytes, B lymphocytes and NK cells, are noted in insulin resistant individuals (Ballesteros-Pomar et al., 2014).

Moreover, some investigators have looked at the differential effect on inflammation between SG and RYGB, the evidence being somewhat contradictory. Indeed, most studies fail to show any difference in serum inflammatory biomarkers between RYGB and SG, particularly CRP (Fenske et al., 2013), IL-6 (Kelly et al., 2016; Viana et al., 2013), TNFα (Viana et al., 2013), MCP-1 (Fenske et al., 2013), adiponectin (Kelly et al., 2016) and leptin (Kelly et al., 2016). However, some studies did show a greater reduction in CRP (Iannelli et al., 2011, 2013) with RYGB than sleeve gastrectomy.

To our knowledge, there is currently no data comparing inflammatory biomarkers between incretin agents and bariatric surgery procedures.

7. Conclusion and future directions

There is an increasing amount of evidence, both clinical and experimental, supporting the role of incretin agents and bariatric surgery in reducing the pro-inflammatory milieu associated with obesity. Aiming to treat this chronic low-grade inflammatory state and consequently preventing the development of atherosclerosis should be a main concern to clinicians managing obesity.

A valuable direction for future research would be to thoroughly investigate the factors most strongly correlated with changes in inflammatory biomarkers, beyond changes in BMI, potentially including the incretins themselves. It is necessary in future studies to determine if the improvement in inflammation associated with bariatric surgery is explained in part by changes in incretins or other gut-brain interactions. For instance, this may be explored by comparing the effects on inflammatory mediators between different incretin agents and bariatric surgery. Finally, long-term follow-up studies on the anti-inflammatory effects of both bariatric surgery and incretin-based therapies are needed in order to clarify their impact on cardiovascular clinical endpoints.

Author contributions

All authors contributed to the writing and revision of this review.

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