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MESTRADO INTEGRADO EM MEDICINA

Sofia Ferreira Dias

Fármacos usados no tratamento da dislipidemia e da
obesidade: foco no tecido adiposo /
Drugs involved in dyslipidemia and obesity treatment:
focus on adipose tissue

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Drugs involved in dyslipidemia and obesity treatment: focus on adipose tissue

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Aos meus pais,

irmã e

amigos

DRUGS INVOLVED IN DYSLIPIDEMIA AND OBESITY TREATMENT: FOCUS ON ADIPOSE TISSUE

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List of Abbreviations

MS	Metabolic syndrome
CVD	Cardiovascular disease
AT	Adipose tissue
T2DM	Type 2 diabetes mellitus
11β-HSD1	11β-Hydroxysteroid dehydrogenase type 1
TNFα	Tumour-necrosis factor α
IL-6	Interleukin-6
CCL2 or MCP-1	CC-chemokine ligand 2
PAI-1	Plasminogen-activator inhibitor type 1
AdipoR	Adiponectin receptor
AMPK	AMP-activated protein kinase
IL-1RA	IL-1 receptor antagonist
IFN-γ	Interferon- γ
TLR	Toll-like receptors
NF-κB	factor nuclear kappa B
LMW and HMW	Low- and high- molecular-weight
SRB1	Scavenger receptor class B type 1
PPARs	Peroxisome proliferator-activated receptors
CXCL8/ IL-8	CXC-chemokine ligand 8

VCAM-1	Vascular cell adhesion molecule-1
E-selectin	Endothelial-leukocyte adhesion molecule-1
ICAM-1	Intracellular adhesion molecule-1
SREBP1	Sterol regulatory element-binding protein 1
OBRb	Leptin receptor
cAMP	Cyclic adenosine monophosphate
PKA	cAMP-dependent protein kinase A
ERK	Extracellular-signal-regulated kinase
MAPK	p38 mitogen-activated protein kinases
NK cells	Natural killer-cells
iNOS	Inducible nitric-oxide synthase
ROS	Reactive oxygen species
TNFR	TNF receptor
IKKβ	Inhibitor of NF-κB kinase-β
JNK	JUN N-terminal kinase
ER	Endoplasmic-reticulum
IRS1	Insulin receptor substrate 1
WAT	White AT
UCP	Uncoupling protein
CAP1	Adenylyl cyclase-associated protein 1
ET-1	Endothelin-1
CCR2	CCL2 receptor
FFA	Free fatty acids
AR	Adrenoceptors
NPs	Natriuretic peptides
ANP	Atrial natriuretic peptide
BNP	Brain natriuretic peptide
AC	Adenylate cyclase
cGMP	Cyclic guanosine monophosphate
PKG	cGMP-dependent protein kinase
GC	Guanylyl cyclase
TG	Triglycerides
ATGL	Triglyceride lipase
HSL	Hormone-sensitive lipase
MGL	Monoacylglycerol lipase
PI3-K	Phosphoinositide 3-kinase-dependent

PKB/Akt	Protein kinase B
PDE3B	Phosphodiesterase 3B
AC	Adenylyl cyclase
PGC-1α	PPARγ coactivator 1
ACS	Acyl-CoA synthetase
CD36/FAT	Fatty acid translocase
MCD	Malonyl-CoA decarboxylase
CPT-1	Carnitine palmitoyl transferase 1
SIRT1	Sirtuin 1
BAT	Brown adipose tissue
PRDM16	PR domain containing 16
HDLs	High-density lipoproteins
apo	apolipoproteins
ABCA1	ATP binding cassette A1
LPL	Lipoprotein lipase
VLDL	Very low-density lipoprotein
Glycerol-3P	Glycerol-3-phosphate
DGAT	Diacylglycerol acyltransferase
GLUT4	Glucose transporter type 4
ACC	Acetyl-coenzyme A carboxylase
BMPs	Bone morphogenetic proteins
C/EBP	CCATT enhancer-binding proteins
RXRα	Retinoid X receptor-α
FABP4	Fatty acid-binding protein-4
SCD1	Stearoyl-coA desaturase-1
SRE	Sterol response elements
FAS	Fatty acid synthase
CEPT	Cholesteryl ester transfer protein
PCSK9	Proprotein convertase subtilisin/kexin type 9
LDL	Low density lipoprotein
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
MEKK1	Mitogen-activated protein kinase kinase Kinase 1
HFD	High fat diet
ox-LDL	Oxidized LDL
SCAT	Subcutaneous AT
PPRE	Peroxisome proliferators response element

ACO	Acyl-CoA oxidase
VAT	Visceral AT
CD40	Cluster of differentiation 40
AOX1	Aldehyde oxidase 1
PUFAs	Polyunsaturated fatty acids
LXRα	Liver X receptor alpha
CRP	C-reactive protein
NA	Noradrenaline
5-HT	5-hydroxytryptamine
DA	Dopamine
POMCs	Pro-opiomelanocortin
MC	Melanocortin
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
GABA	Gamma-aminobutyric acid
GLP-1RA	Glucagon-like peptide 1 receptor agonist
ZAG	Zinc alpha2 glycoprotein
FGF21	Fibroblast growth factor-21

Abstract

Metabolic syndrome (MS) can be defined as a state of disturbed metabolic homeostasis characterized by the combination of visceral obesity, atherogenic dyslipidemia, arterial hypertension and insulin resistance. The growing prevalence of MS will contribute to the burden of cardiovascular disease (CVD). Obesity and dyslipidemia are main features of MS and both can present with adipose tissue (AT) dysfunction, involved in the pathogenic mechanisms underlying MS. Considering this, increase the knowledge about the role of AT and the drugs that modulate its functions can become the next step in order to tackle these diseases. In this article, we revised the effects of the current approved drugs for dyslipidemia and obesity treatment on AT and their underlying mechanisms. Their main adipocyte effects upon metabolism, inflammation, atherogenesis, insulin sensitivity, and adipogenesis were reviewed to explore how these drugs can modulate these complex pathways. Furthermore, we denote differences between drugs of the same class and that, despite a favorable clinical effect, some drugs can have adverse effects on adipocyte functions. Summing up, it is important to question whether answers to these problems will be found in new advances in pharmacology or in further adjustments and combinations between drugs already developed. To better understand the effect of drugs used in dyslipidemia and obesity on AT is not only challenging for physicians but could be the next step to tackle CVD.

Key words: Adipose Tissue; Dyslipidemia; Obesity; Anti-dyslipidemic drugs; Anti-obesity drugs.

1 Introduction

Metabolic syndrome (MS) is a cluster of metabolic abnormalities that increase the risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). It can be defined as a state of disturbed metabolic homeostasis characterized by the combination of visceral obesity; atherogenic dyslipidemia; arterial hypertension and insulin resistance (Grundy 2003). CVD is the leading cause of mortality worldwide (Mehra 2007) and the growing prevalence of MS will certainly contribute to the burden of CVD in the future. Although obesity per se is not a required feature for the diagnosis of MS, several evidences suggest that visceral obesity has a key role in the pathogenic mechanisms underlying this syndrome (Ribeiro Filho et al. 2006). In order to tackle the obesity epidemic, research on adipose tissue (AT) has been gaining momentum. In the last years numerous facts have been discovered about this organ, despite many metabolic complex pathways remain unknown.

Since obesity and dyslipidemia are main features of MS and both can present with AT dysfunction, in this article we revised the effects of the current approved drugs for both dyslipidemia and obesity treatments on AT as their underlying mechanisms.

A methodological assessment of the literature on PubMed and SciELO databases was conducted without setting limits for year publication though selecting English, Spanish and Portuguese papers with full text availability. The following terms were used: adipose tissue; dyslipidemia; fibrates; statins; niacin; resins; ezetimibe; obesity; orlistat; sibutramine; diethylpropion; phentermine/topiramate; bupropion and naltrexone; liraglutide. The retrieved articles until 10/10/2016 were first selected based on title and abstract. Then, the 145 remaining articles were fully read to assess for eligibility and 29 were excluded owing to focus on effects in other organs (liver, pancreas, brain) rather than AT, inadequacy to the theme, being duplicated or full text unavailability. The final 116 articles were further analysed.

1.1 The Adipose Tissue

AT is nowadays recognized as a major active endocrine organ, secreting several hormones called adipokines. Through these hormones, AT has a major role in several physiological systems, such as regulation of food intake and body weight, insulin sensitivity, inflammation, coagulation or vascular function. These actions are achieved through complex pathways. Adipokines act locally within the AT, exerting autocrine and paracrine actions, but also endocrine in distant organs through systemic circulation. AT is composed of different cell types, such as mature adipocytes, pre-adipocytes, vascular cells and macrophages (Romacho et al. 2014). Adipokines and cytokines secreted from these different cells are able to influence each other (Romacho et al. 2014) as a variety of organs, being their balance necessary to maintain health. AT also has the capacity to modulate some biological functions, as is the case of those related with cortisol, through the conversion of cortisone to this corticosteroid by 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) action (Stimson et al. 2009) (fig. 1.1 B)). The main adipokines produced by adipocytes are adiponectin and leptin. Tumour-necrosis factor α (TNFα), interleukin-6 (IL-6), IL-1, CC-chemokine ligand 2 (CCL2 or MCP-1), Fractalkine, plasminogen-activator inhibitor type 1 (PAI-1), visfatin and complement factors are also produced by adipocytes, though in lesser extent, and mostly by stromal-vascular cells. This interplay is summarized on figure 1.1.

Adiponectin is the classical anti-inflammatory cytokine. It acts through adiponectin receptor (AdipoR) 1/2, enhancing the AMP-activated protein kinase (AMPK) pathway. In AT, adiponectin acts mainly in macrophages, reducing their phagocytic capacity (Wolf et al. 2004); inducing the production of IL-10 and IL-1 receptor antagonist (IL-1RA) (Wolf et al. 2004); supressing the production of interferon- γ (IFN-γ) (Wolf et al. 2004) and inhibiting the Toll-like receptors (TLR)-induced factor nuclear kappa B (NF-κB) pathway activation (Yamaguchi et al. 2005). Although

the differences between the effects of low- (LMW) and high- (HMW) molecular-weight adiponectin still remain unclear, both adiponectin forms induce activation of AMPK pathway and suppression of scavenger receptor class B type 1 (SRB1) expression by macrophages (Neumeier et al. 2006). Nevertheless, only the LMW form is responsible for inducing IL-10 and suppressing IL-6, through peroxisome proliferator-activated receptors (PPARs) stimulation (Neumeier et al. 2006). In contrast, the HMW adiponectin can even induce the expression of CXC-chemokine ligand 8 (CXCL8; also known as IL-8) after an inflammatory stimulation (Neumeier et al. 2006). In endothelial cells, it modulates the inflammatory atherosclerosis process, by inhibiting the expression of adhesion-molecule vascular cell adhesion molecule-1 (VCAM-1), endothelial-leukocyte adhesion molecule-1 (E-selectin), and intracellular adhesion molecule-1 (ICAM-1) induced by TNFα (Ouchi et al. 1999). Moreover, it can induce β-oxidation in the liver while decreases the expression of sterol regulatory element-binding protein 1 (SREBP1), therefore inhibiting lipogenesis. **Leptin** is, in contrast, a pro-inflammatory cytokine that acts through the leptin receptor (OBRb), activating the cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA)-extracellular-signal-regulated kinase (ERK) 1/2 and p38 mitogen-activated protein kinases (MAPK) pathways (Zhao et al. 2005). Through these pathways, leptin upregulates the expression of TNFα, IL-6 and IL-12 in macrophages (Gainsford et al. 1996). It also has a role on controlling appetite, angiogenesis, haematopoiesis, neuroendocrine system and immunity (La Cava and Matarese 2004). In fact, leptin can regulate neutrophil chemotaxis and natural killer-cells (NK cells) activity (Tian et al. 2002). It also upregulates inducible nitric-oxide synthase (iNOS) expression in AT and, thereby, increases the production of reactive oxygen species (ROS), mostly from macrophages (Weisberg et al. 2003; Lumeng et al. 2007). By this mechanism, leptin induces macrophage phagocytosis and differentiation of monocytes. **TNFα** activates TNF receptor (TNFR) which activates the inhibitor of NF-κB kinase-β (IKKβ), in turn, activating the NF-κB pathway (Yuan et al. 2001). In addition, TNF (and also TLRs stimulation) can also stimulate the JUN N-terminal kinase (JNK) family of serine/ threonine protein kinases (Hirosumi et al. 2002). This latter mechanism is involved in the inhibition of insulin signalling pathway, promoting insulin resistance (Lee et al. 2003), and in insulin sensitivity inhibition as endoplasmic-reticulum (ER) stress leads to the phosphorylation of insulin receptor substrate 1 (IRS1) (Ozcan et al. 2004). TNFα increases iNOS expression in adipocytes, which appears to supress uncoupling protein (UCP) 2 expression that could lead to decreasing energy expenditure of white AT (WAT) (Merial et al. 2000). **Resistin** is also a pro-inflammatory cytokine. The production of resistin is enhanced by other pro-inflammatory cytokines such as IL-1, IL-6 and TNFα (Kaser et al. 2003). Endorsing a positive feedback of inflammation, resistin also increases the expression of IL-1, IL-6, TNFα and IL-12 upon different types of cells (Silswal et al. 2005; Kaser et al. 2003). This inflammatory amplification is driven by adenylyl cyclase-associated protein 1 (CAP1) in monocytes, by which resistin increases cAMP concentration, PKA activity and NF-κB leading thereby to upregulation of the aforementioned cytokines (Lee et al. 2014). Moreover, resistin is also able to induce the expression of VCAM-1, ICAM-1 and CCL2 in endothelial cells, inducing endothelin-1 (ET-1) secretion (Verma et al. 2003). In this way, resistin contributes to atherosclerosis development. **MCP-1** is a potent chemoattractant of monocytes and macrophages to AT and acts through the CCL2 receptor (CCR2) (Takahashi et al. 2003). **Fractalkine** (or CX3CL1) and its receptor (CX3CR1) are also involved in this process (Shah et al. 2011). **PAI-1** is a pro-thrombotic agent, inhibitor of plasminogen activators, which expression is induced by TNFα and stress oxidative (Alessi et al. 2007), insulin, glucocorticoids, angiotensin II, fatty acids (FA), TNF-α, and TGF-β (Correia and Haynes 2006; Skurk and Hauner 2004). It negatively affects physiological metabolism and local vascular biology by interacting with the renin-angiotensin-aldosterone system. Moreover, PAI-1 suppresses adipocyte differentiation in adipocytes (Liang et al. 2006). **Visfatin** acts through insulin receptor, although binding to a different site than insulin (Fukuhara et al. 2005), acting as a pro-inflammatory cytokine (Chang et al. 2010). It also induces adipocyte differentiation (Fukuhara et al. 2005).

AT is the main regulator of whole body fat storage, which depends on the balance between energy expenditure and intake. In fact, there is a straight modulation between lipid deposition and mobilization though these metabolic pathways are affected by several hormones. Lipid mobilization is enhanced in fasting conditions. Likewise, glucagon, catecholamines (through β- adrenoceptors (AR)) and atrial or brain natriuretic peptide (ANP/BNP) promote lipolysis (Sengenes et al. 2000). In the complex process of lipolysis, after hormonal stimulation, there is an activation of adenylate cyclase (AC) enzyme, which activates cAMP-PKA pathway and, consequently, the phosphorylation of lipases responsible for lipolysis (Lafontan and Langin 2009). The exception for this mechanism is for natriuretic peptides (NPs), since they act trough the cyclic guanosine monophosphate (cGMP)-dependent protein kinase (PKG) pathway, by activating NPR-A-dependent guanylyl cyclase (GC) activity (Moro et al. 2004). These pathways activate three main lipases: adipocyte triglyceride (TG) lipase (ATGL), hormone-sensitive lipase (HSL) and monoacylglycerol lipase (MGL) (Tsiloulis and Watt 2015). Their sequential action leads to the hydrolysis of TG into diglycerides and ultimately into monoglycerides. Also, phosphorylation of perilipin, a lipid droplet-associated protein, causes its decoupling from lipid droplets, which promotes lipolysis by allowing HSL to gain access to it (Tsoli et al. 2016; Arner and Langin 2014; Krintel et al. 2009). This process culminates with the release of FA and glycerol that are uptaken by other tissues (mainly, skeletal muscle, liver and heart that use FA for energy production, and liver glycerol in gluconeogenesis). On the contrary, insulin and cathecolamines (through α2-AR) inhibit lipid mobilization (Sengenes et al. 2000). Insulin inhibits this process through phosphoinositide 3-kinase-dependent (PI3-K) pathway, protein kinase B (PKB/Akt), and activation of phosphodiesterase 3B (PDE3B), which degradates cAMP. By lowering cAMP levels and by inhibiting adenylyl cyclase (AC) through an inhibitory GTP-binding protein (Gi)-coupled receptor, insulin inhibits PKA pathway and ultimately lipolysis (Morigny et al. 2016).

FA β-oxidation is responsible for mitochondrial breakdown of long-chain acyl-CoA to acetyl-CoA, used for mitochondrial energy production. The PPARs and PPARγ coactivator 1 (PGC-1α) are the most well-known transcriptional regulators of FA β-oxidation (Huss and Kelly 2004). These regulators enhance the expression of proteins involved in this process such as acyl-CoA synthetase (ACS), fatty acid translocase (CD36/FAT), malonyl-CoA decarboxylase (MCD), carnitine palmitoyl transferase 1 (CPT-1). In this context, FAs can undergo the action of ACS and CPT1 and thereby be used to β-oxidation. AMPK phosphorylates PGC-1α protein leading to its activation. On the contrary, sirtuin 1 (SIRT1) (a protein deacetylase involved in cellular regulation to stress) deacetylates PGC-1α. PGC-1α induces the expression of PPARα, mostly expressed in highly metabolic tissues such as liver, heart, skeletal muscle, brown adipose tissue (BAT), enhancing the expression of mitochondrial genes and β-oxidation genes (Huss and Kelly 2004).

Although, it has been settled down that certain stimulus, such as PPAR-α agonists, can cause browning of white AT. This process is marked by the expression of PR domain containing 16 (PRDM16) and PPARγ, and of UCP1 (all markers of BAT), which attributes to WAT a more oxidative metabolism (Harms and Seale 2013; Bargut et al. 2017). In lipid mobilization, high-density lipoproteins (HDLs) are responsible for the reverse cholesterol transport, transporting cholesterol from extra-hepatic tissues (including arterial macrophages and AT) to the liver (Chapman 2006). These lipoproteins are constituted by cholesterol, triglycerides, phospholipids and apolipoproteins A (mainly apoA-I and apo A-II), apo-C and apo-E. The interaction between apoA-I and receptors in peripheral tissues, namely ATP binding cassette A1 (ABCA1) transporters and SRB1 are responsible for cholesterol transportation (Chapman 2006). Once filled with cholesterol, HDL can deliver the cholesterol into the liver (Chapman 2006).

Lipid deposition, on the other side, can occur by uptake of circulating FA (in a higher extent) and lipogenesis de novo from non-lipid precursors. The former is driven by lipoprotein lipase (LPL), secreted by adipocytes, located in the lumen of AT capillaries (Fielding and Frayn 1998). This enzyme hydrolysis TG associated to lipoproteins (such as very low-density lipoprotein (VLDL) or chylomicrons) into FA, facilitating their uptake by adipocytes (Kersten 2014). Upon uptake, they can suffer reesterification, combining FA with glycerol-3-phosphate (Glycerol-3P), leading to TG synthesis (Harris et al. 2011). This process is catalysed by diacylglycerol acyltransferase (DGAT) and stimulated by insulin (Harris et al. 2011). Through the lipogenesis *de novo* process,

insulin induces the uptake of glucose by adipocytes (through glucose transporter type 4 (GLUT4)) and, through glycolysis, is converted to Acetyl-Coenzyme A. The Acetyl-CoA is converted by acetyl-coA carboxylase (ACC) to malonyl-CoA, leading to FA synthesis (Assimacopoulos-Jeannet et al. 1995). At the same time, insulin inhibits the translocation of FA to mitochondria by CPT1 and therefore β-oxidation (Su and Abumrad 2009). The metabolic functions of AT are summarized on fig. 1.2.

Adipogenesis (summarized on fig.1.1 A)) is a tightly regulated cellular differentiation process through which preadipocytes are converted into mature adipocytes. It is essential to the renewing of AT and to the modulation of fat deposition process. Adipogenesis comprises two phases: 1) the commitment of pluripotent stem cell to a unipotent preadipocyte and 2) differentiation of preadipocytes into mature adipocytes (fig. 1.1 A)). In the first phase, bone morphogenetic proteins (BMPs) and TAK1 pathways are involved, whereas in the second terminal differentiation phase, other transcription factors such as PPARγ, CCATT enhancer-binding proteins (C/EBP) and SREBP1 take action (Kim and Spiegelman 1996). After hormonal stimulation, there is an increase in intracellular cAMP, leading to transcription of C/EBPβ and C/EBPδ in preadipocytes, which translocate to the nucleus and enhance the expression of C/EBPα and PPARγ (Roesler et al. 1998). PPARγ heterodimerizes with retinoid X receptor-α (RXRα) and bind to DNA, promoting transcription of the adipocyte-specific genes, leptin, adiponectin, fatty acid-binding protein-4 (FABP4) and perilipin (Rosen et al. 2000). In addition, C/EBPα also enhances the transcription of leptin and FABP4, as well as other genes, such as GLUT4 and stearoyl-coA desaturase-1 (SCD1) (Guo et al. 2015). During differentiation, SREBP1 is activated and translocated to the nucleus, where it binds to sterol response elements (SRE) and induces the expression of lipogenic enzymes such as ACC, fatty acid synthase (FAS), LPL, and SCD1 (Kim and Spiegelman 1996; Alvarez et al. 2014).

1.2 Obesity and dyslipidemia: two disorders walking together

Obesity and dyslipidemia are two main features of MS. Dyslipidemia refers to a range of lipid profile disorders, resulting from quantitative (higher or lower lipid or/and lipoprotein levels) or qualitative alterations (structural alterations in lipoprotein molecules) (Brunzell JD 2010). In respect to aetiology, these disorders are classified as primary, in which exists a primary disorder of lipid metabolism, and secondary. This last type, the most common (80%), is a consequence of medical conditions such as T2DM and obesity, unhealthy lifestyle habits, mainly excessive alcohol consumption and cigarette smoking and the use of some drugs (Eaton 2005; Brunzell 2007; Jellinger et al. 2017). Dyslipidemia is a primary, major risk factor for CVD (Jellinger et al. 2017). Obesity is a multifactorial disease, characterised by a local and systemic chronic low-grade inflammation state causing metabolic abnormalities and adipocyte dysfunction (Curat et al. 2004), that ultimately lead to CVD. This state has also been implicated in the development of obesity-related complications such as insulin resistance, T2DM, arterial hypertension, dyslipidemia and cancer (Ng et al. 2014). The growing MS prevalence seems to be closely related to the obesity epidemic (Heinl et al. 2016). Additionally, obesity also seems to be associated with the rising prevalence of dyslipidemia, as studies have suggested a positive correlation between body mass index (BMI) and dyslipidemia (Cohen et al. 2010; Lamon-Fava et al. 1996).

Obesity, mainly hypertrophy, is characterized by AT dysregulation (Gustafson et al. 2013). Eventually, this dysfunctional AT can cause dyslipidemia. It is known that dysfunctional adipocytes become insulin resistant, favouring lipolysis. This is due to an increase in HSL activity, releasing FFA, cytokines and adipokines (Sun et al. 2011; Despres and Lemieux 2006; Hyun et al. 2008). FFA not oxidized for fuel, are uptaken by liver, increasing intrahepatic fat and causing liver steatosis (Fabbrini et al. 2009; Fabbrini et al. 2008). The removal of intrahepatic TG occurs within the VLDL-TG; and rate of hepatic VLDL-TG secretion seems to be greater in subjects with high intra-hepatic TG content (Fabbrini et al. 2009), thus the more intra-hepatic fat, the more the VLDL-TG turnover. FFA, but also insulin resistance (Panarotto et al. 2002) and inflammation

(Kawakami et al. 1987), cause a decrease in LPL expression and activity, leading to an increase in circulating TG (VLDL-TG and chylomicrons). Body fat accumulation also seems to enhance cholesteryl ester transfer protein (CEPT) activity causing a decrease in HDL levels (Arai et al. 1994). In fact, the simultaneous increase of TG and decrease of HDL (Castelli 1998) constitutes the atherogenic dyslipidemia pattern most common in obese individuals (Poirier et al. 2006). Hiperleptinemia is present in obesity, and leptin, through enhancement of hepatocyte nuclear factor 1 homeobox A expression (which binds to proprotein convertase subtilisin/kexin type 9 (PCSK9) promotor and MAPK pathway) seems to be able to upregulate the expression of PCSK9, thereby inhibiting the expression of low density lipoprotein (LDL) receptors and, consequently, LDL uptake in hepatocytes (Du et al. 2016). Thus, hyperleptinemia alone, by increasing LDL levels, can contribute to the development of CVD associated to obesity (Du et al. 2016). Globally, when obesity is associated with AT dysfunction, ectopic fat accumulation, especially in liver, and inflammation, it favours the development of dyslipidemia (Fon Tacer and Rozman 2011).

2 Drugs used in dyslipidemia

2.1 HMG-CoA reductase inhibitors (Statins)

3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, act by inhibiting in a competitive manner the rate-limiting step of cholesterol synthesis in liver, namely the conversion of HMG-CoA to mevalonic acid. Statins increase LDL receptors expression in liver, which in turn increases LDL catabolism and lowers total cholesterol concentration. Their metabolic effect includes a LDL reduction of 21-55%, a TG reduction of 6%-30% and an increase in HDL of 2%-10%. New-onset diabetes may be increased in patients treated with statins; however, it is dose-related and seems to be less common with pravastatin and possibly pitavastatin (Jellinger et al. 2017). Increasing evidence has shown that there is much more to reveal about this drug.

2.1.1 Effects upon adipocyte metabolic functions

AT acts as a buffer of plasmatic cholesterol and statins have an important role decreasing basal cholesterol release (Bencharif et al. 2010) and content (Krautbauer et al. 2013) in adipocytes. In fact, they are capable of reverting basal cholesterol release from adipocytes, though not after apo-A-I stimulation (inducing cholesterol release and apo-E secretion by adipocytes) (Bencharif et al. 2010). In mature adipocytes, pitavastatin upregulates HSL expression, enhancing lipolysis, decreasing lipid accumulation and preventing adipocyte hypertrophy, and increasing the number of small adipocytes (Ishihara et al. 2010). Intensive treatment with atorvastatin also leads to the regression of epicardial AT volume (Alexopoulos et al. 2013). Statins seem to induce mRNA LPL expression in preadipocytes (Bey et al. 2002; Saiki et al. 2006) as well as enhance lipoprotein lipase (LPL) activity in 3T3-L1 pre-adipocytes (Bey et al. 2002) and adipocytes (Saiki et al. 2006). The underlying mechanism involves different transcription factors, such as SREBP or PPARγ (Bey et al. 2002). These effects contribute to lower triglyceride and VLDL levels (Bey et al. 2002; Saiki et al. 2006). In contrast, it has been shown that in a bone marrow stromal cells model, statins can reduce LPL mRNA expression (Song et al. 2003).

Although the enhancement of LPL activity seems to be a common effect of this class, different statins have shown divergent effects on LPL expression in adipocytes. Authors refer the following mechanisms to explain this: 1. different affinities to adipocytes due to statins hydrophilic proprieties; 2. drug metabolites such as pro-drugs; and finally, 3. existence of different tissues expressing LPL that could interfere with the *in vivo* effect. Moreover, authors suggest that these differential effects could be due to a direct or indirect effect, respectively, upon LPL expression and/or upon HDL levels and LDL size (Saiki et al. 2006).

2.1.2 Effects upon inflammation

Many studies support an anti-inflammatory effect of statins in AT. After exposure to a stressful and inflammatory stimulus, the expression of pro-inflammatory adipokines and cytokines, such as Leptin (Krysiak et al. 2014c; Labuzek et al. 2011; Maeda and Horiuchi 2009; Zhao and Wu 2005; Krysiak et al. 2014d), Resistin (Ichida et al. 2006; Labuzek et al. 2011; Li et al. 2016), IL-6 (Labuzek et al. 2011; Zhao and Zhang 2003; Dobashi et al. 2008; Yin et al. 2007; Wang et al. 2014; Abe et al. 2008), Plasminogen activator inhibitor-1 (PAI-1) (Laumen et al. 2008; Lobo et al. 2012; Sakamoto et al. 2011), MCP-1 (Lobo et al. 2012; Wu et al. 2013; Wang et al. 2014; Takagi et al. 2008; Abe et al. 2008), Visfatin (Krysiak et al. 2014d) and TNF-α (Krysiak et al. 2014c; Labuzek et al. 2011; Wu et al. 2013; Wang et al. 2014; Krysiak et al. 2014d; Takagi et al. 2008) increases. Statins can reduce pro-inflammatory cytokines and adipokines expression

(Ichida et al. 2006; Labuzek et al. 2011; Laumen et al. 2008; Lobo et al. 2012; Maeda and Horiuchi 2009; Sakamoto et al. 2011; Zhao and Zhang 2003; Dobashi et al. 2008; Yin et al. 2007; Zhao and Wu 2005; Wu et al. 2013; Krysiak et al. 2014d; Li et al. 2016; Wang et al. 2014; Krysiak et al. 2014c; Ishihara et al. 2010), while enhancing anti-inflammatory adipokines expression and secretion by adipocytes (Labuzek et al. 2011; Lobo et al. 2012; Yin et al. 2007; Ishihara et al. 2010; Li et al. 2016; Krysiak et al. 2014c). For instance, by upregulating PPARγ expression in adipocytes, statins decrease IL-6 expression and plasma concentration (Zhao and Zhang 2003). Moreover, these drugs can decrease high sensitivity C-reactive protein (CRP) plasma levels (Krysiak et al. 2014c). In addition, the combination of two drugs, statins and fibrates, has evidenced a higher reduction in pro-inflammatory cytokines secretion (Labuzek et al. 2011). The combination of Ezetimibe-simvastatin treatment, as opposed to simvastatin treatment in monotherapy, demonstrated a higher effect in reducing pro-inflammatory adipokines and increasing adiponectin levels (Krysiak et al. 2014d). This suggests a direct modulation of both production and secretion of these adipokines (Krysiak et al. 2014d) and these effects were more prominent in insulin resistant individuals (Krysiak et al. 2014d). In addition to an anti-inflammatory effect, it seems that cholesterol-lowering effect of statins can contribute to inhibit ER stress (Wu et al. 2013). Statins inhibit leptin expression due to alterations in RNA processing that reduce heterogeneous nuclear RNA abundance (Maeda and Horiuchi 2009). Moreover, statins inhibit PI3K pathway through protein prenylation suppression. This allows the activation of PKA and, consequently, suppression of leptin expression in 3T3-L1 cells. A reduced mRNA C/EBPα expression seems to be partially involved in this last effect, which emphasises the importance of leptin expression to regulate adipocyte differentiation (Maeda and Horiuchi 2009). As IL-6 is able to raise leptin levels, statins, by reducing IL-6 levels, can also reduce leptin levels (Zhao and Wu 2005). Statins also reduce the expression of resistin in human monocyte/macrophages in vitro as well as in 3T3-L1 adipocytes, supporting their anti-inflammatory role (Wu et al. 2013; Li et al. 2016). However, atorvastatin treatment in vivo for 6 months did not significantly reduced serum resistin levels (Wu et al. 2013). Statins appear to inhibit the PAI-1 promoter activity, through mitogen-activated protein kinase kinase Kinase 1 (MEKK1) and, in a lesser extent, NFκB. Since isoprenoids, such as geranylgeranyl pyrophosphate and farnesylpyrophosphate, were able to revert rosuvastatin effect in PAI-1 expression, proteins geranylation or/and farnesylation could be the involved mechanisms (Maeda and Horiuchi 2009). In animal studies, statins are able to decrease inflammation in pericarotidal AT from high fat diet (HFD) treated mice (Wang et al. 2014) and in WAT of hypercholesterolemic pigs (Busnelli et al. 2013). This effect is achieved by downregulation of 5-lipoxygenase, decreased macrophagic infiltration (Wang et al. 2014) and downregulation of pro-inflammatory adipokines/cytokines (Wang et al. 2014). In hypercholesterolemic pigs WAT, statins also prevent adipocyte hypertrophy and diminish T lymphocyte infiltration (Busnelli et al. 2013). Statins can partially contain AT inflammation in obese mice (Abe et al. 2008), through downregulation of mRNA MCP-1 and IL-6 expression (Abe et al. 2008) and also through inhibition of TLR4-induced expression of interferon gamma in macrophages (Abe et al. 2008).

Statins have different roles in the regulation of iNOS according to cell type. In 3T3-L1 preadipocytes, statins inhibit NO production after inflammatory exposure. This effect is mediated by NFκB pathway inhibition, reducing iNOS mRNA expression (Dobashi et al. 2008). In contrast, in 3T3-L1 mature adipocytes, statins enhance iNOS expression, increasing NO levels (Araki et al. 2007). This effect is dependent on the type of statin (Araki et al. 2007) and the underlying mechanism seems to be NFκB activation, which contributes to up-regulation of iNOS gene and, ultimately, to a higher NO production (Araki et al. 2007). Moreover, NFκB activation is achieved through diminishing metabolites of cholesterol synthesis, such as isoprenoid and small G proteins (Araki et al. 2007).

2.1.3 **Effects upon atherogenesis**

Atherogenesis is a degenerative process in which arteries walls become occupied with excess and modified lipids in circulation (Singh et al. 2002). It involves adhesion of monocytes and lymphocytes to the endothelial cell surface; migration of monocytes into the sub-endothelial space and differentiation into macrophages; ingestion of LDL and modified or oxidized LDL (ox-LDL) by macrophages, leading to accumulation of cholesterol esters and formation of "foam cells". Moreover, vascular smooth muscle cells migrate from the media into the intima and proliferate occurring the formation of atherosclerotic plaques (Ross and Agius 1992). Macrophages phagocytosis of ox-LDL is mediated by SRB1 (Singh et al. 2002). Adipocytes can also uptake ox-LDL, a mechanism positively correlated with PPARγ and SRB1 expression and negatively with LDL concentration (Zhao and Zhang 2004; Breen et al. 2012). Statins are able to induce PPARγ and SRB1 expression in adipocytes (Zhao et al. 2006; Zhao and Zhang 2004). Despite not fully understood, this suggests both indirect, through lowering cholesterol, and direct effects, possibly through SRB1 stimulation (Zhao et al. 2006). Moreover, as statins reduce lipid accumulation in adipocytes (Ishihara et al. 2010), there is a disinhibition of PPARγ expression that per se could enhance the ox-LDL uptake by adipocytes (Zhao et al. 2006).

By decreasing the expression of pro-inflammatory and increasing anti-inflammatory adipokines statins have a fundamental role in inflammatory related-processes, such as atherosclerosis (Krysiak et al. 2014c; Li et al. 2016), with the recent evidence supporting an anti-atherogenic effect of these drugs.

2.1.4 **Effects upon insulin sensitivity**

Recently, evidence on the association between insulin resistance, T2DM *de novo* and statin treatment has been increasing. Caveolae are plasma membrane microdomains, composed by cholesterol, sphingolipids, and different coat proteins named caveolins, considered anchor points to molecules (i.e. in this context, insulin receptor and GLUT4), facilitating their interaction, in order to activate cell signalling and transport (Cohen et al. 2003; Liu et al. 2008; Chidlow and Sessa 2010).
Caveolins are modulated by cavins and cavin-2 is pointed out as a cholesterol-dependent protein essential to define caveolar structure (Breen et al. 2012). Through cholesterol depletion, statins cause caveolae collapse in adipocytes inducing proteasomal degradation of cavin-2 and redistribution of cavin-1 to the cytosol (Breen et al. 2012). Taking into account the importance of caveolae in insulin signalling pathways in adipocytes (Cohen et al. 2003; Liu et al. 2008), evidence show that insulin resistance is due, at least partially, to caveolae dysfunction. Moreover, statins disruption of caveolar formation seems to reduce HMW adiponectin secretion by adipocytes (Krautbauer et al. 2013), a mechanism that can reduce insulin sensitivity. Lipophilic statins can also induce structural alterations in GLUTs (Nowis et al. 2014) and impair GLUT4 protein expression (Ganesan and Ito 2013), leading to inhibition of GLUT4 translocation and, consequently, decreasing insulin-stimulated glucose uptake in 3T3-L1 adipocytes (Takaguri et al. 2008). However, co-treatment with coenzyme Q10, an endogenous cellular antioxidant, seems to attenuate this effect (Ganesan and Ito 2013). Although being a lipophilic statin, atorvastatin can improve insulin sensitivity in an obese mice model (Poletto et al. 2015), through an increase in mRNA and protein expression of slc2a4 gene (which codifies GLUT4) and a decrease in mRNA and protein expression of IL6 in subcutaneous AT (SCAT) (Poletto et al. 2015). Authors also suggest a possible role of IKK/NFκB pathway in these effects (Poletto et al. 2015). On the other hand, hydrophilic statins generally improve insulin sensitivity, even in HFD-induced overweight mice, with no changes in body weight, AT mass or adipocyte size (de las Heras et al. 2013; Valero-Munoz et al. 2014). These statins also increase PPARγ and GLUT4 expression and reduce leptin expression in AT (de las Heras et al. 2013; Valero-Munoz et al. 2014). Hydrophilic statins augment basal and insulin-stimulated glucose uptake in AT (Salunkhe et al. 2016; Takagi et al. 2008), thus decreasing hyperglicemia.

2.1.5 Effects upon adipogenesis

Statins are responsible for inhibiting preadipocytes differentiation through downregulation of PPARγ2 and 422aP. Instead, they induce upregulation of RunX2/Cfbal, promoting osteoblastic differentiation (Zhang et al. 2013). In fact, it has been shown that statins stimulate osteoblastic differentiation, proliferation, maturation and synthesis of new bone (Pengde et al. 2008; Song et al. 2003; Zhang et al. 2013). Moreover, statins also inhibit adipogenesis through a reduction in LPL mRNA expression (Song et al. 2003). In a 3T3-F442A cell model, statins have shown a higher sensitivity to inhibit adipocyte differentiation comparing to 3T3-L1 cells (Elfakhani et al. 2014). However, pitavastatin does not affect the preadipocyte differentiation/maturation *in vitro* (Ishihara et al. 2010). Mevastatin in turn, inhibits orbital preadipocytes differentiation through blockage of PPARγ expression (Yi and Xu 2010). In the early phase of adipogenesis, statins seem to induce a phenotype change leading to 3T3-L1 cells rounding-up at 6h and their detachment at 48h after the onset of differentiation (Tomiyama et al. 1999), an effect not observed in the late phase of adipogenesis (Tomiyama et al. 1999). Statins downregulate the expression of crucial genes to adipocyte differentiation including C/EBPα, PPARγ and SREBP-1 and maturation markers such as leptin, FABP4 and adiponectin (Elfakhani et al. 2014). An inhibitory effect of PI3K can also be an underlying mechanism for this effect (Tomiyama et al. 1999). Moreover, Tomiyama et al. mentioned a possible contribution of isoprenoids synthesis and Ras-Raf1-MAPK pathway inhibition (Tomiyama et al. 1999). More recently, it was reported that statins, by reducing mevalonate-derived non-sterols isoprenoids (intermediate metabolites of cholesterol biosynthesis, crucial to adipocyte differentiation (Chamberlain 2001)), can cause a compensatory upregulation of HMG-CoA reductase (Elfakhani et al. 2014). Despite these results, *in vivo* studies have shown that statins stimulate adipocyte differentiation (Khan et al. 2009; Phillips et al. 2001), which evidences the complex mechanism that underlie AT proliferation and differentiation.

2.2 Fibric acid derivatives (Fibrates)

The most pronounced effects of fibrates are the decrease in plasma TG-rich lipoproteins (Staels et al. 1998). In one hand, they increase lipoprotein lipolysis, but on the other, they increase FFA hepatic uptake and reduce hepatic TG production (Rosenson 2017), achieving TG reductions of 35 to 50%. Fibrates also increase HDL cholesterol in 5-20%, due to an increase in apo-A-I and apo-A-II production in liver, which may contribute to a more efficient reverse cholesterol transport (Rosenson 2017) and trough the activation of PPARα (Derosa et al. 2017). LDL cholesterol generally decreases in individuals with elevated baseline plasma concentrations (Staels et al. 1998), with reductions of 20-25% (Jellinger et al. 2017). Fibrates convert small cholesterol-depleted LDL particles to large-cholesterol-enriched LDL particles. By shifting LDL particles to a larger size, these particles are removed from circulation more efficiently (Rosenson 2017) thus improving the atherogenic profile (Jellinger et al. 2017). Fibrates are synthetic ligands of PPARα (Yan et al. 2014), acting by peroxisome proliferators response element (PPRE) stimulation, whose activation leads to increased hepatic β-oxidation of FA, reduced hepatic TG secretion and increased LPL activity and consequent VLDL clearance (Derosa et al. 2017). Gemfibrozil, however, may increase LDL levels in 10%-15% (Jellinger et al. 2017). Despite these clinical similarities, fibrates may have a different spectrum of effects upon AT.

2.2.1 Effects upon adipocyte metabolic functions

Bezafibrate, a non-selective PPAR (α, δ/β, γ) agonist, regulates energetic homeostasis by upregulation PPARα and UCP1, 2 and 3 (Cabrero et al. 2001; Vazquez et al. 2001). It induces mRNA

acyl-CoA oxidase (ACO) expression which stimulates FA oxidation in mitochondria and peroxisomes of adipocytes (Cabrero et al. 2001; Vazquez et al. 2001; Goto et al. 2011). The oxidative rate is higher in preadipocytes than in mature adipocytes (Cabrero et al. 2001). Moreover, as FA concentrations reduce, it also inhibits lipogenesis (Cabrero et al. 2001).

On the contrary, gemfibrozil, a PPARα agonist, induces a fast increase in TG synthesis in both preadipocytes and adipocytes (Baldo et al. 1994). Gemfibrozil improves their capacity for subtract uptake (glucose and oleate) and enhances activity of enzymes needed for this synthesis (Baldo et al. 1994). By increasing FA uptake and TG synthesis in peripheral tissues, gemfibrozil decrease FA plasma concentration, which enhances extracellular hydrolysis by LPL present in endothelial cells (Baldo et al. 1994).

Fenofibrate, another PPARα agonist, is able to decrease body mass independently of food intake (Rachid et al. 2015b) and to reduce visceral AT (VAT) mass (Elfakhani et al. 2014) through PPARα stimulation and upregulation of FA oxidation enzymes in AT, such as CPT-1 (Gonzalez et al. 2009; Ferreira et al. 2014) and ACO (Ferreira et al. 2014). It also increases the number of small, in detriment of large, adipocytes in diet-induced obese and insulin resistant mice (Elfakhani et al. 2014). Fenofibrate can increase energy expenditure in diet-induced obese mice (Rachid et al. 2015b), since it seems to upregulate, through PPARα pathway, thermogenesis-related genes such as UCP-1, PRDM16, PGC-1α, nuclear respiratory factor 1 and mitochondrial transcription factor A) (Rachid et al. 2015b, a). Moreover, increasing PGC-1α expression, fenofibrate increases irisin levels, which enhances UCP-1 expression (Rachid et al. 2015a). Through this mechanism, in SCAT, fenofibrate induces the browning of adipocytes of WAT, converting them in beige adipocytes (having a higher basal metabolic rate) (Rachid et al. 2015a). Fenofibrate decreases uptake of FA in AT due a reduced LPL activity (Ferreira et al. 2006) and by increasing HSL activity (Brandes et al. 1986), decreases lipogenesis and increases lipolysis (Ferreira et al. 2006).

On the other hand, fenofibrate was also described to increase adiposity in epididymal, liver and kidneys AT in an insulin resistant and hypertriglyceridemic rat model (Sedova et al. 2004). In humans, fenofibrate treatment has been shown to increase liver TG synthesis, through PPARα, leading to hepatic steatosis (Yan et al. 2014).

Most of the evidence suggest that fibrates, by decreasing body weight (Chen et al. 2014; Vazquez et al. 2001; Jeong and Yoon 2009; Gonzalez et al. 2009; Ferreira et al. 2014; Rachid et al. 2015b, a), reduce plasma leptin concentration thus increasing caloric intake (Vazquez et al. 2001). Different experimental models and fibrates might explain these opposite effects.

2.2.2 Effects upon inflammation

Fenofibrate enhances adiponectin (Labuzek et al. 2011; Oki et al. 2007) (HMW form in hypertriglyceridemic patients (Oki et al. 2007)) and vaspin expression and secretion (by PPRE, with a stronger contribution of PPARα than PPARγ) (Chen et al. 2014), and, when in high concentrations, diminishes MCP-1 (Toyoda et al. 2008) and TNFα secretion (Labuzek et al. 2011; Toyoda et al. 2008; Zhao and Wu 2004; Jeong and Yoon 2009). In a co-culture model of 3T3-L1 adipocytes and RAW264 macrophages, TNFα lowering effect was related to the inhibition of NF-kB pathway (Toyoda et al. 2008), although with no changes in both macrophage infiltration and lipolysis (Toyoda et al. 2008).

In an obesogenic environment, AdipoR1 and 2 protein expression in VAT is diminished (Bauer et al. 2010), supporting the notion that VAT is more prone to inflammatory processes. Fenofibrate, however, upregulates AdipoR2 expression in 3T3-L1 adipocytes (Bauer et al. 2010) and, when combined with statins, lowers others pro-inflammatory cytokines secreted by adipocytes (Labuzek et al. 2011). Furthermore, bezafibrate also downregulates PPARγ and TNFα expression while upregulates FABP4 (Cabrero et al. 2001) and adiponectin expression (partially through PPARα, enhancing the PPRE site located in adiponectin promoter) in adipocytes (Nakano et al. 2007; Hiuge et al. 2007). In contrast with other species, in human adipocytes, visfatin seems not to be regulated by fenofibrate (Oki et al. 2007).

In TNFα stimulated-adipocytes, fenofibrate activates AMPK pathway, up-regulating the expression of SIRT1 (Wang et al. 2013), thus inducing NF-kBp65 deacetylation, which inhibits adipocyte cluster of differentiation 40 (CD40) expression (a costimulatory protein present in antigen presenting cells, essential for their activation in inflammatory pathways), impairing the obesity-related low-grade chronic inflammation state (Wang et al. 2013).

Bezafibrate lowers 11β-hydroxysteroid dehydrogenase type 1 mRNA expression in AT and liver (Nakano et al. 2007) and its activity in adipocytes (Nakano et al. 2007).

Aldehyde oxidase 1 (AOX1) is an enzyme responsible for drugs catabolism and activation (Weigert et al. 2008), producing ROS. ROS are related to obesity-induced insulin resistance, impairment of adipogenesis, decrease of lipid storage in WAT and release of adiponectin (Weigert et al. 2008). Although mainly expressed in liver, it is also expressed in mature adipocytes, mainly in VAT (Weigert et al. 2008). Fenofibrate, partially by PPARα stimulation, reduces protein AOX1 expression (Weigert et al. 2008) leading to both antioxidant and anti-inflammatory effects (Weigert et al. 2008).

2.2.3 Effects upon atherogenesis

Fenofibrate ameliorates uptake and degradation of oxLDL, thus potentiating oxLDL blood clearance by adipocytes (Zhao et al. 2004). Moreover, fenofibrate by downregulation of PPARγ expression and upregulation of SRB1 expression in AT (Zhao et al. 2004), increases oxLDL both uptake and degradation by adipocytes (Zhao et al. 2004). Globally, fibrates seem to reduce adiposity and atherogenesis, despite the complex underlying molecular mechanisms remain partially unknown (Zhao and Wu 2004; Zhao et al. 2004; Ferreira et al. 2014).

2.2.4 Effects upon insulin sensitivity

Fenofibrate can improve insulin sensitivity and glucose tolerance, even in insulin resistant models. It increases basal and insulin-stimulated glucose uptake by adipocytes (Ferreira et al. 2014) and lowers plasma FFA, TG, insulin and glucose concentrations (Jeong and Yoon 2009; Rachid et al. 2015a). Besides lowering TNFα expression, fenofibrate also decreases leptin expression (Jeong and Yoon 2009; Rachid et al. 2015a) causing insulin secretion in the postprandial period (Rachid et al. 2015a). Fibrates upregulate phosphoenolpyruvate carboxykinase expression in adipocytes (independently of protein synthesis) (Glorian et al. 1998) retaining FA output from AT to bloodstream (Glorian et al. 1998; Sedova et al. 2004).

2.2.5 Effects upon adipogenesis

Through direct binding to PPARα, fibrates induce adipogenesis (Goto et al. 2011), increasing the activity of enzymes involved in FA synthesis, and leading to lipid accumulation in small and numerous droplets in adipocytes (Verrando et al. 1981; Brandes et al. 1986; Baldo et al. 1994). In orbital fibroblasts, fibrates also upregulate mRNA and protein expression of non-histone chromosomal high mobility group AT-hook 2, leptin and functional TSH receptor inducing preadipocyte differentiation (Pasquali et al. 2004).

Furthermore, fibrates reduce LPL activity, which suggests that they could rise serum lipoproteins concentration that can serve as substrates to TG storage in adipocytes (Brandes et al. 1986).

Summing up, fibrates have an important role in metabolism and inflammation control and in adipogenesis modulation. Fibrates can improve obesity-related mitochondrial metabolic dysfunction and chronic low-grade inflammation as insulin resistance (Nakano et al. 2007; Chen et al. 2014; Labuzek et al. 2011; Oki et al. 2007; Toyoda et al. 2008; Jeong and Yoon 2009; Sedova et

al. 2004; Zhao and Wu 2004; Bauer et al. 2010; Glorian et al. 1998; Hiuge et al. 2007; Wang et al. 2013; Weigert et al. 2008).

2.3 **Niacin (nicotinic acid)**

Niacin is one of the most effective agents currently available capable of increasing HDL levels (Garg et al. 2017). It acts inhibiting hepatocyte HDL-apo A-I holoparticle receptor, responsible for HDL catabolism. Moreover, studies have demonstrated that niacin increases PPARγ expression, through macrophage ABCA1, which affects reverse cholesterol transport (Kamanna and Kashyap 2008). Niacin also affects the remaining lipid profile, decreasing total cholesterol, LDL, TG, and lipoprotein (a) levels (Garg et al. 2017; Zhao et al. 2008). Niacin is able to decrease TG synthesis and its availability for VLDL assembly, resulting in increased posttranslational intrahepatic apo-B degradation, thus decreasing plasma TG and liver secretion of apo-B– containing lipoproteins, including VLDL and LDL particles (Kamanna and Kashyap 2008). In respect to deleterious effects, it is known that niacin, at high dosages, increases uric acid levels and can aggravate glucose levels (Jellinger et al. 2017). Niacin is used in high doses in refractory dyslipidaemia treatment despite its limited use due to poor tolerability (mostly due to flushing, hepatotoxicity, myopathies (Probstfield and Hunninghake 1994; Etchason et al. 1991)).

2.3.1   **Effects upon adipocyte metabolic functions**

Niacin, through HM74a receptor (coupled to Gi/o proteins (Karpe and Frayn 2004)), reduces basal (Zhao et al. 2008; Zhang et al. 2005; Plaisance et al. 2009) and noradrenaline (NA)-induced release of plasma FFAs (Carlson 1963) and inhibits lipolysis (Carlson 1963; Plaisance et al. 2009; Zhang et al. 2005).
Chronic treatment with niacin was shown to decrease plasma FFAs levels, although a rebound effect can occur (Oh et al. 2011). A prolonged treatment enhances β-AR responsivity via post-receptor signalling alterations (Heemskerk et al. 2014b; Oh et al. 2011). Moreover, niacin also decreases the expression of genes involved in TG synthesis and FFAs reesterification, leading to an increase in lipolysis (Oh et al. 2011). Additionally, a decrease in perilipin and adipose phospholipase A2 protein expression could also contribute to FFAs rebound (Oh et al. 2011).
A long term niacin treatment increases n-3 polyunsaturated fatty acids (PUFAs) synthesis in AT, but not in liver (Heemskerk et al. 2014a), thus suggesting that the main source of n-3 PUFAs is AT, through lipolysis (Heemskerk et al. 2014a). In this regard, niacin leads to upregulation of unsaturated FA biosynthesis genes (Elovl6, Elovl5, Tecr) in hyperlipidemic mice, thus increasing the elongation, but not desaturation of FA (Heemskerk et al. 2014a). Although prolonged niacin treatment enhances plasma n-3 PUFAs levels, it does not alter significantly arachidonic acid-derived proinflammatory oxylipins (Heemskerk et al. 2014a). In addition, n-3 PUFAs compete directly with n-6 PUFAs, contributing to CV protection (Heemskerk et al. 2014a).

2.3.2   **Effects upon inflammation**

Niacin directly decreases the TNFα-induced inflammatory profile of AT. It reduces MCP1, RANTES, Fractalkine (all involved in macrophage and T cells inflammatory recruitment) gene and protein expression, thus inhibiting macrophage chemotaxis (Digby et al. 2010). It also decreases TNFα-induced iNOS gene expression, which lowers ROS synthesis (Digby et al. 2010). In contrast, in adipocytes, niacin increases adiponectin gene expression though not affecting its secretion (Digby et al. 2010).
Binding of niacin to HM74a receptor, after either acute or chronic exposure, increases adiponectin secretion (total and HMW forms), even in adipocytes from MS patients (Plaisance et al. 2009). In these patients, acute treatment with niacin decreases plasma NEFAs concentrations (without an effect upon both resistin and leptin concentrations) (Plaisance et al. 2009). However, chronic niacin treatment increases leptin levels even without changing other adipokines (Westphal et al. 2007).

2.3.3 Effects upon atherogenesis

Niacin enhances cholesterol efflux rate in adipocytes through, at least partly, the PPARγ activation and, consequently, LXRα (liver X receptor alpha, an essential transcriptional factor for metabolism and transport of cholesterol in peripheral tissues) and ABCA1 transporter expression (Wu and Zhao 2009; Zhao et al. 2008). Through this mechanism, niacin treatment could increase HDL-induced cholesterol efflux from adipocytes and plasma HDL levels (Wu and Zhao 2009; Zhao et al. 2008). The mechanism involved in overexpression of these factors is unclear, although a role of HM74a as the initial trigger has been pointed out (Zhao et al. 2008).
Niacin stimulates PPARγ expression and activity increasing anti-inflammatory prostaglandin synthesis and secretion by macrophages (Knowles et al. 2006).
Nevertheless, prolonged treatment with niacin seems not to change endothelial function and inflammatory activity in MS patients (Westphal et al. 2007).

2.3.4 Effects upon insulin sensitivity

Prolonged treatment with niacin seems to induce insulin resistance (Westphal et al. 2007; Heemskerk et al. 2014b). In fact, in dyslipidemic mouse models, niacin downregulates genes involved in insulin (such as INSR and PDE3B) and β-adrenergic (such as β-1,2,3-AR) signalling pathways (Heemskerk et al. 2014b), whereas prolonged treatment enhances β-AR responsivity (Heemskerk et al. 2014b; Oh et al. 2011). The authors suggest that the duration needed to increase adiponectin levels could be counterbalanced by other adverse effects, such as, a rebound increase in plasma FFAs (Westphal et al. 2007).

2.3.5 Effects upon adipogenesis

Niacin stimulates adipogenesis (enhancing PPARγ, FABP4, adiponectin and leptin expression) in 3T3-L1 cells, while supresses C/EBPβ and, thereby, cyclooxygenase-2 expression, which is responsible for PGF2α (anti-adipogenic factor) decrease in adipocytes (Fujimori and Amano 2011).

2.4 Ezetimibe

Ezetimibe acts by inhibiting intestinal cholesterol absorption (through Niemann-Pick C1-Like 1 (NPC1L1) transporter) and by decreasing its delivery to liver, leading to upregulation of hepatic LDL receptors (Jellinger et al. 2017). Used in monotherapy it can achieve LDL reductions of 10%-18% and, in combination with statins, LDL reductions of 34%-61% (Jellinger et al. 2017). Ezetimibe is also able to reduce Apo-B levels (11%-16%) (Jellinger et al. 2017). Currently, ezetimibe displays a supportive role in dyslipidemia treatment, being used mostly in combination with other antidyslipidemic (Takase et al. 2012).

2.4.1 Effects upon adipocyte metabolic functions

Ezetimibe decreases fat visceral accumulation, without affecting total body weight (Takase et al. 2012). It also improves hepatic steatosis (Takase et al. 2012).

2.4.2 Effects upon inflammation

Ezetimibe seems to affect plasma adipokines (Krysiak et al. 2014b). Indeed, by acting in AT, ezetimibe has been shown to lower visfatin, while increasing adiponectin plasma levels (Krysiak et al. 2014b; Takase et al. 2012). The combination of Ezetimibe-simvastatin treatment for 30 days was able to partially revert AT dysfunction and decrease systemic inflammation, independently of the lipid-lowering effect (Krysiak et al. 2014a). This combination decreases leptin, visfatin, TNFα and increases adiponectin levels, supporting a direct effect on AT production/secretion of these adipokines (Krysiak et al. 2014a).

2.4.3 Effects upon insulin sensitivity

Ezetimibe is able to improve insulin resistance, especially in patients with MS (Takase et al. 2012). Moreover, ezetimibe effects seem to be more potent in insulin-resistant patients (Krysiak et al. 2014b).

The effects of the drugs used on dyslipidemia upon the AT are summarized on table 2.1 and fig. 2.1 and 2.2.

3 Drugs used in obesity

3.1 Orlistat

Orlistat inhibits gastric and pancreatic lipases (Heck et al. 2000), thus reducing fat intestinal absorption. As a result, orlistat decreases body weight (weight loss of 3% (Orlistat prescribing information)), improves glucose intolerance and ameliorates lipid parameters (total cholesterol and LDL) (Beg et al. 2015; Kim et al. 2013). In addition, orlistat can reverse liver steatosis but not adipocyte hypertrophy (Beg et al. 2015).

3.1.1 Effects upon adipocyte metabolic functions

Orlistat partially inhibits lipolysis in adipocytes by suppressing AMPK activation and decreasing AMP/ATP ratio induced by forskolin, isoproterenol and IBMX (agents that increase cAMP levels), without altering PKA activity and cAMP levels (Gauthier et al. 2008). On the other hand, orlistat has a lipolytic effect, inducing TG degradation in AT and liver and downregulating leptin expression (Kim et al. 2013).

3.1.2 Effects upon inflammation

Orlistat combined with a hypocaloric diet was able to produce a marked reduction in plasma concentrations of leptin, CRP, IL-6, TNFα and resistin, while increasing adiponectin levels (Bougoulia et al. 2006; Hsieh et al. 2005). Thus, orlistat seems to have a role in improving obesity-related AT dysfunction (Bougoulia et al. 2006; Hsieh et al. 2005).

3.2 Anorexiants/ Central nervous system stimulants

3.2.1 Sibutramine

Sibutramine is an inhibitor of NA and 5-hydroxytryptamine (5-HT) neuronal reuptake. It has been withdrawn of the market due to its nefast cardiovascular side-effects. Sibutramine induces weight loss of 5%, decreases waist circumference and improves several metabolic parameters (Valsamakis et al. 2004). Sibutramine decreases serum TG and CRP, while increasing serum HDL levels and insulin sensitivity (Valsamakis et al. 2004). Globally, it exhibits an anti-inflammatory role, lowering both leptin and resistin and increasing adiponectin levels (Valsamakis et al. 2004).

3.2.2 Diethylpropion

Diethylpropion, a sympathomimetic amine similar to amphetamine, is a prodrug metabolized to 2-ethylamino-1-phenyl-propan-1-one and N, N-diethylnorephedrine metabolites (Yu et al. 2000), the latter being responsible for diethylpropion effects. This metabolite acts as substrate for NA transporter, with a higher potency (10 times higher than dopamine (DA)) leading to inhibition of NA reuptake, while stimulating NA release (Yu et al. 2000). It also acts as a reuptake inhibitor of both DA and 5-HT transporters (Yu et al. 2000). The increase in NA concentrations in brain could justify both the anorexiant effect and the side-effects common to amphetamine use (Yu et al. 2000).

3.2.3 Phentermine and Lorcaserin

Phentermine is a sympathomimetic amine similar to amphetamine, though with residual additive potential. Additionally, it acts as DA receptor agonist and, partially, as NA receptor partial agonist or antagonist (Dobrzanski and Doggett 1979) while Lorcaserin (Bays 2009, 2011) is a 5-HT 2c receptor agonist. Both drugs decrease food intake while increase satiety, causing weight losses of (Bays 2009, 2011; Dobrzanski and Doggett 1979), respectively 5% (Phentermine prescribing information 2012) and 8% (Lorcaserin prescribing information).

3.3 Antidepressants

3.3.1 Naltrexone and Bupropion

Naltrexone and Bupropion are respectively, an antagonist of opioid-receptors in pro-opiomelano-cortin (POMCs) neurons, and a NA and DA reuptake inhibitor. The combined treatment with these drugs decreases food intake, body weight (weight loss exceeding 8% of baseline body weight (Naltrexone SR-bupropion SR prescribing information.)) and fat mass (without changing lean mass) in diet-induced obese rats (Clapper et al. 2013; Smith et al. 2013). Noteworthy, this combination decreases VAT mass (Smith et al. 2013).The addition of amylin (a peptide co-released with insulin by pancreatic β cells) to the combined treatment produces an additive effect, showing even better results in the referred parameters (Clapper et al. 2013), due to modulation of melanocortin (MC) pathway (increasing the expression of MC4 receptor in hypothalamic neurons) (Clapper et al. 2013).

3.4 Antiepileptics

3.4.1 Topiramate

Topiramate is an antiepileptic drug that acts as antagonist of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors and positively modulates gamma-aminobutyric acid (GABA) receptors. It is also used as anticonvulsiant, analgesic and humor-stabilizer. Topiramate induces a significant weight loss (Abo-Elmatty and Zaitone 2011). Moreover, it decreases glycemia, insulinemia, insulin resistance and TG, while increases adiponectin plasma levels in diet-induced obesity rats (Abo-Elmatty and Zaitone 2011). Topiramate does not affect arterial pressure or anxiety. The mechanisms involved in these effects are not fully understood. Nonetheless, inhibition of food ingestion, downregulation of leptin expression and upregulation of UCP-2 and 3 expressions in WAT and BAT seem to be mechanisms also involved (York et al. 2000).

3.5 Liraglutide

Liraglutide is a glucagon-like peptide 1 receptor agonist (GLP-1RA) firstly approved as anti-diabetic drug, though more recently in higher doses as anti-obesity drug, providing 9% weight

loss (Nordisk 2016). It is indicated for obese or overweight adults with at least one obesity-related comorbidity (Nordisk 2016). GLP-1 is an endogenous incretin, secreted by L cells in distal intestine (Kieffer and Habener 1999; Holst et al. 1987). Liraglutide, by increasing GLP-1 levels, reduces food ingestion, appetite (Inoue et al. 2011; Shao et al. 2015; Jensterle et al. 2015; Hoang et al. 2015; Nonogaki et al. 2014; Heppner et al. 2015) and change food preferences, namely improving eating behaviours and decreasing emotional eating, which increases weight loss (Inoue et al. 2011; Jensterle et al. 2015). Liraglutide can slow gastric emptying (Hoang et al. 2015), a mechanism contributing to reduce food intake.

GLP-1 was described as having anti-adipogenic, anti-lipogenic and pro-lipolytic effects in human mature adipocytes (El Bekay et al. 2016). Furthermore, GLP-1 was discovered to activate GLP-1R in central nervous system (CNS) leading to an increase in BAT activity and energy expenditure (Heppner et al. 2015).

3.5.1 Effects upon adipocyte metabolic functions

Even in short-term treatment, liraglutide induces a sustained decrease of body weight and BMI (Li et al. 2014; Tang et al. 2015; Suzuki et al. 2013; Yang et al. 2012; Inoue et al. 2011; Jendle et al. 2009; Yan et al. 2011; Morano et al. 2015; Shao et al. 2015; Jensterle et al. 2015; Hoang et al. 2015; Nonogaki et al. 2014; Beiroa et al. 2014) mainly due to a reduction in total fat mass and in fat thickness of different depots (although not equally) (Li et al. 2014; Tang et al. 2015; Suzuki et al. 2013; Yang et al. 2012; Inoue et al. 2011; Jendle et al. 2009; Morano et al. 2015; Beiroa et al. 2014). Noteworthy, liraglutide is also capable of changing regional distribution of fat depots (Li et al. 2014; Tang et al. 2015; Suzuki et al. 2013; Yang et al. 2012; Inoue et al. 2011; Jendle et al. 2009; Morano et al. 2015; Shao et al. 2015; Hoang et al. 2015) and acts mainly by decreasing VAT (Li et al. 2014; Tang et al. 2015; Suzuki et al. 2013; Yang et al. 2012; Inoue et al. 2011; Jendle et al. 2009; Morano et al. 2015; Shao et al. 2015; Jensterle et al. 2015; Hoang et al. 2015). In contrast, other studies describe a preferential liraglutide effect in SCAT (Suzuki et al. 2013). Even in models of insulin resistance, adiponectin and apo-E knockout and polycystic ovarian syndrome models (not responding to metformin and typical weight-loss strategies), liraglutide seems able to decrease body weight (Yang et al. 2012; Jensterle et al. 2015; Hoang et al. 2015).

The liraglutide-induced weight loss seems to increase NPs concentrations (Li et al. 2014), which induces lipid oxidation (Beiroa et al. 2014; Li et al. 2014). The ANP and BNP increase is higher in patients that lose more than 5% of their body weight and seems to be significantly correlated with liraglutide effects on body composition (Li et al. 2014). Besides, reducing lipid storage in WAT, decreases lipogenesis (Shao et al. 2015). These effects seem to be driven by downregulation of Akt and PI3K pathways and upregulation of AMPK and ACC genes (Shao et al. 2015). Furthermore, liraglutide was shown to increase energy expenditure, by inducing the browning of WAT and BAT, increasing thermogenesis (Beiroa et al. 2014; Li et al. 2014; Heppner et al. 2015). This browning effect was also shown to be driven by an increase in NP which stimulates MAPK pathway (Li et al. 2014). Nevertheless, the magnitude of increase in BAT activity is modest and seems not to justify the extent of liraglutide effect in weight loss (Heppner et al. 2015). Liraglutide, through stimulation of CNS GLP-1R on ventromedial hypothalamic nuclei and modulation of AMPK pathway, was shown to decrease body weight (Beiroa et al. 2014), independently of 5-HT2CR and MC4R pathways (Nonogaki et al. 2014).

3.5.2 Effects upon inflammation

Liraglutide has been described to regulate adipokines secretion in opposite directions. In T2DM patients, it decreases total adiponectin levels while increases pentraxin 3, a marker of inflammatory cardiovascular disease, and proinsulin levels (Suzuki et al. 2013). This latter demonstrates a

beneficial effect upon pancreas β-cell function (Suzuki et al. 2013). On the other hand, in obese patients, liraglutide increases adiponectin expression and inhibits glucose uptake in adipocyte stem cells (Cantini et al. 2015). Liraglutide also decreases TNFα and adiponectin expression in human adipocytes (El Bekay et al. 2016).

3.5.3 Effects upon atherogenesis

Besides improving lipid profile, liraglutide decreases CRP levels and soluble ICAM-1 (Inoue et al. 2011). Thus, it seems to have pleiotropic effects and an anti-atherosclerotic role (Inoue et al. 2011).

3.5.4 Effects upon obesity-related cardiovascular comorbidities

GLP-1R are more expressed in adipocytes from VAT and obese T2DM patients, comparing to those of lean patients (El Bekay et al. 2016).

Liraglutide can improve insulin sensitivity, even in insulin resistant models. Omentin (an adipokine mainly produced by VAT), through Akt/PKb signaling pathway stimulation (Yang et al. 2006; Bai et al. 2007), increases glucose transport induced by insulin, improving insulin sensitivity and glucose metabolism (Yan et al. 2011). The omentin plasma levels are decreased in T2DM (suggesting a deregulation of omentin biosynthesis or a response to hyperglycemia and hyperinsulinemia) and liraglutide can increase omentin plasma levels (Yan et al. 2011). Liraglutide increases ZAG (Zinc alpha2 glycoprotein), a protein involved in multiple effects such as body weight control and lipolysis, and adiponectin plasma levels. ZAG levels are decreased in obesity and T2DM, suggesting that it could be involved in insulin resistance pathogenesis (Yang et al. 2013).

Moreover, liraglutide improves insulin secretion (Li et al. 2014; Yan et al. 2011; Hoang et al. 2015; Yang et al. 2012), increasing glucose uptake in peripherical tissues (Nonogaki et al. 2014). Liraglutide increases PPARγ activity, stimulating liver production of fibroblast growth factor-21 (FGF21) expression, which leads to an increase in FGF21 plasma levels (Nonogaki et al. 2014). In obese or T2DM patients, FGF21 mRNA expression and plasma levels are elevated (a compensatory mechanism to decrease insulin resistance). It reflects a decrease in FGF receptor (FGFR) supporting an FGF21 resistance in these conditions (Yang et al. 2012). Furthermore, in AT, liraglutide also upregulates the expression of FGFR3 and B-Klotho (necessary to the binding of FGF21 to its receptor) while, in liver, it upregulates FGFR1-3, B-klotho and phospho-FGFR1 expression (Yang et al. 2012). In this way, since FGF21 is an important regulator of insulin effects upon glucose and lipid metabolism, liraglutide could contribute to improve insulin action (Nonogaki et al. 2014; Yang et al. 2012).

Liraglutide has been described as a fat liver modulator. In contrast with some studies, showing no effect upon fat liver parameters (Tang et al. 2015), liraglutide has been shown to decrease hepatic fat, even in obese and/or T2DM patients (Suzuki et al. 2013; Jendle et al. 2009; Cuthbertson et al. 2012). The decrease in intrahepatic lipids does not correlate with changes in weight, abdominal fat, VAT, SCAT or adiponectin levels, but rather with a decrease in HbA1c (Cuthbertson et al. 2012). Authors proposed that this effect is due to an increase in glucose tolerance, thus reducing hyperinsulinemia (Cuthbertson et al. 2012), which is followed by a decrease in lipogenesis rate and an increase in FA oxidation. Treatment with liraglutide improves systolic blood pressure and lipid profile, decreasing plasma total cholesterol and TG, while increasing HDL levels (Jendle et al. 2009; Hoang et al. 2015; Yang et al. 2012; Inoue et al. 2011; Li et al. 2014).

3.5.5 Effects upon adipogenesis

GLP-1 and GLP-1RA are able to regulate preadipocyte differentiation, even they act differently according to adipocyte origin or differentiation stage.

Liraglutide stimulates the early phase of adipogenesis in 3T3-L1 cells by inducing the expression of PPARγ, C/EBPβ and δ, and GLP-1R, a target gene of PPARγ (Challa et al. 2012). This effect is due to modulation of both survival and proliferation pathways, mainly, ERK1/2, PKCβ and Akt (Challa et al. 2012).

In contrast, liraglutide inhibits both proliferation and differentiation of ASCs obtained from obese patients, by binding directly to GLP-1R (Cantini et al. 2015). GLP-1RA decreases the expression of adipogenesis and lipogenesis related genes, while increasing expression of lipolytic ones (El Bekay et al. 2016). In contrast to 3T3-L1 cells, in human adipocytes, GLP-1 anti-adipogenic effect is not mediated by the same pathways, Akt and ERK1/2, instead it is driven through inactivation of the AC/cAMP pathway (El Bekay et al. 2016).

The effects of drugs used in obesity upon AT are summarized on table 3.1 and figures 2.1 and 2.2.

4 Conclusion

Adipose tissue is a complex organ with marked effects on whole-body physiology. AT dysregulation, rather than the amount of fat mass, seem to be a key factor in the pathophysiology of obesity and related morbidities. Despite the increase in the number of drugs available to treat these conditions, dyslipidemia and obesity prevalence still remains rising. AT dysregulation is a main feature present in both dyslipidemia and obesity. In this review, the effects of drugs used to treat dyslipidemia and obesity were analysed focusing on AT. The main adipocyte metabolic effects, the effects on inflammation, atherogenesis, insulin sensitivity, and adipogenesis were revised to explore how these drugs can modulate these complex pathways. Furthermore, we denote differences between drugs of the same class that could be of major importance for clinical practice. At the same time, despite a favourable clinical effect, some drugs can have adverse effects on adipocyte function. Gathering all this evidence, is relevant to question whether answers to these difficulties will be found through new advances in pharmacology or in further adjustments and combinations between drugs already in use. A thoroughly understanding of the role of AT in these conditions, as the impact these drugs have on its functions can become the next step in order to tackle CVD, becoming part of the challenges that physicians face nowadays.

Figures legends

Fig. 1.1 Schematic illustration of the main intracellular pathways underlying: A) differentiation of preadipocytes into mature adipocytes. This process is on dependence of PKA pathway, which activates transcriptional factors such as C/EBPβ, C/EBPδ, C/EBPα and PPARγ, that ultimately lead to increase of adipogenesis genes (such as Leptin; Adiponectin, FABP4, perilipin, GLUT4, SCD1) expression **and B) immune and endocrine functions of WAT.** Adipocyte exerts autocrine and paracrine actions, through secreting adipokines (mainly Leptin and Adiponectin) and also endocrine in distant organs through circulation. See text for more details. <u>Symbols:</u> → stimulates; ⊣ inhibits; <u>Abbreviations:</u> adenylyl cyclase (AC); cyclic adenosine monophosphate (cAMP); cAMP-dependent protein kinase A (PKA); CCATT enhancer-binding proteins (C/EBP); peroxisome proliferator-activated receptors (PPARs); sterol regulatory element-binding protein-1 (SREBP1); retinoid X receptor-α (RXRα); sterol response elements (SRE); scavenger-receptor 1 (SRB1); natural killer cells (NK cells); Cluster of differentiation 40 (CD40); CD40 ligand (CD40L); 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1); Tumour-necrosis factor α (TNFα); interleukin (IL); CC-chemokine ligand 2 (CCL2 or MCP-1); plasminogen-activator inhibitor type 1 (PAI-1); adiponectin receptor (AdipoR); IL-1 receptor antagonist (IL-1RA); interferon- γ (IFN-γ); Toll-like receptors (TLR); nuclear factor kappa B (NF-kB); scavenger-receptor 1 (SR-B1); vascular cell adhesion molecule-1 (VCAM-1), endothelial-leukocyte adhesion molecule-1 (E-selectin), and intracellular adhesion molecule-1 (ICAM-1); leptin receptor (OBRb); extracellular-signal-regulated kinase (ERK); p38 mitogen-activated protein kinases (MAPK); inducible nitric-oxide synthase (iNOS); reactive oxygen species (ROS); TNF receptor (TNFR); NF-κB kinase-β (IKKβ); JUN N-terminal kinase (JNK); endoplasmic-reticulum (ER); insulin receptor (IR) substrate (IRS); uncoupling protein (UCP); adenylyl cyclase-associated protein 1 (CAP1); endothelin-1 (ET-1).

Fig. 1.2 Schematic illustration of the main intracellular pathways underlying WAT metabolic functions: β-oxidation (*through upregulation of ACS, CD36, MCD, CPT1 genes expression and, when upon certain stimulus, as PPAR-α agonist or adrenergic receptor stimulation, through upregulation of AMPK pathway); **lipolysis** (through the sequential action of ATGL; HSL; MGL); **lipogenesis** (*through upregulation of GLUT4; ACC genes)**.** See text for more details. <u>Symbols:</u> → stimulates; ⊣ inhibits; <u>Abbreviations:</u> triglycerides (TG); fatty acid (FA); cholesterol (Ch); lipoprotein lipase (LPL); very low-density lipoproteins (VLDL); diacylglycerol acyltransferase (DGAT); enzyme acetyl-coenzyme A carboxylase (ACC); sterol regulatory element-binding protein 1 (SREBP1); carbohydrate response element-binding protein (ChREBP); glucose transporter type 4 (GLUT4); phosphoinositide 3-kinase-dependent (PI3-K); phosphodiesterase 3B (PDE3B); adenylyl cyclase (AC); cyclic adenosine monophosphate (cAMP); cAMP-dependent protein kinase A (PKA); Protein Kinase B (PKB/Akt); guanylyl cyclase activity (GC); cyclic guanosine monophosphate (cGMP); cGMP-dependent protein kinase (PKG); adipocyte triglyceride lipase (ATGL); hormone-sensitive lipase (HSL); monoacylglycerol lipase (MGL); peroxisome proliferator-activated receptors (PPARs); peroxisome proliferator activated receptor γ coactivator 1 (PGC-1α); acyl-CoA synthetase (ACS); fatty acid translocase (CD36/FAT); carnitine palmitoyl transferase 1 (CPT1); adrenoceptors (AR); atrial or brain natriuretic peptide (ANP/BNP); natriuretic receptor A (NPR-A); insulin receptor (IR) substrate (IRS); adenosine monophosphate-activated protein kinase (AMPK); sirtuin 1 (SIRT1); brown adipose tissue (BAT); high-density lipoproteins (HDLs); , LXRα (liver X receptor alpha); ATP binding cassette A1 (ABCA1) transporter; scavenger-receptor 1 (SRB1).

Fig. 2.1 Schematic illustration of the effects of drugs used in dyslipidemia and obesity upon WAT metabolic functions and their underlying pathways. Statins induce adipocyte FA uptake, reinforcing this effect by increasing LPL expression, while decreasing cholesterol release. *only in obese models, statins stimulate *lipogenesis de novo*; globally, fibrates inhibit lipogenesis and stimulate FA oxidation (*through upregulation of ACS, CD36, MCD, CPT1 genes expression) and thermogenesis (*through upregulation of PRDM16, PPAR-γ and UCP-1 genes expression); Niacin inhibits lipolysis and increases lipogenesis genes expression (*GLUT4; ACC); Orlistat enhances TG degradation. *AMPK pathway stimulation occurs upon certain stimulus, such as PPAR-α agonists or adrenergic receptor stimulation. See text for more details. <u>Symbols:</u> → stimulates; ⊣ inhibits; Anti-obesity drugs are inserted in green boxes while anti-dyslipidemic drugs are inserted in purple boxes. <u>Abbreviations:</u> triglycerides (TG); fatty acid (FA); cholesterol (Ch); lipoprotein lipase (LPL); very low-density lipoproteins (VLDL); diacylglycerol acyltransferase (DGAT); enzyme acetyl-coenzyme A carboxylase (ACC); sterol regulatory element-binding protein 1 (SREBP1); carbohydrate response element-binding protein (ChREBP); glucose transporter type 4 (GLUT4); phosphoinositide 3-kinase-dependent (PI3-K); phosphodiesterase 3B (PDE3B); adenylyl cyclase (AC); cyclic adenosine monophosphate (cAMP); cAMP-dependent protein kinase A (PKA); Protein Kinase B (PKB/Akt); guanylyl cyclase activity (GC); cyclic guanosine monophosphate (cGMP); cGMP-dependent protein kinase (PKG); adipocyte triglyceride lipase (ATGL); hormone-sensitive lipase (HSL); monoacylglycerol lipase (MGL); peroxisome proliferator-activated receptors (PPARs); peroxisome proliferator activated receptor γ coactivator 1 (PGC-1α); acyl-CoA synthetase (ACS); fatty acid translocase (CD36/FAT); carnitine palmitoyl transferase 1 (CPT1); adrenoceptors (AR); atrial or brain natriuretic peptide (ANP/BNP); natriuretic receptor A (NPR-A); insulin receptor (IR) substrate (IRS); adenosine monophosphate-activated protein kinase (AMPK); sirtuin 1 (SIRT1); brown adipose tissue (BAT); high-density lipoproteins (HDLs); ,

LXRα (liver X receptor alpha); ATP binding cassette A1 (ABCA1) transporter; scavenger-receptor 1 (SRB1); n-3 polyunsaturated fatty acids (PUFAs).

Fig. 2.2 Schematic illustration of the effects of drugs used in dyslipidemia and obesity upon: A) differentiation of preadipocytes into mature adipocytes Statins and liraglutide inhibit adipogenesis while niacin and fibrates stimulate, by inducing upregulation of adipogenesis genes (*Leptin; Adiponectin, FABP4, perilipin, GLUT4, SCD1) expression **and B) immune and endocrine functions of WAT** Most of drugs exhibit an anti-inflammatory role through modulation of adipokine expression. Moreover, through modulation of leucocyte chemotaxis, affect NK cells activity and macrophage phagocytosis. See text for more details. <u>Symbols:</u> → stimulates; ⊣ inhibits; Anti-obesity drugs are inserted in green boxes while anti-dyslipidemic drugs are inserted in purple boxes. <u>Abbreviations:</u> adenylyl cyclase (AC); cyclic adenosine monophosphate (cAMP); cAMP-dependent protein kinase A (PKA); CCATT enhancer-binding proteins (C/EBP); peroxisome proliferator-activated receptors (PPARs); sterol regulatory element-binding protein-1 (SREBP1); retinoid X receptor-α (RXRα); sterol response elements (SRE); scavenger-receptor 1 (SRB1); natural killer cells (NK cells); Cluster of differentiation 40 (CD40); CD40 ligand (CD40L); 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1); Tumour-necrosis factor α (TNFα); interleukin (IL); CC-chemokine ligand 2 (CCL2 or MCP-1); plasminogen-activator inhibitor type 1 (PAI-1); adiponectin receptor (AdipoR); IL-1 receptor antagonist (IL-1RA); interferon- γ (IFN-γ); Toll-like receptors (TLR); nuclear factor kappa B (NF-kB); scavenger-receptor 1 (SR-B1); vascular cell adhesion molecule-1 (VCAM-1), endothelial-leukocyte adhesion molecule-1 (E-selectin), and intracellular adhesion molecule-1 (ICAM-1); leptin receptor (OBRb); extracellular-signal-regulated kinase (ERK); p38 mitogen-activated protein kinases (MAPK); inducible nitric-oxide synthase (iNOS); reactive oxygen species (ROS); TNF receptor (TNFR); NF-κB kinase-β (IKKβ); JUN N-terminal kinase (JNK); endoplasmic-reticulum (ER); insulin receptor (IR) substrate (IRS); uncoupling protein (UCP); adenylyl cyclase-associated protein 1 (CAP1); endothelin-1 (ET-1).

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Appendix

Figures
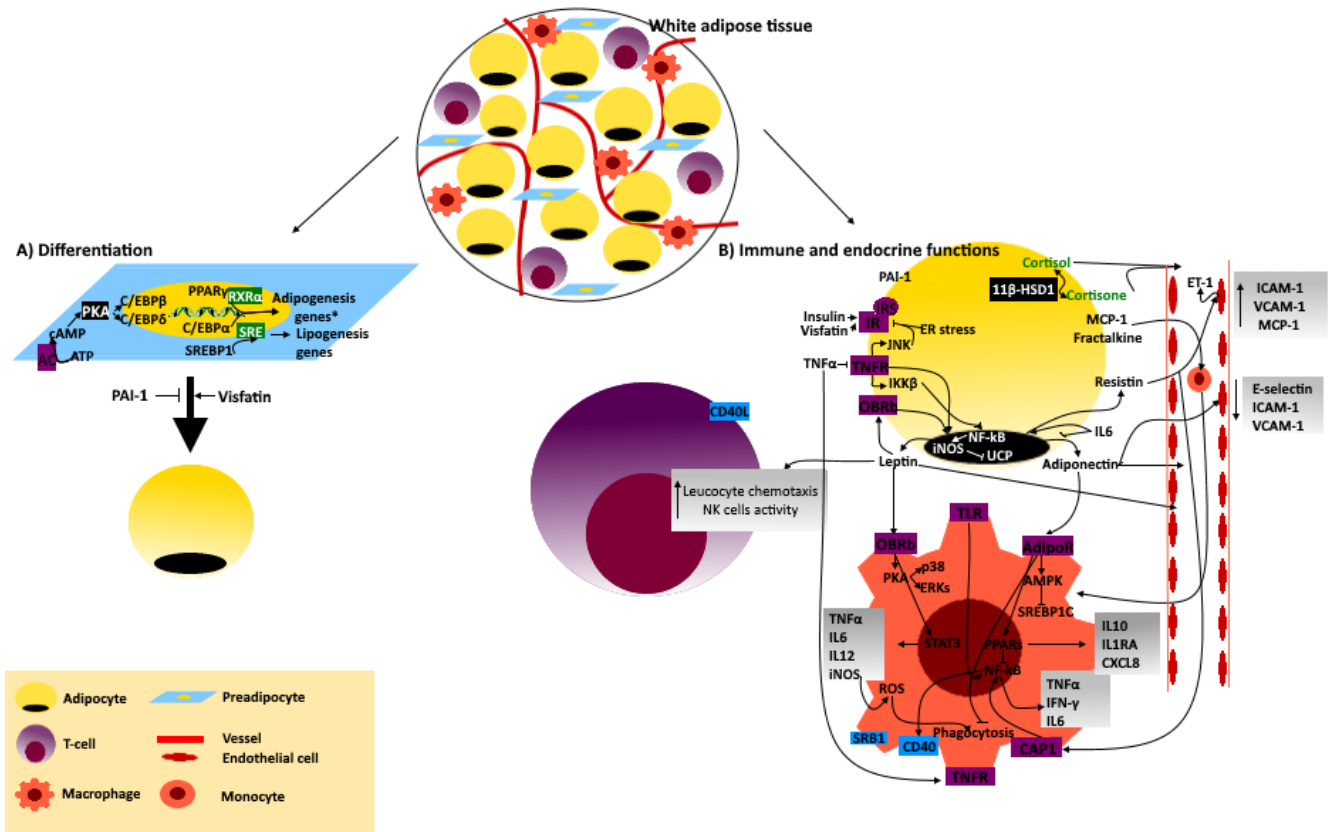
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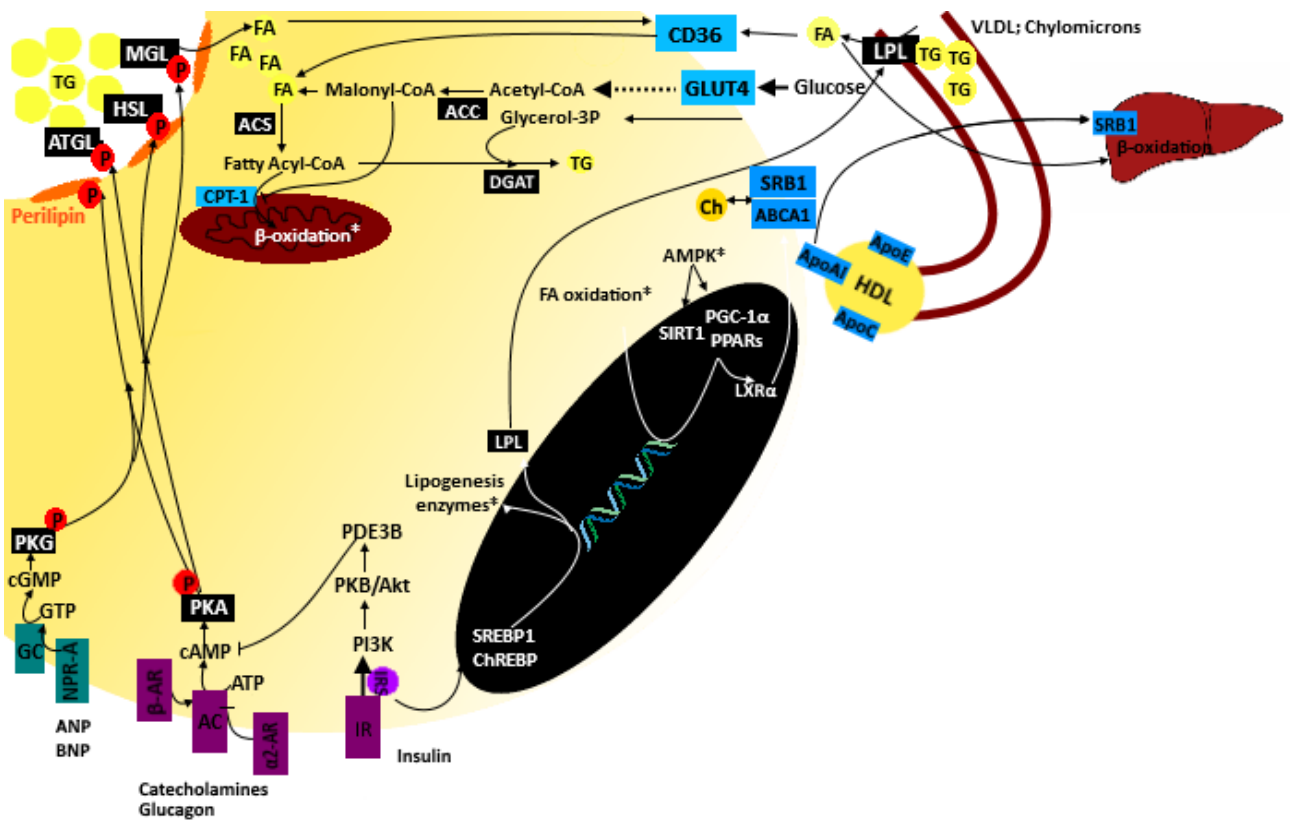
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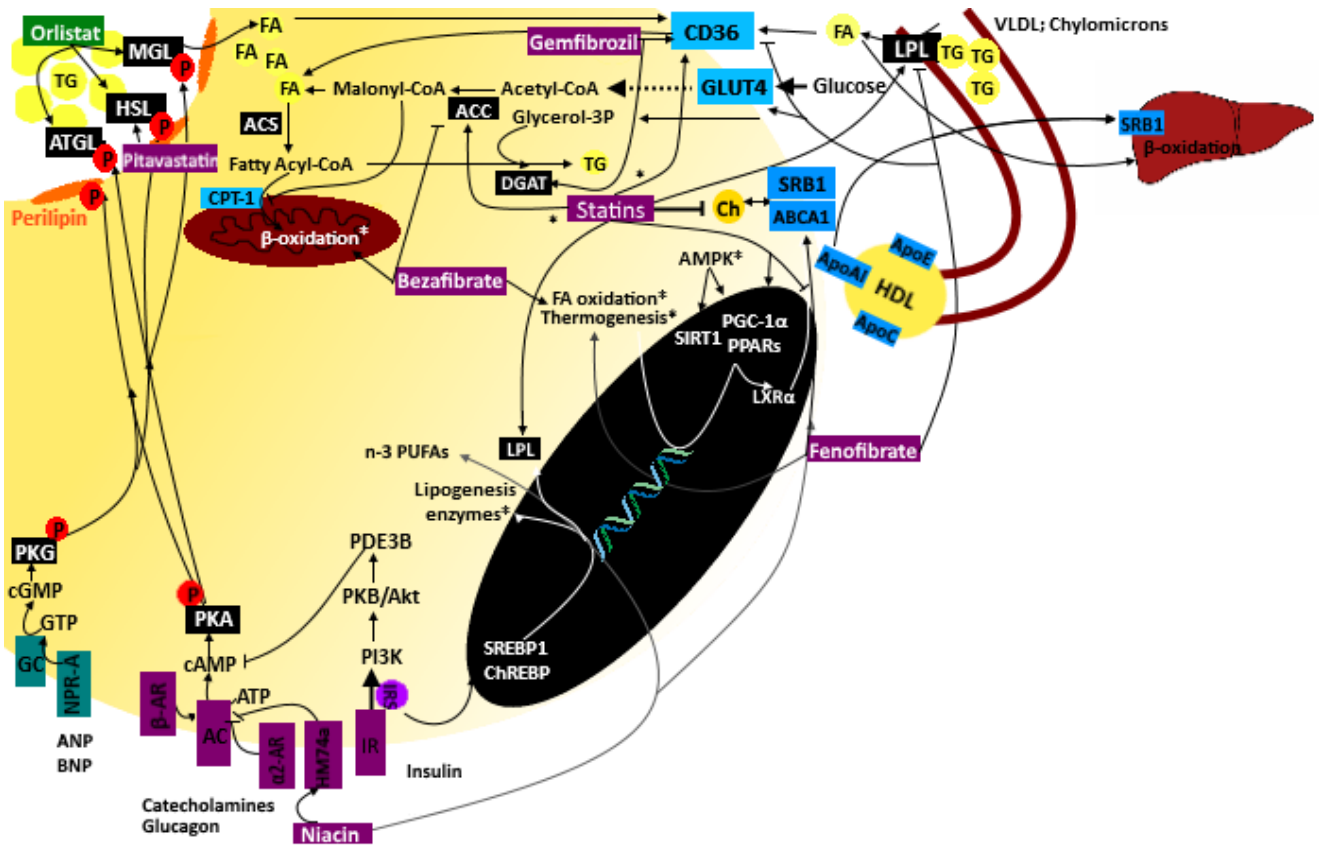
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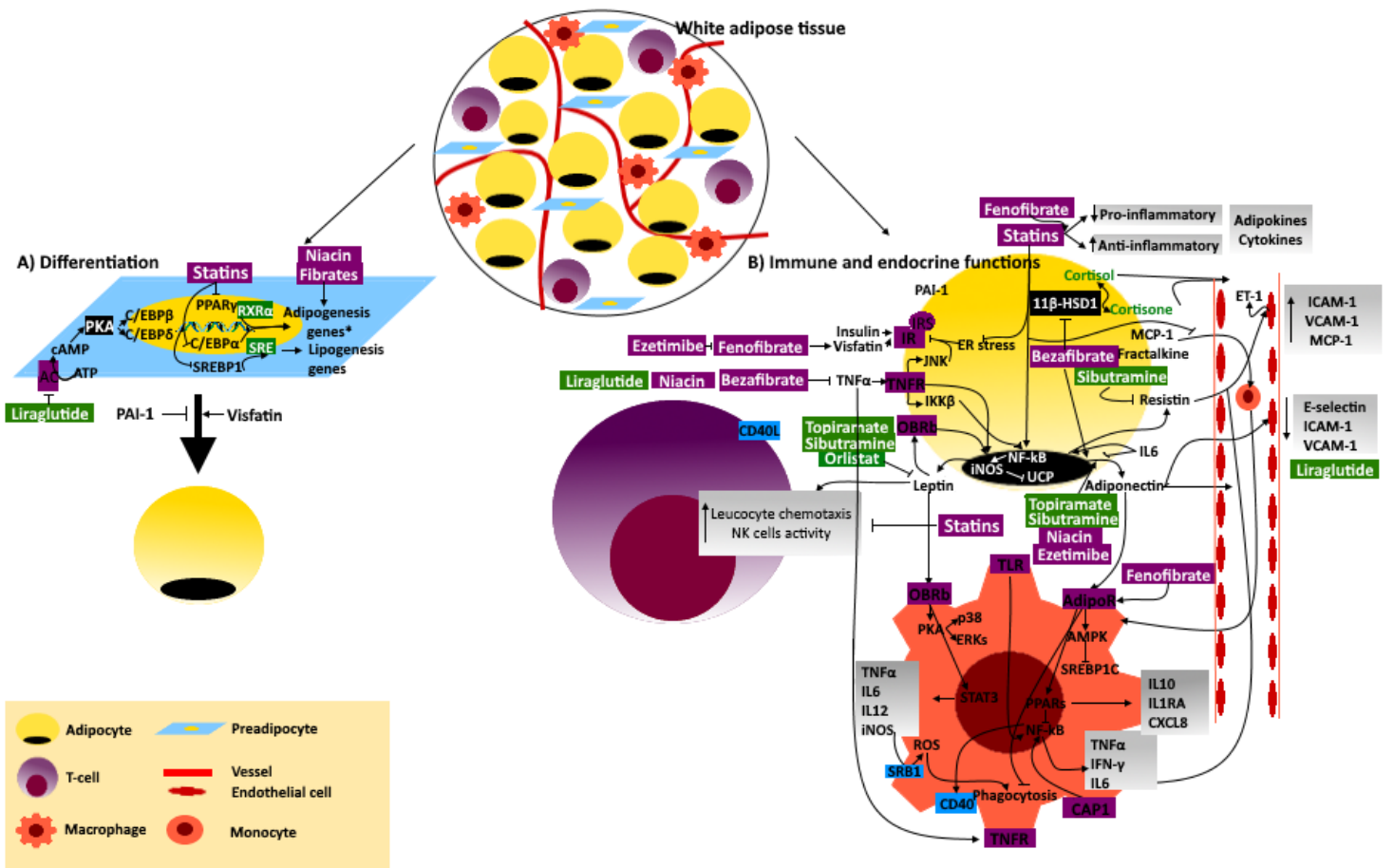
Fig. 2.2

Tables

Table 2.1 Drugs used in Dyslipidemia: classical effects, effects upon adipose tissue and weight

Drugs used in Dyslipidemia	Classical mechanism of action	AT mass/ AT depots	Glucose metabolism/ Insulin sensitivity	Lipid metabolism	Adipose tissue effects — Adipokines expression ↑	Adipose tissue effects — Adipokines expression ↓	Anti-atherogenic	Adipogenesis	Browning effect	Anti-inflammatory	Weight
Statins	⊖ HMG-CoA reductase enzyme	↓ EAT (Alexopoulos et al. 2013)	⊖ caveolae dysfunction (Breen et al. 2012); ⊖ GLUT4 expression and translocation (Ganesan and Ito 2013); NLRP3 inflammasome activation (Henriksbo et al. 2014); ⊕ ↑ SIRT1 and PGC-1α leading to PPARγ and GLUT4 (de las Heras et al. 2013; Valero-Munoz et al. 2014; Poletto et al. 2015); modulation of adipokines expression (Takagi et al. 2008; Poletto et al. 2015)	⊕ lipolysis (Ishihara et al. 2010) ↓ lipid accumulation (⊕ LPL) (Bey et al. 2002; Saiki et al. 2006) ⊕ lipogenesis and ↑ lipid accumulation (Aguirre et al. 2013)	Adiponectin (Labuzek et al. 2011; Lobo et al. 2012; Yin et al. 2007; Ishihara et al. 2010; Li et al. 2016; Krysiak et al. 2014c)	Leptin (Krysiak et al. 2014c; Labuzek et al. 2011; Maeda and Horiuchi 2009; Zhao and Wu 2005; Krysiak et al. 2014d), Resistin (Ichida et al. 2006; Labuzek et al. 2011; Li et al. 2016), IL-6 (Labuzek et al. 2011; Zhao and Zhang 2003; Dobashi et al. 2008; Yin et al. 2007; Wang et al. 2014; Abe et al. 2008), PAI-1 (Laumen et al. 2008; Lobo et al. 2012; Sakamoto et al. 2011), MCP-1 (Lobo et al. 2012; Wu et al. 2013; Wang et al. 2014; Takagi et al. 2008; Abe et al. 2008); Visfatin (Krysiak et al. 2014d) and TNF-α (Krysiak et al. 2014c; Labuzek et al. 2011; Wu et al. 2013; Wang et al. 2014; Krysiak et al. 2014d; Takagi et al. 2008)	⊕ PPARγ and SR-BI expression (adipocyte uptake of ox-LDL) (Zhao et al. 2006; Zhao and Zhang 2004); *Vide adipokines expression modulation.*	⊖ (Pengde et al. 2008; Song et al. 2003; Zhang et al. 2013; Elfakhani et al. 2014) ⊕ *in vivo* (Khan et al. 2009; Phillips et al. 2001)		⊖ ER stress (Wu et al. 2013); ⊕ iNOS expression (Araki et al. 2007; Dobashi et al. 2008);	− (de las Heras et al. 2013; Valero-Munoz et al. 2014)

Drugs used in Dyslipidemia	Classical mechanism of action	AT mass/ AT depots	Glucose metabolism/ Insulin sensitivity	Lipid metabolism	Adipokines expression ↑	Adipokines expression ↓	Anti-atherogenic	Adipogenesis	Browning effect	Anti-inflammatory	Weight
Fibrates	**PPARα agonists**							⊕ (Goto et al. 2011; Brandes et al. 1986)			↓ (Chen et al. 2014; Vazquez et al. 2001; Jeong and Yoon 2009; Gonzalez et al. 2009; Ferreira et al. 2014; Rachid et al. 2015b, a)
Bezafibrate	**Non-selective**			⊕ **FA oxidation** (Cabrero et al. 2001; Vazquez et al. 2001; Goto et al. 2011) ⊖ **lipogenesis** (Cabrero et al. 2001)	**Adiponectin** (Nakano et al. 2007; Hiuge et al. 2007)	**TNFα** (Nakano et al. 2007; Hiuge et al. 2007)			⊕ **UCP-1,2,3 expression** (Cabrero et al. 2001; Vazquez et al. 2001)		
Gemfibrozil	**Selective**			⊕ **lipogenesis** (Baldo et al. 1994)							
Fenofibrate	**selective**	↓ **VAT** (Jeong and Yoon 2009)	⊕ (Jeong and Yoon 2009; Rachid et al. 2015a; Ferreira et al. 2014)	⊕ **FA oxidation** (Gonzalez et al. 2009; Ferreira et al. 2014) ⊖ **lipogenesis** (Ferreira et al. 2006)	**Adiponectin** (Labuzek et al. 2011; Oki et al. 2007); **Vaspin** (Chen et al. 2014)	**MCP1** (Toyoda et al. 2008); **TNFα** (Labuzek et al. 2011; Toyoda et al. 2008; Zhao and Wu 2004; Jeong and Yoon 2009); **Leptin** (Jeong and Yoon 2009; Rachid et al. 2015a)	⊕ **oxLDL uptake** (Zhao et al. 2004) ⊕ **CD36 expression** (Zhao et al. 2004)		⊕ (Rachid et al. 2015b, a)	⊖ **CD40 expression (AMPK pathway)** (Wang et al. 2013) ⊖ **AOX1 expression** (Weigert et al. 2008)	↓ (Ferreira et al. 2014; Jeong and Yoon 2009; Gonzalez et al. 2009; Rachid et al. 2015b, a)
Ezetimibe	⊖ **NPC1L1**	↓ **VAT** (Takase et al. 2012)	⊕ (Takase et al. 2012)		**Adiponectin** (Takase et al. 2012)	**Visfatin** (Krysiak et al. 2014b)					− (Takase et al. 2012)

Drugs used in Dyslipi demia	Classical mechanis m of action	Adipose tissue effects									
		AT mass/ AT depots	Glucose metabolism/ Insulin sensitivity	Lipid metabolism	Adipokines expression		Anti- atherogenic	Adipoge nesis	Brownin g effect	Anti- inflammat ory	Weight
					↑	↓					
	transport er										
Niacin	⊖ **HDL- apo A-I holoparti cle receptor in hepatocy tes**		⊖ (Westphal et al. 2007; Heemskerk et al. 2014b)	⊕ lipolysis (Carlson 1963; Plaisance et al. 2009; Zhang et al. 2005) ⊖ **lipogenesis**	**Adiponectin (Plaisance et al. 2009);Leptin (chronic treatment)** (Westphal et al. 2007)	**MCP1, RANTES, Fractalkine** (Digby et al. 2010)	↑ **n-3 PUFAs and its metabolites** (Heemskerk et al. 2014a); ⊕ **HDL- induced cholesterol efflux from adipocytes; ↑ HDL levels** (Wu and Zhao 2009; Zhao et al. 2008)	⊕ (Fujimori and Amano 2011)		*Vide adipokines effects*	

Symbols: ⊕ stimulates; ⊖ inhibits; - without effect; Abbreviations: adipose tissue (AT); triglycerides (TG); 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA); glucose transporter type 4 (GLUT4); NOD-like receptor family, pyrin domain containing 3 (NLRP3); sirtuin 1 (SIRT1); peroxisome proliferator-activated receptors (PPARs); peroxisome proliferator activated receptor γ coactivator 1 (PGC-1α); lipoprotein lipase (LPL); tumour-necrosis factor α (TNFα); interleukin (IL); CC-chemokine ligand 2 (CCL2 or MCP-1); plasminogen-activator inhibitor type 1 (PAI-1); scavenger-receptor 1 (SRB1); oxidized LDL (oxLDL); fatty acid translocase (CD36/FAT); endoplasmic-reticulum (ER); inducible nitric-oxide synthase (iNOS); uncoupling protein (UCP); Niemann-Pick C1-Like 1 (NPC1L1); visceral AT (VAT); fatty acid (FA); adenosine monophosphate-activated protein kinase (AMPK); Aldehyde oxidase 1 (AOX1); Cluster of differentiation 40 (CD40); soluble intracellular adhesion molecule-1 (sICAM-1); high-density lipoproteins (HDLs); n-3 polyunsaturated fatty acids (PUFAs).

Table 3.1 Drugs used in Obesity: classical effects, effects upon adipose tissue and weight

Drugs used in Obesity	Classical mechanism of action	Adipose tissue effects									Appetite regulation
		AT mass/ AT depots	Glucose metabolism/ Insulin sensitivity	Lipid metabolism	Adipocytokines expression		Anti-atherogenic	Adipogenesis	Browning effect	Anti-inflammatory	
					↑	↓					
Orlistat	Reversible inhibitor of gastric and pancreatic lipase		⊕ (Beg et al. 2015; Kim et al. 2013)	⊕ lipolysis (Kim et al. 2013)		Leptin (Kim et al. 2013)					
Sibutramine	sympathomimetic amine; inhibition of NA and 5-HT reuptake			↓ TG (Valsamakis et al. 2004) ↑ HDL (Valsamakis et al. 2004)	Adiponectin (Valsamakis et al. 2004)	Leptin and Resistin (Valsamakis et al. 2004)	↓ CRP (Valsamakis et al. 2004)				
Diethylpropion	sympathomimetic amine; inhibition of NA, 5-HT; DA reuptake										⊖ (Yu et al. 2000)
Phentermine	sympathomimetic amine; noradrenergic modulation;										⊖, promotes saciety (Dobrzanski and Doggett 1979)

Drugs used in Obesity	Classical mechanism of action	AT mass/ AT depots	Glucose metabolism/ Insulin sensitivity	Lipid metabolism	Adipocytokines expression ↑	Adipocytokines expression ↓	Anti-atherogenic	Adipogenesis	Browning effect	Anti-inflammatory	Appetite regulation
	DA receptor agonist										
Lorcaserin	5-HT2c receptor agonist										⊖, promotes saciety (Bays 2009, 2011)
Naltrexone and Bupropion	Antagonist of opioid-receptors in POMCs neurons and inhibitor of reuptake of NA and DA	↓ , mainly VAT (Smith et al. 2013)									
Topiramate	Antagonist of AMPA receptors and stimulation of GABA receptors		⊕ (Abo-Elmatty and Zaitone 2011)		Adiponectin (Abo-Elmatty and Zaitone 2011)	Leptin (York et al. 2000)			⊕ UCP 2/3 expression (York et al. 2000)		⊖ (York et al. 2000)

Drugs used in Obesity	Classical mechanism of action	Adipose tissue effects									Appetite regulation
		AT mass/ AT depots	Glucose metabolism/ Insulin sensitivity	Lipid metabolism	Adipocytokines expression		Anti-atherogenic	Adipogenesis	Browning effect	Anti-inflammatory	
					↑	↓					
Liraglutide	**GLP-1R agonist**	↓ (Li et al. 2014; Tang et al. 2015; Suzuki et al. 2013; Yang et al. 2012; Inoue et al. 2011; Jendle et al. 2009; Morano et al. 2015; Beiroa et al. 2014), **mainly VAT** (Li et al. 2014; Tang et al. 2015; Suzuki et al. 2013; Yang et al. 2012; Inoue et al. 2011; Jendle et al. 2009; Morano et al. 2015; Shao et al. 2015; Jensterle et al. 2015; Hoang et al. 2015)	⊕ (Li et al. 2014; Yan et al. 2011; Hoang et al. 2015; Yang et al. 2012)	⊕ **FA oxidation** (Beiroa et al. 2014; Li et al. 2014); ⊖ **lipogenesis** (Shao et al. 2015);	**Adiponectin (in dysfunctional adipocyte)** (Cantini et al. 2015; Yang et al. 2013); **Omentin** (Yan et al. 2011)	**TNFα** (El Bekay et al. 2016)	↓ **CRP and sICAM-1 levels** (Inoue et al. 2011)	⊕ (Challa et al. 2012)	⊕ (Beiroa et al. 2014; Li et al. 2014; Heppner et al. 2015)	*Vide adipokines regulation*	⊖ **promotes saciety and improves eating behaviour** (Inoue et al. 2011; Shao et al. 2015; Jensterle et al. 2015; Hoang et al. 2015; Nonogaki et al. 2014; Heppner et al. 2015)

Symbols: ⊕ stimulates; ⊖ inhibits; Abbreviations: adipose tissue (AT); triglycerides (TG); high-density lipoproteins (HDLs); C-reactive protein (CRP); noradrenaline (NA) and 5-hydroxytryptamine (5-HT); dopamine (DA); pro-opiomelanocortin (POMCs) neurons; visceral AT (VAT); α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors; gamma-aminobutyric acid (GABA) receptors; fatty acid (FA); tumour-necrosis factor α (TNFα); glucagon-like peptide 1 receptor (GLP-1R); soluble intracellular adhesion molecule-1 (sICAM-1).

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Anexos

Guidelines da revista *Reviews of Physiology, Biochemistry and Pharmacology*

Manuscript Guidelines
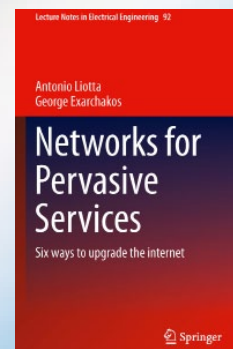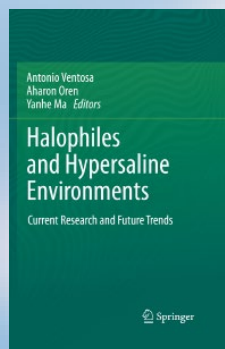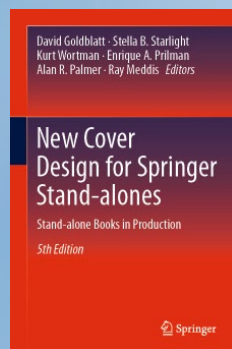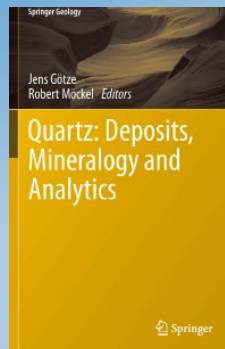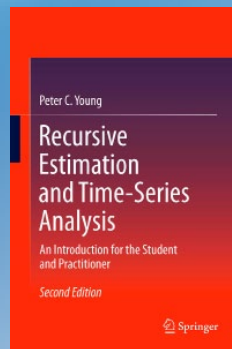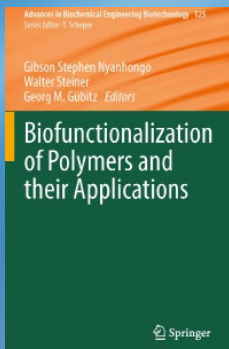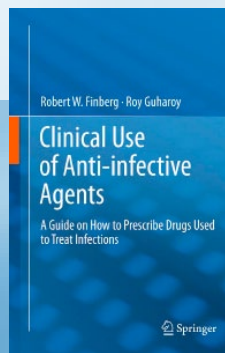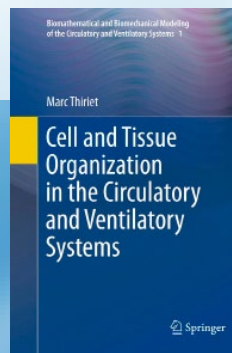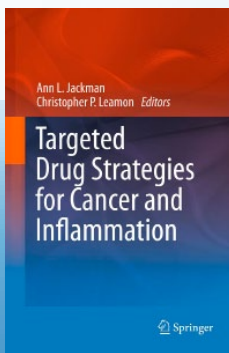
# Contents

1 Introduction

Publishing a book is a joint effort between you and Springer. We feel it is important that our authors concentrate on the content of the chapter or a book. When writing a book for Springer, please do not be concerned with the final layout. That is Springer's role. To ensure that we always keep pace with all current online and print requirements, Springer structures the content in XML as the basis for presentation in print or in digital formats for such devices as Amazon Kindle™, Apple iPad™/iPhone™, and Google Android™. We utilize standard layouts with style specifications suitable for multiple display formats.

- What advantages do these provide for you in manuscript preparation? It means you can focus on the content and Springer will professionally typeset the book and, with XML structuring, will ensure that your content will be available to readers in many formats for many years to come. To ensure this works, please follow the instructions for manuscript formatting, preparation, and delivery under Manuscript Preparation. For *Lecture Notes in Computer Series (LNCS)* preparation guidelines click here.

> **Tip**
>
> A key part of the publication process (and in response to the changing requirements of the book industry) is the standard corporate book covers that Springer introduced for each subject area which it publishes. These covers provide a strong, corporate brand identity for Springer books, making them instantly recognizable amongst the scientific community. In addition the covers also assist the speed of publication, as having standardized versions greatly reduces the time traditionally spent on creating individual covers for each title.

2 Manuscript Preparation Tools for Word and LaTeX

- Springer provides manuscript preparation tools for **Word** and **LaTeX** users that help structure the manuscript, e.g., define the heading hierarchy. Predefined style formats are available for all the necessary structures that are supposed to be part of the manuscript, and these formats can be quickly accessed via hotkeys or special toolbars.

Note: These tools are **not** intended for the preparation of the final page layout. The final layout will be created by Springer according to our layout specifications.

►Manuscript preparation tool for Word

►LaTeX2e macro packages for monographs and for contributed books

- The usage of these tools is not mandatory. Alternatively, you may either use a blank Word document or the standard LaTeX book class (for monographs) or article class (for individual contributions) and apply the default settings and styles (e.g., for heading styles, lists, footnotes, etc.).

> **Tip**
>
> If you cannot use our **Word** tool:
> - Open a blank Word document.
> - Use the default styles in Word to identify the heading levels.
> - Use the standard Word functions for displayed lists, type styles such as bold or italics, the indexing function, and the footnote function.
> - Use a single main font for the entire text. We recommend Times New Roman.
> - For special characters, please use Symbol and/or Arial Unicode.

3 Permissions

- If excerpts from copyrighted works (including websites) such as illustrations, tables, animations, or text quotations are included in your manuscript, please obtain permission from the copyright holder (usually the original publisher) for both the print and online format.

- Some publishers such as Springer have entrusted the Copyright Clearance Center in the US to manage the copyright permission procedure on their behalf. Please contact RightsLink for further information. Alternatively, Springer can provide you with a template to use when requesting permissions.

► RightsLink

- Please comply with the instructions stipulated in the permission(s) concerning acknowledgements or credit lines within your manuscript (e.g., reference to the copyright holder in captions) and keep the written confirmation of the permission in your possession with the copy of your manuscript.

- Please be aware that some publishers do not always grant right of reproduction for free due to different reasons. Springer will not be able to refund any costs that may have been incurred in receiving these permissions. As an alternative, material from other sources should be used.

4 Manuscript Preparation

To guarantee a smooth publication process and a seamless transformation of your manuscript into the final layout and various electronic formats (e.g., HTML for online publication, ePub for e-book readers), the manuscript needs to be structured as follows:

- **Front Matter:** Title page, Dedication (optional), Foreword (optional), Preface (optional), Table of Contents, List of abbreviations (optional).

- **Text Body:** It comprises the chapters containing the content of the book, i.e., text, figures, tables, and references. Chapters can be grouped together in parts.

- **Back Matter:** After the last chapter, the back matter can contain an appendix, a glossary, and/or an index, all of which are optional.

4.1 Front Matter

The title page and the **table of contents** precede the actual content of a book.

The preface (optional) should be about the book: why it was written, who it is for, its organization, or the selection of contributors. An **introduction** to the subject of the book, however, should appear as the first chapter of the book.

Other optional items in the front matter at the beginning of a book are e.g., **dedication**, a **foreword** or a **list of abbreviations**.

4.1.1 Title Page

- Please include all author names (for contributed books, the editor names) and their affiliations, the book title and subtitle. Ensure that the sequence of the author names is correct and the title of your book is final when you submit your manuscript.

- Please also supply all the email addresses and telephone numbers and in case of multiple authors or editors, clearly indicate the corresponding author or editor.

- Once the manuscript has been delivered to Springer Production, changes to title or authorship are no longer possible.

4.1.2 Foreword (optional)

- If you intend to include a foreword, please submit it with the manuscript.

> **Tip**
> – A foreword is usually written by an authority on the subject, and serves as a recommendation of the book.
> – The name of the foreword's contributor is always given at the end of the foreword; affiliations and titles are generally not included, but the date and place of writing may be.

4.1.3 Preface (optional)

- A preface should not contain a reference list.
- An introduction to the **subject** of the book should not be confused with a preface. The introduction does not belong in the front matter, but should appear as the first chapter of the book.

> **Tip**
> – The preface should be about the book: why it was written, who it is for, its organization, or the selection of contributors.
> – Acknowledgments of support or assistance in preparing the book can be included as the last paragraph(s) of the preface. If the acknowledgment is more than one page long, it should start on a separate page under the heading **Acknowledgments**.

4.1.4 Table of Contents

- List all parts, chapters, and back matter material (e.g., an index) in the final sequence.

- If your chapters are numbered, use **Arabic** numerals and number the chapters consecutively throughout the book (Chapter 1, Chapter 2, etc.), i.e., do not start anew with each part.

- If there are parts, use **Roman** numerals for parts (Part I, Part II, etc.).

Key Style Points: Table of Contents

4.1.5 List of Abbreviations (optional)

> **Tip**
> – A **list of abbreviations** and/or symbols is optional but it may be very helpful if numerous abbreviations and special symbols are scattered throughout the text.

4.2 Chapters

Chapters contain the actual content of the book, i.e., text, figures, tables, and references. Chapters can be grouped together in **parts**; subparts are not possible. Only one chapter (i.e., an introduction) may precede the first part and would be the first chapter.

- Decide the numbering style for the chapters and apply this style consistently to all chapters: consecutively numbered (monographs or textbooks) or unnumbered (contributed volumes).

- If an introduction to the subject of the book (historical background, definitions, or methodology) is included, it should appear as the first chapter and thus be included in the chapter numbering. It can contain references, figures, and tables, just as any other chapter.

4.2.1 Language

- Either **British** or **American** English can be used, but be consistent within your chapter or book. In contributed books chapter-wise consistency is accepted.

- Check for consistent **spelling** of names, terms, and abbreviations, including in tables and figure captions.

Tip
- For American spelling please consult *Merriam–Webster's Collegiate Dictionary*; for British spelling you should refer to *Collins English Dictionary*.
- If English is not your native language, please ask a native speaker to help you or arrange for your text to be checked by a professional editing service. Please insert their final corrections into your data before submitting the manuscript.

▶More about language editing

4.2.2 Chapter Title and Authors

- For contributed volumes, please include each chapter's authors' names (spelled out as they would be cited), affiliations and e-mail addresses and telephone numbers after the chapter title. (The telephone number will not be published but may be needed as contact information during the publishing process.)

Key Style Points: Chapter Title Page

4.2.3 Abstract

- **Begin each chapter with an abstract** that summarizes the content of the chapter in 150 to 250 words. The abstract will appear **online** at SpringerLink and be available with unrestricted access to facilitate online searching, using, e.g., Google, and allow unregistered users to read the abstract as a teaser for the complete chapter

- If no abstract is submitted, we will use the first paragraph of the chapter instead.

- Abstracts appear only in the **printed edition** of contributed volumes unless stipulated otherwise.

Tip
- Don't include reference citations or undefined abbreviations in the abstract, since abstracts are often read independently of the actual chapter and without access to the reference list.
- For further tips on writing an effective abstract, see the website on Search Engine Optimization.

4.2.4 Keywords (if applicable)

- Some books also publish keywords. Please check with the editor of your book or with the publishing editor to see if keywords are required.

Tip
- Each keyword should not contain more than two compound words, and each keyword phrase should start with an uppercase letter.
- When selecting the keywords, think of them as terms that will help someone locate your chapter at the top of the search engine list using, for example, Google. Very broad terms (e.g., 'Case study' by itself) should be avoided as these will result in thousands of search results but will not result in finding your chapter.

4.2.5 Headings and Heading Numbering

- Heading levels should be clearly identified and each level should be uniquely and consistently formatted and/or numbered.

- Use the **decimal system** of numbering if your headings are numbered.

- Never skip a heading level. The only exceptions are run-in headings which can be used at any hierarchical level.

Key Style Points: Headings

Tip
- In **cross-references**, for hyperlink purposes, refer to the chapter or section number (e.g., see Chap. 3 or see Sect. 3.5.1).
- In addition to numbered headings, two more (lower) heading levels are possible. Their hierarchical level should be identified with the help of Springer's templates or the standard Word or LaTeX heading styles.
- Another option for lower level headings is a run-in heading, i.e., headings that are set immediately at the beginning of the paragraph. Such headings should be formatted in bold or italics.

4.2.6 Terminology, Units and Abbreviations

- Technical terms and **abbreviations** should be defined the first time they appear in the text.

- Please always use internationally accepted signs and symbols for units, so-called **SI units**.

- **Numerals** should follow the British/American method of decimal points to indicate decimals and commas to separate thousands.

Key Style Points: Abbreviations, Numbers, Units and Equations

Tip
- If the manuscript contains a large number of terms and abbreviations, a list of abbreviations or a **glossary** is advised.

4.2.7 Formal Style and Text Formatting

- Manuscripts will be checked by a copy editor for formal style. Springer follows certain standards with regard to the presentation of the content, and the copy editors make sure that the manuscript conforms to these styles.

Key Style Points: Formal Style, Text formatting

Tip
- Remember not to make changes that involve only matters of style when you check your proofs. We have generally introduced forms that follow Springer's house style.

Emphasis and special type

Key Style Points: Formal Style, Text formatting

Tip
- **Italics** should be used for emphasized words or phrases in running text, but do not format entire paragraphs in italics.
- In addition, use italics for species and genus names, mathematical/physical variables, and prefixes in chemical compounds.
- **Bold** formatting should only be used for run-in headings and **small capitals** for indicating optical activity (D- and L-dopa).

– **Sans serif** (e.g., Arial) and **nonproportional font** (e.g., Courier) can be used to distinguish the literal text of computer programs from running text.

Boxes

- Do not set entire pages as boxes, because this affects online readability.

Tip
– Additional text elements for **professional and text books** such as examples, questions or exercises, summaries or key messages can be highlighted with Springer's manuscript preparation tool. If you do not use the tool, use a consistent style for each of these elements and submit a list of the styles used together with your manuscript.

4.2.8 Footnotes

- Always use footnotes instead of endnotes and never use footnotes instead of a reference list.
- Footnotes should not consist of a reference citation. Footnotes should not contain figures, tables and/or the bibliographic details of a reference.

Key Style Points: Formal Style, Text formatting

4.2.9 Equations and Program Code

- In **Word**, use the Math function of Word 2007 or 2010, MathType, or Microsoft Equation Editor with Word 2003 to create your equations, and insert the graphic into your text file as an object.
- In **LaTeX**, use the Math environment to create your equations.

Key Style Points: Abbreviations, Numbers, Units and Equations

Tip
– Prepare the whole equation in this way and not just part of it.

4.3 Tables

- Give each table a caption. Add a reference citation to the table source at the end of the caption, if necessary.
- Number tables consecutively using the chapter number (e.g. Table 1.1 for the first table in Chap. 1) and ensure that all tables are cited in the text in sequential order. Do not write "the following table".
- Use the table function to create and format tables. Do not use the space bar or multiple tabs to separate columns and do not use Excel to create tables as this can cause problems when converting your tables into the typesetting program and other formats.

Key Style Points: Tables and Lists

Tip
– Simple, one-column lists should not be treated as tables. Use the displayed list function instead.
– Save the tables in the same file as text, references, and figure captions.
– Do not manually insert table rules in the manuscript, because they cannot be retained.

4.4 Figures and Illustrations

4.4.1 Numbering

- Number the figures chapter-wise using the chapter number (e.g., Fig. 1.1 for the first figure in Chap. 1) and ensure that all figures are cited in the text in sequential order. Do not write "the following figure".

4.4.2 Figure Captions

- Give each figure a concise caption, describing accurately what the figure depicts. Include the captions at the end of the text file, not in the figure file.

- Identify all elements found in the figure in the figure caption and use boxes, circles, etc. as coordinate points in graphs instead of color lines.

- If a figure is reproduced from a previous publication, include the source as the last item in the caption.

Key Style Points: Figures and Illustrations

4.4.3 Figure and Illustration Files

A figure is an object that is drawn or photographed. It does not consist solely of characters and thus cannot be keyed.

- Do not submit tabular material as figures.

- **Graphics and diagrams** should be saved as EPS files with the fonts embedded. Microsoft Office files (Excel or PowerPoint) can be submitted in the original format (xls, xlsx, ppt, pptx). Scanned graphics in TIFF format should have a minimum resolution of 1200 dpi.

- **Photos** or drawings with fine shading should be saved as TIFF with a minimum resolution of 300 dpi.

- A **combination** of halftone and line art (e.g., photos containing line drawings or extensive lettering, color diagrams, etc.) should be saved as TIFF with a minimum resolution of 600 dpi.

Tip

- **Color figures** will appear in color in the eBook but may be printed in black and white. In that case, do not refer to color in the captions and make sure that the main information will still be visible if converted to black and white. A simple way to check this is to make a black and white printout to see if the necessary distinctions between the different colors are still apparent. Color illustrations should be submitted as RGB (8 bits per channel).
- Ensure consistency by using similar **sizing** and lettering for similar figures. Ideally, you should size figures to fit in the page or column width. For books in Springer's standard format, the figures should be 78 mm or 117 mm (3 or 4 1/2 inches) wide and not higher than 198 mm (7 3/4 inches).
- To add **lettering**, it is best to use Helvetica or Arial (sans serif fonts) and avoid effects such as shading, outline letters, etc. Keep lettering consistently sized throughout your final-sized artwork, usually about 2–3 mm (8–12 pt). Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label.

4.5 References

4.5.1 Reference Citations

- Cite references in the text with author name/s and year of publication in parentheses ("Harvard system"):

  – One author: (Miller 1991) or Miller (1991)
  – Two authors: (Miller and Smith 1994) or Miller and Smith (1994)
  – Three authors or more: (Miller et al. 1995) or Miller et al. (1995)

- If it is customary in your field, you can also cite with reference numbers in square brackets either sequential by citation or according to the sequence in an alphabetized list:

  – [3, 7, 12].

4.5.2 Reference List

- Include a **reference list at the end of each chapter** so that readers of single chapters of the eBook can make full use of the citations. References at the end of the book cannot be linked to citations in the chapters. Please do not include reference lists at the end of a chapter section, at the end of a book part, in a preface or an appendix.

- Include all works that are cited in the chapter and that have been published (including on the Internet) or accepted for publication. Personal communications and unpublished works should only be mentioned in the text. Do not use footnotes as a substitute for a reference list.

- Entries in the list must be listed alphabetically except in the numbered system of sequential citation. The rules for alphabetization are:

  – First, all works by the author alone, ordered chronologically by year of publication.
  – Next, all works by the author with a coauthor, ordered alphabetically by coauthor.
  – Finally, all works by the author with several coauthors, ordered chronologically by year of publication.

> **Tip**
> – For authors using EndNote software to create the reference list, Springer provides output styles that support the formatting of in-text citations and reference list.
> ► EndNote software: Springer reference styles
> – For authors using BiBTeX, the style files are included in Springer's LaTex package.

4.5.3 Reference Styles

Springer follows certain standards with regard to the presentation of the reference list. They are based on reference styles that were established for various disciplines in the past and have been adjusted to facilitate automated processing and citation linking. This allows us, for example, to easily cross link the cited references with the original publication.

> **Tip**
> – Always select one of the reference list styles that are supported by **Springer** and suits your publication best or follow the instructions received from your book editor. There are, however, recommended styles depending on the **discipline**.
> – The copy editor will check the references against the reference style applicable for the book and correct the format if necessary.

Springer Style	Disciplines	Key Style Points: Reference styles	EndNote software: Springer reference styles
Springer Basic Style Based on *Harvard style* and rec-ommendations of the *Council of Biology Editors* (CBE)	Medicine, Biomedicine, Life Sciences, Chemistry, Geosci-ences, Computer Science, En-gineering, Economics	Springer Basic Style	Springer Basic End-Note Style
Springer Vancouver Style Based on the NLM guidelines *Cit-ing Medicine*	Medicine, Biomedicine	Springer Vancouver Style	Springer Vancouver EndNote Style
Springer MathPhys Style	Mathematics, Physics, Statis-tics	Springer MathPhys Style	Springer MathPhys EndNote Style
Springer Physics Style Based on the reference list style of the *American Physical Society* (APS)	Physics	Springer Physics Style	Springer Physics EndNote Style
Springer SocPsych Style Based on the reference list style that was established by the *American Psychological Associa-tion* (APA)	Social Sciences, Psychology	Springer SocPsych Style	Springer SocPsych EndNote Style
Springer Humanities Style Based on the reference list style as suggested by the *Chicago Manual of Style* (15th edn.)	Humanities, Linguistics, Phi-losophy	Springer Humani-ties Style	Springer Humani-ties EndNote Style

4.6 Back Matter

After the last chapter, the back matter of the book can contain an **appendix**, a **glossary**, and/or an **in-dex**.

- Do not include a reference list containing the cited literature in the back matter, as references are then not linked to citations in the chapters. Instead, include reference lists at the end of each chapter. A list of further reading may be included in the back matter.

4.6.1 Appendix

- An appendix cannot include a reference list.

Tip
– Include important original content within a chapter or a chapter appendix, not in the book ap-pendix, as any appendix in the back matter of a book will appear with unrestricted access in the eBook on SpringerLink.

4.6.2 Index (if applicable)

- If an index is desired, please submit the index entries with the manuscript.

Tip
– Use the indexing function in Word or the index command in LaTeX to identify the index term as you write your text and indicate, on average, one or two index entry terms per manuscript page to be included in the index.

– Information should be listed under the term that most readers will probably look at first. Use cross-references to list variations or written-out versions and abbreviations/acronyms.
– If you provide a list with index terms, the index, with page numbers, will be generated by our production partner.

5 Final Check and Submission

- Check the table of contents for the correct sequence of part, chapter and heading numbering and update the chapter titles and subheadings if necessary.

- Save each chapter or contribution, including the accompanying references, figure legends, and tables, in a separate file in the original source file format and give each file your name and the chapter number (e.g., Myers-Chap1). Save the original figure files separately and name them with your name, the chapter, and figure number (e.g., Myers-Fig1.1).

- Ensure the text and figures of your manuscript are complete and final and that you have kept to the agreed-upon length.

- Submit your manuscript to your Springer Publishing Editor. Please include:

– Original source files (Word, LaTeX) and figure files.
– A PDF file of your manuscript and figure files, ideally with all fonts embedded, that can be used as a reference. This is especially important if text or figures contain special characters or unusual fonts. **Please check the PDF to ensure that text appears as it should**.

- Ensure all third-party permissions have been obtained.

- For contributed volumes, ensure that all signed Consent to Publish forms are enclosed in a separate folder.

- Submission is possible via FTP (please contact your Springer Publishing Editor for access details).

- Before you submit your final manuscript, use the following Manuscript Submission Checklist to make sure you have covered everything.

Manuscript Submission Checklist

Title page	Title (and subtitle) final	o
Authors/Editors	All author/editor names included	o
	e-mail address of corresponding author included	o
Front matter	Complete with the following elements: o Dedication o Foreword o Preface o Acknowledgments o **Table of contents** (required) o List of contributors o List of abbreviations	o
Table of contents	Monographs: first 2 levels of headings appearing in chapters are included	o
	Contributed books: chapter titles and author names included	o
	Headings correspond to those in the text	o
Book structure	Number of parts: Number of chapters:	o
	All chapters numbered sequentially throughout the book (or not numbered at all)	o
	Chapter sequence and numbering final	o
Abstract	Included for each chapter	o
Text	Heading levels and special text elements consistently styled	o
	No heading levels skipped	o
References	Reference list included at the end of each chapter	o
	Citations in text agree with reference list	o
	Reference list style according to Springer's guidelines	o
Figures	All figures mentioned in text enclosed, complete, and as separate files	o
	Consecutively numbered within chapter	o
	Consecutively cited in text	o
	Figure captions included at the end of the text file	o
Tables	Prepared with the table function	o
	Consecutively numbered within chapter	o
	Consecutively cited in text	o
Electronic manuscript	File folder/zip archive labeled with book title and author/editor name	o
	Each chapter saved as a separate file in the original file format	o
	Graphics saved as separate files in tif, eps, xls, xlsx, ppt, pptx format	o
	PDF file with all fonts embedded	o
Contributed books	e-mail addresses and affiliation included for at least the corresponding author of each chapter	o
	Consent to publish for each chapter	o
Permissions	Obtained for all material from other works	o