# Charles University

## Faculty of Pharmacy in Hradec Kralove

## Department of Biological and Medical Sciences


**Pathophysiology of Metabolic Syndrome and Current Therapeutic Approaches**

**Patofyziologie metabolického syndromu a současné léčebné postupy.**

(Master's Thesis)

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Hradec Kralove 2019

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*I declare that this thesis is my original work. All literature and other resources which were used during the preparation of this review are listed in bibliography and properly cited.*

*Date:* *Signature*

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## Abstrakt

Cílem této diplomové práce je znalost a rozbor metabolického syndromu a jeho souvislosti s chorobami kardiovaskulárního systému. V práci budou uvedeny epidemiologické a patofyziologické aspekty a komplikace.

V práci budou rozebrány obecně známé farmakologické i nefarmakologické způsoby léčby metabolického syndromu. V práci jsou diskutovány i nové terapeutické postupy z hlediska jejich přínosů a toxicity.

## Abstract

The goal of this thesis is the knowledge and analysis of the Metabolic Syndrome and its association with the cardiovascular diseases. Aspects such as epidemiology, pathophysiology, and complications will be discussed in this thesis.

The general and known pharmacological and non-pharmacological approaches towards the syndrome will be analyzed. It is also discussed in this thesis the new therapeutic approaches towards the syndrome, with the benefits and toxicities listed.

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## Abbreviations

- WHO – World Health Organization
- HDL – High density Lipoproteins
- LDL – Low density Lipoproteins
- VLDL – Very low density Lipoproteins
- TG – Triglycerides
- BMI – Body Mass Index
- EGIR – European Group for Insulin Resistance
- IDF – International Diabetes Federation
- NCEP – National Cholesterol Education Program
- IL-6 – Interleukin 6
- TNFα – Tumor necrosis factor α
- CT – Computed Tomography
- MRI – Magnetic Resonance Imaging
- IGF-1 – Insulin like Growth Factor 1
- GLUT 4 – Glucose Transporter type 4
- Apo-B – Apolipoprotein type B
- RAS – Renin angiotensin System
- ROS – Reactive Oxygen Species
- C1q – Complement Component 1
- RA – Rheumatoid Arthritis
- CRP – C-Reactive Protein
- VEGF – Vascular Endothelial Growth Factor
- IGFBP-1 – Insulin like Growth Factor Binding Protein 1
- HMG-CoA – Hydroxymethyl glutaryl Co-enzmyme A
- PPAR – Peroxisome Proliferator Activated Receptor
- FDA – Food and Drug Administration
- ACE – Angiotensin Converting Enzyme
- GLP-1 – Glucagon like Peptide 1

- DPP IV – Dipeptidyl Peptidase IV
- 5-HT – 5-Hydroxytryptamine
- RIP-140 – Receptor Interacting Protein 140
- CDDO-Im - 1-(2-cyano-3,12-dioxooleana-1,9-dien-28-oyl) imidazole
- NFE2L2 - Nuclear Factor (Erythroid-Derived 2) - like 2
- FDKP - Fumaryl Diketopiperazine
- PEG – Polyethylene Glycol
- PON1 – Paraxonase 1
- Lp-PLA2 – Lipoprotein-associated phospholipase A2
- EMA – European Medical Agency
- CB1 – Cannabinoid 1
- IR – Immediate Release
- PCSK9 - Proprotein convertase subtilsin-kexin type 9

# I. Introduction

Metabolic syndrome is the interconnection of physiological, clinical, biochemical and metabolic factors that directly increase risk factors of atherosclerotic cardiovascular diseases, and overall increase mortality. (Kaur, 2014) The cluster of certain risk factors; including hypertension, hyperglycemia, and dyslipidemia, has been classified as metabolic syndrome. Most adults that develop cardiovascular diseases have one or more risk factors. There are six components of metabolic syndrome; abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance, and/or glucose intolerance, and proinflammatory and prothrombic states. The WHO (World Health Organization) clinical criteria for metabolic syndrome requires insulin resistance as a diagnosis, along with two other risk factors from high blood pressure, elevated triglycerides, low HDL, increased waist circumference or BMI, and microalbuminuria. (Beilby, 2004) The WHO definition also mandates that insulin resistance must be present for the patient to have metabolic syndrome. Without it, even if all other criteria were met, the patient would be considered not to have the disease. Similar to the WHO definition, EGIR (European Group for study of Insulin Resistance) defined two additional criteria, selected from obesity, hypertension, and dyslipidemia. Obesity has been simplified to waist circumference, and microalbuminuria, which was considered a criterion according to WHO, was eliminated as a diagnosis. (Huang, 2009)

According to WHO clinical criteria for metabolic syndrome, it is generally defined as:

Insulin resistance, one of the following-

- Type II diabetes
- Impaired fasting glucose
- Impaired glucose tolerance

Plus any two of the risk factors-

- Hypertension (>140 mmHg systolic or >90 mmHg diastolic)

- Plasma triglycerides (>1.7 mmol/L)
- HDL cholesterol (<0.9 mmol/L in men, and <1.0 mmol/L in women)
- BMI >30 kg/$m^2$ and/or waist/hip ratio >0.9 in men, and >0.85 in women (Beilby, 2004)

The presence of metabolic syndrome indicates risk for cardiovascular diseases, as well as diabetes mellitus II; however, a greater risk is related to other factors such as age, sex, smoking, and gender. Women, for instance, have higher concentration markers (C-reactive protein) in comparison with men, possibly due to the increased accumulation of visceral, or/and subcutaneous fat. (Kassi et al., 2011)

## II. History of Metabolic Syndrome

Metabolic syndrome was a concept that originated in 1920 by the Swedish physician, Kylin, which demonstrated the association of hypertension, hyperglycemia, and gout. Later in 1947, Vague found that visceral obesity was associated with metabolic abnormalities, associated with type 2 diabetes and cardiovascular disease. In 1965, at the European Association for the Study of Diabetes, it was described as a syndrome that comprised hypertension, hyperglycemia, and obesity. Following 1988, Reaven described it as "a cluster of risk factors for diabetes and cardiovascular disease", and named it "Syndrome X". His contribution was introducing insulin resistance concept; however, he missed the addition of visceral obesity from the definition. Afterwards, in 1922, it was named as "Insulin Resistance Syndrome". Many groups attempted to develop diagnostic criteria for the disease; with the first attempt by WHO in 1998. (Kaur, 2014)

## III. Epidemiology

Metabolic syndrome prevalence is available in~ 25% adults worldwide, according to International Diabetes Federation (IDF), and increases with advanced age.(Nolan et al., 2017) However, this estimate varies widely due to age, ethnicity and gender of the population examined. Higher socioeconomic status, higher BMI, sedentary lifestyle, genetic background,

diet, smoking, levels of physical activity, family history of diabetes, and education all as well contribute to metabolic syndrome. (Kaur, 2014)

The presence of one diagnosis of metabolic syndrome at a young age increases the risk of developing the disease later in life, as well as risk of cardiovascular disease. Therefore, it is important to identify the prevalence of metabolic syndrome in the young population (ages 18-30), not only to prevent risk of cardiovascular diseases, but also to prevent the syndrome by targeted interventions. (Nolan et al., 2017)

## IV. Pathophysiology of Metabolic Syndrome

Metabolic syndrome is a complex mixture between genetic and environmental factors. Understanding the pathophysiology will help identify the people at risk of developing cardiovascular diseases, thus helping in early intervention for prevention of the disease. (G and P, 2013)

Criteria for diagnosis of metabolic syndrome have been defined variably by different organizations; however, the most accepted criteria were adopted by NCEP (National Cholesterol Education Program) and IDF (International Diabetes Federation), as shown in table 1. (Han and Lean, 2016)

Table 1.

Criteria for diagnosis of the metabolic syndrome as defined by the NCEP[5] and more recent proposals from the IDF[6].

| Risk factor | Defining level | |
|---|---|---|
| | NCEP proposals: any three features | IDF proposals: large waist plus two other features |
| Large waist circumference | | |
| Men | ≥102 cm (40 in) | ≥94 cm (37 in) |
| Women | ≥88 cm (35 in) | ≥80 cm (32 in) |
| Raised triglycerides | ≥1.7 mmol/L (150 mg/dL) | ≥1.7 mmol/L (150 mg/dL) |
| Reduced HDL cholesterol | | |
| Men | <1.03 mmol/L (40 mg/dL) | <1.03 mmol/L (40 mg/dL) |
| Women | <1.29 mmol/L (50 mg/dL) | <1.29 mmol/L (50 mg/dL) |
| Raised blood pressure | ≥130/≥85 mmHg | ≥130/≥85 mmHg |
| Raised fasting plasma glucose | ≥6.1 mmol/L (110 mg/dL) | ≥5.6 mmol/L (100 mg/dL) |

Note: All individual components are below treatment thresholds, but combined in the metabolic syndrome, coronary heart disease risk is doubled. If body mass index ≥30 kg/$m^2$ then assume waist circumference is above treatment level.

Table 1. Criteria for diagnosis of the metabolic syndrome as defined by NCEP and IDF.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4780070/#bibr5-2048004016633371

### i. Obesity

Metabolic syndrome is also known as “central obesity syndrome”; according to the new criteria of IDF (International Diabetes Federation). Central obesity is more metabolically active than peripheral fat. Studies have shown that central obesity precedes all the other diagnosis of metabolic syndrome; therefore, the best way to prevent it is by weight reduction. Although insulin resistance is the major factor for development of metabolic syndrome, central obesity is found to be the link between insulin resistance, hypertension and dyslipidemia factors.

Lipotoxicity is when metabolic products of visceral fats are released directly into the portal circulation, which carries the blood moving straight to the liver. Accumulation of free fatty acids occur in the pancreas, heart and other organs; leading to organ dysfunction. This produces impaired insulin regulation, blood cholesterol, and abnormal heart functions. (G and P, 2013)

Enlarged and dysfunctional adipose cells are related to the development of visceral fat deposits, also known as abdominal adiposity. Proinflammatory biomarkers, such as prostaglandins, C-reactive protein, and cytokines such as interleukins (IL-6), tumor necrosis factors (TNF-α), and leptin, are secreted by the dysfunctional adipose tissue. With increasing obesity, there is a decrease in levels of adiponectin; which is an anti-atherosclerotic adipokine. Development of type II diabetes, hyperlipidemia, and cardiovascular diseases are contributed to the inflammatory mediators released by adipose tissues. When there is a high proportion of fat to muscles, there is a higher contribution to this metabolic dysfunction due to the increase of free fatty acids circulation, which requires greater insulin secretion to control glucose metabolism. This results in hyperinsulinemia, which desensitizes insulin-sensitive tissues, and therefore, makes the individual more susceptible to type II diabetes. The inhibition of insulin receptor proteins is also influenced by the decrease of adiponectin secretion. (Paley and Johnson, 2018)

Computed tomography (CT) or magnetic resonance imaging (MRI) can be used to evaluate abdominal obesity, and to measure the amount of visceral fat. CT or MRI can be used to evaluate abdominal obesity, and to measure the amount of visceral fat. (G and P, 2013)

Guidelines for healthy weight have been based on BMI, and most recently, waist circumference; as shown in table 2. (Han and Lean, 2016)

Table 2.

Classification of body mass index and waist circumference and risk of obesity related co-morbidities.

| | Body mass index[a] | | |
|---|---|---|---|
| Men and women | 18.5–24.9 kg/m$^2$ | 25–29.9 kg/m$^2$ | ≥30 kg/m$^2$ |
| Classification | Normal weight | Overweight | Obese |
| Risk of co-morbidities | Low | Increased | High |
| | Waist circumference[b] | | |
| Men | <94 cm | 94–101.9 cm | ≥102 cm |
| Women | <80 cm | 80–87.9 cm | ≥88 cm |
| Classification | Normal fat distribution | Moderate central fat accumulation | High central fat accumulation |
| Risk of co-morbidities | Low | Increased | High |

[a]WHO.[12]
[b]Lean et al.[4]

Table 2. Classification of BMI and waist circumference and risk of obesity related co-morbidities.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4780070/#bibr5-2048004016633371

## ii. Insulin Resistance (Type II Diabetes Mellitus)

Metabolic syndrome is also known as insulin resistance syndrome, because it is the most accepted hypothesis to describe the pathophysiology of the syndrome. Insulin resistance is a defect in the insulin action, resulting in hyperinsulinemia. (Aganović and Dušek, 2007) Insulin is a dipeptide, containing A and B chains. It is synthesized in the β-cells of the pancreatic islets of Langerhans as a precursor, proinsulin. (Wilcox, 2005) It promotes glucose uptake in liver, muscles, and adipose cells. Moreover, it can also influence lipolysis, as well as the production of glucose by the hepatocytes. (G and P, 2013) Insulin acts in harmony with the growth hormone and insulin-like growth factor 1 (IGF -1); growth factor is secreted in response to insulin secretion, to prevent insulin induced hypoglycemia. There are other counter regulatory hormones that work against the action of insulin to raise blood glucose levels in response to hypoglycemia; they include glucagon, glucocorticoids, and catecholamines. They promote glycogenolysis, lipolysis, and gluconeogenesis. Secretion of these hormones in excess may contribute to insulin resistance. (Wilcox, 2005)

Overabundance of free fatty acids circulating, released by the adipose tissue mass, is the mediator for development of insulin resistance. Free fatty acids decrease the muscle sensitivity to insulin by inhibiting insulin-mediated glucose uptake. As the levels of circulating glucose increase, insulin secretion from the pancreas also increases, resulting in hyperinsulinemia. In the liver, the free fatty acids increase the production of glucose, triglycerides, and very low density lipoproteins (VLDL). As a result, the glucose transformation to glycogen is decreased, while the lipid accumulation in triglyceride is increased. (Aganović and Dušek, 2007)

A common condition associated with insulin resistance is type 2 diabetes mellitus; insulin resistance predates diabetes development. The defect exists in muscle cells and adipocytes, where impaired GLUT-4 results in impaired insulin-mediated glucose transport. Impaired glucose tolerance and diabetes develop as the β-cells fail to compensate for the insulin resistance. Function of β-cells deteriorates as glucose levels rise, reducing glucose sensitivity and worsening hyperglycemia. The islets cells mass is usually reduced in size in diabetic patients. (Wilcox, 2005) There are several causes for development of severe insulin resistance, which are shown in the table (Table 3) below. (Church and Haines, 2016)

Causes of Severe Insulin Resistance (3)

Syndromes of severe insulin resistance

- Type A, due to defects in the insulin receptor gene
- Type B, due to insulin receptor antibodies
- Type C, cause unknown (also known as HAIR-AN [Hyperandrogenism, Insulin Resistance, and Acanthosis Nigricans] syndrome)

Medications

- Glucocorticoids
- Atypical antipsychotics
- Calcineurin inhibitors
- Protease inhibitors
- Oral contraceptives

Endocrine disorders

- Acromegaly
- Glucagonoma
- Thyrotoxicosis
- Cushing's syndrome
- Pheochromocytoma

Table 3. Causes of Severe Insulin Resistance.
Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4833480/

### iii. Diabetic dyslipidemia

Dyslipidemia is an endocrine and metabolic disorder related to genetic predisposition; however, there are other factors, including obesity, diet, and lifestyle that play a role in acquiring dyslipidemia. Lipids are compounds that are insoluble in aqueous media; they include cholesterol, phospholipids, and triglycerides. Cholesterol and triglycerides are important to the body, but due to their insolubility, they should be packed into lipoproteins to facilitate their transport. The lipoprotein molecule consists of cholesteryl esters, triglycerides, fatty acids, and fat-soluble vitamins. The outer layer of lipoprotein molecule is polarized and helps with lipid transport into the blood. There is a hydrophilic layer of apolipoproteins, which are recognized by enzymes. Apo B induces the formation of VLDL in the liver.

HDL, a lipoprotein considered as “good cholesterol”, collects the abundant glycerol, cholesterol, and fatty acids from the blood and returns them back to the liver. This is called reverse cholesterol transport, unlike the VLDL activity.

Dyslipidemia can be classified into;

- Primary dyslipidemia- caused by monogenic or polygenic mutations. It is usually associated with overproduction of lipoproteins, or a decreased clearance from the circulation.
- Secondary dyslipidemia- they are disorders that can be subdivided into different grades of severity, with no genetic disorder.
    a) Hypercholesterolemia- associated with hyperthyroidism, obstructive liver disease, nephrotic syndrome, and the use of certain drugs; cyclosporine, thiazides.
    b) Hypertriglyceridemia- associated with obesity, diabetes mellitus, and the use of drugs; beta-blockers, glucocorticoids.
    c) Low HDL- associated with obesity, diabetes mellitus type 2, rheumatoid arthritis, and drugs such as beta-blockers. (Devi and Jyothi, 2017)

Dyslipidemia is also known as increased in free fatty acids flux, increased triglycerides levels, low HDL cholesterol levels, increased LDL values, and elevated apolipoprotein B values. It is a risk factor for cardiovascular diseases; it has been connected with both myocardial infarction and stroke in patients with metabolic syndrome. The increase of the free fatty acids is due to the inability to integrate to triglycerides by the adipose tissues; consequently, there is reduced fatty acids trapping and retention by the adipocytes. This results in an increased flow of the free fatty acids back to the liver. The increased flux of the free fatty acids to the liver stimulates triglycerides synthesis from the hepatocytes, which stimulates the secretion of VLDL containing triglycerides, and the apo-B synthesis in the liver.

Adipose tissue has been shown to be an endocrine organ producing adipocytokines, including leptin, angiotensin, TNF-α, IL-6, and transforming growth factor β. These proteins are all increased in the state of obesity, and can induce diabetes or obesity related insulin resistance. (Kolovou and Anagnostopoulou, 2005)

The dyslipidemia of type 2 diabetes mellitus is associated with high triglycerides levels, and low HDL levels, as well as the presence of LDL particles. These factors contribute to the

development of atherosclerosis before diagnosis of diabetes mellitus. Usually, in type 1 diabetes mellitus, in the presence of hypertriglyceridemia, HDL levels are normal; unless the control of glycaemia is poor, or there is a case of nephropathy (Schofield et al., 2016). HDL triggers the secretion of insulin from pancreatic β-cells, and enhances glucose uptake from skeletal muscles; therefore, low levels of HDL are associated with cardiovascular diseases. In type II diabetes, HDL levels become dysfunctional, and therefore, alterations in paraxonase 1 (PONS1) and lipoprotein associated phospholipase A2 occur (Femlak et al., 2017). LDL levels are elevated in patients with diabetes due to the reduced catabolism of LDL, which leads to a prolonged duration of LDL in plasma; promoting lipid deposition in arterial walls (Vergès, 2015).

In the below figure, Figure 1, the alterations in free fatty acids metabolism is associated with the pathophysiology of both hyperglycemia and dyslipidemia (Kirk and Klein, 2009).

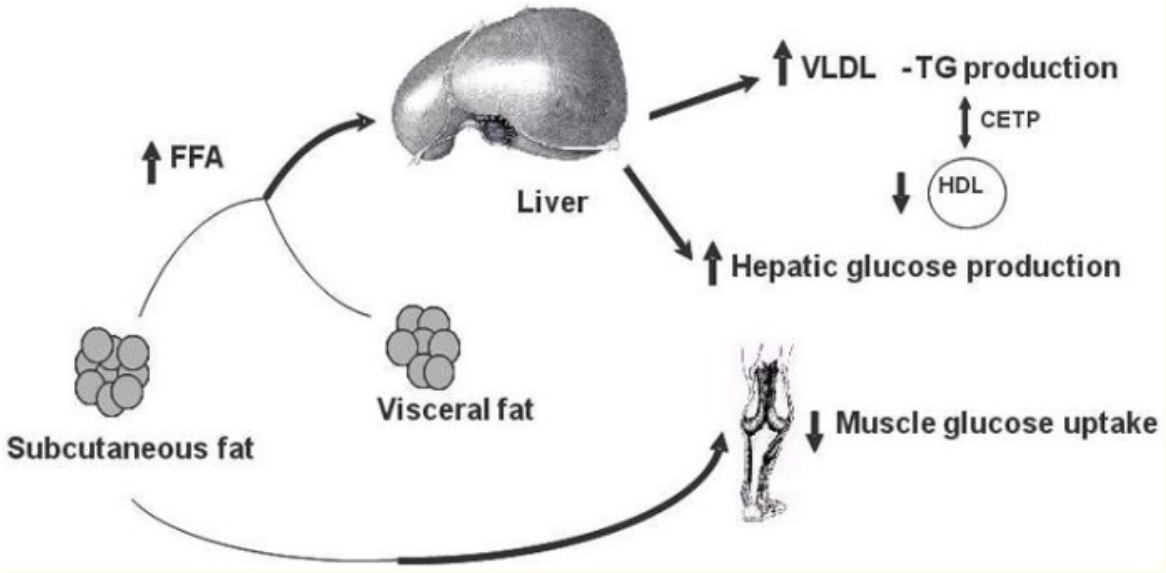


Figure 1. Physiological interrelationship between fatty acids metabolism, insulin resistance, and features of the cardiometabolic syndrome.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2859214/

## iv. Arterial Hypertension

Arterial hypertension is an important symptom of metabolic syndrome, with many complicated underlying mechanisms to its development. Metabolic syndrome is present in one third of patients with hypertension, as it is a classical diagnosis of metabolic syndrome. Visceral obesity and insulin resistance are associated with levels of blood pressure.

Visceral obesity plays a role in the development of hyperglycemia, hyperlipidemia, and hypertension. Adipose tissues have been found to secrete adipocytokines, which induce not only diabetes and insulin resistance, but also hypertension (Yanai et al., 2008). The renin angiotensin system (RAS) is activated in arterial hypertension (Re, 2009). Adipocytes have been found to regulate the production of RAS components, angiotensin I and II, where they have localized receptors on adipocytes. Angiotensin II has been found to regulate the adipocyte growth and differentiation, the lipid metabolism, and the release of adipokines (Cassis et al., 2008). Given that angiotensinogen is synthesized by the adipocytes; thus, increasing the secretion of angiotensinogen will consequently lead to an increase in angiotensin I by renin release, and secondarily the release of angiotensin II. An increase in sympathetic activity could also lead to an increase in renin activity. There is an increase in the renal tubular reabsorption of sodium due to the elevated angiotensin II secretion, as well as stimulation in the synthesis of aldosterone, the sodium-retaining hormone (Re, 2009).

In the figure below (figure 2), the obesity-induced hypertension is shown (Kotsis et al., 2010).

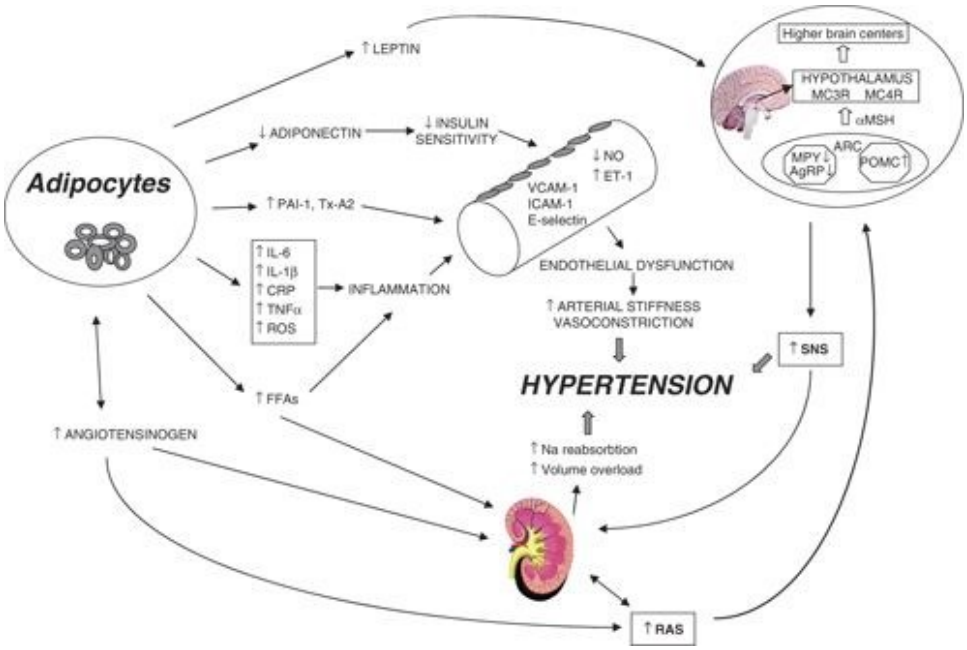


Figure 2. Mechanism of obesity-induced hypertension.

Source: https://www.nature.com/articles/hr20109/figures/1

Being the main pathophysiological feature of metabolic syndrome, insulin resistance is connected with hypertension via several mechanisms. Insulin has an anti-natriuretic effect by stimulating the renal sodium reabsorption; thus, the anti-natriuretic effect is increased in patients with insulin resistance, leading to the development of hypertension in metabolic syndrome.

Some *in-vitro* studies show the relation between insulin and endothelin-1 stimulation, as well as its action on the vascular walls. Endothelin-1 is an amino acid causing vasoconstriction; its levels increase in the plasma when there are high serum insulin levels. Endothelin-1 receptor antagonist has been shown to decrease blood pressure in animals with insulin resistance and hypertensive cases; thus, proving the significance of endothelin-1 in hypertension pathogenesis.

An increase in inflammatory mediators has also shown to be linked with hypertension. TNF-α is linked to the pathophysiology of hypertension by stimulating the production of endothelin-1 and angiotensinogen. Serum TNF-α is shown to be related with systolic blood pressure, and monocyte secretion of TNF-α has been seen from hypertensive patients.

Interleukin-6 (IL-6), a cytokine which mediates inflammatory responses, stimulates the sympathetic nervous system, which results in hypertension. Moreover, IL-6 administration leads to increased heart rate and norepinephrine levels. Furthermore, IL-6 has also shown to increase angiotensinogen and angiotensin II plasma levels; which all lead to the development hypertension. (Yanai et al., 2008)

## V. Clinical complications of Metabolic Syndrome

Metabolic syndrome can lead to a number of complications; these include atherosclerosis, along with other cardiovascular disorders, neuropathy, arthritis, cognitive impairment, and colorectal cancer. (Nerkar et al. 2015)

Systemic inflammation is the link between metabolic syndrome and atherosclerosis. Central obesity in patients with metabolic syndrome and atherosclerosis has been associated with systemic inflammation, overproduction of reactive oxygen species (ROS), TNF-α, and IL-6. Central obesity is also connected with atherosclerosis by both insulin resistance, and dysregulation of adipocytokine production. The disturbance of adipocytokine occurs due to the methylation of different genes, including IL-6, TNF-α, GLUT-4; which are responsible for inflammation and oxidative stress. Insulin resistance is affected by the proinflammatory outcomes, which leads to microvascular and macrovascular alterations; influencing the progression of atherosclerosis. In hyperlipidemia, cholesterol concentrates in macrophages; leading to an inflammatory response. (Fg et al., 2017) Complement component 1 (C1q) is a protein that plays a dual role in atherosclerosis. Activation of the complement causes inflammation, as well as promoting disease progression. However, in the early stages of the disease, it acts as an atheroprotective. (Ho et al., 2016) It increases anti-inflammatory cytokines and decreases proinflammatory cytokines; reducing disease markers such as cholesterol and triglycerides. (Fg et al., 2017)

Neuropathy is a common condition of metabolic syndrome, with significant morbidity especially in the elderly. Hyperglycemia, a component of metabolic syndrome, has been associated with neuropathy. Thus, treating hyperglycemia has been shown to decrease neuropathy in patients with type I diabetes mellitus. However, in patients with type II diabetes, controlling glucose has an insignificant effect in treating neuropathy, proving other factors that

might be causing nerve injury in these patients. Other mechanisms of nerve injury include fat deposition in nerves, extracellular protein glycation, mitochondrial dysfunction, and oxidative stress. (Callaghan and Feldman, 2013) Metabolic syndrome associated hyperglycemia and hyperlipidemia cause cellular damage by reactive oxygen species (ROS) production, which cause mitochondrial dysfunction, as well as endoplasmic reticulum stress; these lead to direct neuronal damage. (Nerkar et al., 2015)

Rheumatoid arthritis (RA) is a chronic autoimmune disease associated with pain, deformity of joints, as well as systemic inflammatory response in lungs, heart, and kidneys. (Lee et al., 2016) It could be caused by a variety of genetics and lifestyle choices, such as smoking. Patients with rheumatoid arthritis are prone to atherosclerosis as well as its complications. Cardiovascular diseases, as well as myocardial infarction, have been shown frequency in rheumatoid arthritis patients, with chronic inflammation, specifically autoimmune systemic inflammatory response, as a major contributor to both metabolic syndrome and atherosclerosis. Metabolic syndrome has been shown to occur in up to 45% of rheumatoid arthritis patients. Patients with RA are more likely to have low levels of HDL cholesterol, high levels of triglycerides, and increased levels of inflammatory markers such as C-reactive protein (CRP). Proinflammatory cytokines, such as TNF-α and IL-1 are produced by the immune cells activated in the atherosclerotic plaque; inducing the production of IL-6, CRP, fibrinogen, and serum amyloid A. Chronic inflammation of CRP leads to uncontrollable inflammation, causing increase risk of cardiovascular diseases. (Cojocaru et al., 2012) The proinflammatory cytokines are secreted into the systemic circulation, and increase the risk of insulin resistance by acting on adipose tissues, skeletal muscles, and the liver. (Lee et al., 2016)

Metabolic syndrome has also been associated with cognitive dysfunction; having a negative impact on cognition. Medical factors such as type II diabetes mellitus, cardiovascular diseases, silent brain lesions, and MRI findings have been controlled; and metabolic syndrome has been found to be linked to memory deficits, processing speed, and overall intellectual functioning. Potential explanatory factors for metabolic syndrome effect on the brain may include neuroinflammation, oxidative stress, abnormal brain lipid metabolism, and impaired vascular reactivity. Impaired cerebrovascular reactivity and increased carotid stiffness has been reported in adults suffering from metabolic syndrome. The carotid artery is the main blood supply to the central nervous system; thus, the carotid atherosclerosis has been linked to

cognitive impairment as well as brain atrophy. Endothelial dysfunction as well as carotid stiffness has been found in children and adult patients of not only metabolic syndrome, but also patients with obesity, hypertension, and type II diabetes mellitus; especially in patients with uncontrolled type II diabetes mellitus, where they suffer from more carotid alterations. (Yates et al., 2012) Other studies have found that vascular risk factors, including glucose intolerance, insulin resistance, central obesity, lipid abnormalities, and hypertension play a role in the pathogenesis of dementia and Alzheimer's disease. Cholesterol, being a main component of myelin and cell membrane, maintains the function of cerebral tissues. Cholesterol disorder decreases the membrane fluidity of the hippocampus, a memory center in Alzheimer dementia. Beta amyloids destroy cerebral tissues cell structure; and cholesterol has been found to reduce beta amyloid formation in the hippocampus neurons, therefore, delaying Alzheimer's onset. Hypertriglyceridemia causes arteriosclerosis by increasing the viscosity of the blood and lowering cognitive functions. Hypertension has also been found to cause cerebrovascular diseases and cerebral infarction. It also decreases nicotinic receptors sensitivity to acetylcholine. Chronic high blood sugar level inhibits the secretion of cerebral acetylcholine, and causes loss of neurons, leading to decrease in cognitive functions. (Oh et al., 2011)

Colorectal cancer accounts for 13% of new cancer cases in Europe, and it is the mostly diagnosed cancer. (Trabulo et al., 2015) Studies have shown a link between hyperinsulinemia and colorectal cancer risk. Adipocytes, in obesity, play a role in colorectal cancer pathogenesis. Adiponectin, a protein hormone secreted by adipocytes, regulates glucose metabolism and breakdown of fatty acids, as well as sensitizing peripheral tissue to insulin. There is a decrease in plasma adiponectin concentrations as visceral fat accumulates. Adiponectin also inhibits the macrophages secretion of TNF-α, and therefore, stimulate angiogenesis by the destructive action on endothelial cells. As adiponectin levels in plasma decrease, tumorigenesis mediated by TNF-α is triggered. Insulin and insulin-like growth factor 1 (IGF-1) trigger mitogenesis and inhibit apoptosis in endothelial cells; leading to tumorigenesis. Increased secretion of vascular endothelial growth factor (VEGF) from the IGF-1 leads to angiogenesis, which plays a role in tumor growth and metastasis. Moreover, insulin inhibits insulin-like growth factor binding protein 1 (IGFBP-1) transcription, which increases IGFs in plasma. The high levels of IGFs in the circulation lead to increased cell proliferation and inhibition of apoptosis; which causes colorectal cancer formation. Therefore, in metabolic syndrome, insulin, IGF-1, and adiponectin

have tumorigenic actions; as well as adiponectin inhibition effect on TNF-α level, which all contribute to an increased risk of colorectal cancer. (Nerkar et al., 2015)

## VI. General therapy of Metabolic Syndrome

Metabolic syndrome is a chronic, inflammatory state with serious systemic side effects; therefore, identification and management of patients is important to reduce the risk of development of diseases. There are effective preventative non-pharmacological approaches that include lifestyle changes, weight loss, diet, and exercise.

There are some therapies for weight loss; including calories restriction, increased physical exercise, and in the appropriate patients, weight reducing drugs can be given. It is recommended a goal for weight loss with a 10% reduction in the first six months, and then a continued weight loss until BMI less than 25 is reached. Minor weight loss of 5-10% could influence blood pressure, blood glucose and insulin levels, and triglycerides levels, as well as increase HDL levels. Regular exercise has shown an effect on abdominal fat weight loss, and to prevent regain of the weight lost. (Kaur, 2014) Studies have shown that exercise and physical activity has an effect in preventing atherosclerotic mortality and morbidity. There are some mechanisms that play a role in the protective effect of physical activity; they may be related to the direct action of physical activity on the heart by increasing myocardial oxygen supply, as well as improving myocardial contraction and electrical stability of the heart.

Diet changes has many beneficial effects; carbohydrate consumption has an effect on weight gain, diabetes mellitus type II, and obesity and therefore, it is important to recognize the problems that can occur due to the wrong intake of carbohydrates, such as simple sugars, while emphasizing the importance of including the right complex carbohydrates, such as potatoes and bread, into the diet. Fats, including oils, fats and waxes, comprise 30% of daily energy intake; however, it is important to clarify the saturated fats promote dyslipidemia and atherogenesis, and therefore, the required fat intake should consist of unsaturated oils, such as vegetable oils, which prevent serious disorders such as atherogenesis and hypertension. In the following figure, Figure 3, the role of non-pharmacological approach to metabolic syndrome is explained briefly. (Pitsavos et al., 2006)

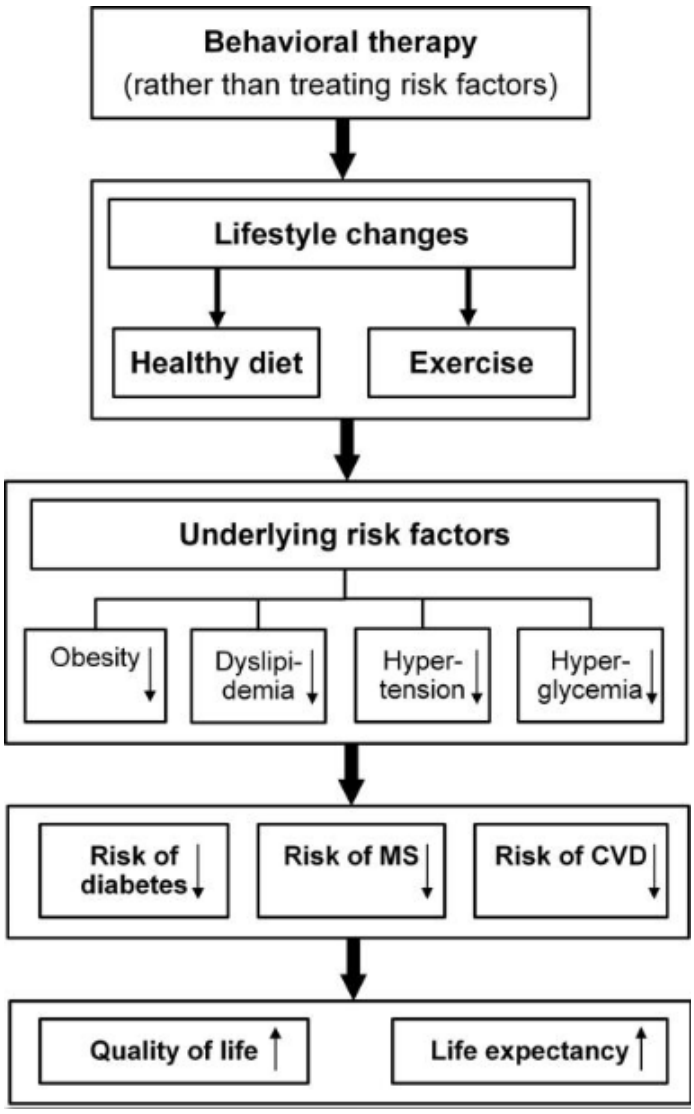


Figure 3. A conceptual model for lifestyle changes and better health.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1783583/

Weight reducing drugs are recommended for patients with BMI of at least 30, along with other comorbidities that influence their weight gain. These pharmacological groups of drugs include two classes; appetite suppressants, and inhibitors of nutrients absorption. Phentermine derivatives, such as Fenfluramine and sibutramine are some appetite suppressants. They are taken in the morning to suppress the appetite for the afternoon and evening. Studies have shown that sibutramine induced weight loss has led to reductions in the risk factors associated with

metabolic syndrome. The treatment with such drugs has an effect on the visceral fat by reducing it, improves the lipid levels, and affects glycosylated hemoglobin and uric acid by decreasing their concentration. Another class of drugs is the inhibitor of nutrient absorption, Orlistat. It works by preventing the absorption of up to 30% of the fat consumed; therefore, it should be taken at the time of consumption. However, it comes along with side effects that may include flatulence and oily leakage into the stool.

Generally, the side effects caused by these anti-obesity drugs are unpleasant, which may lead to non-compliance and low tolerance, especially in long term usages (Kaur, 2014). Phentermine has sympathomimetic actions similar to amphetamine, is approved by the FDA only for the short-term use due to its adverse effects that include dry mouth, insomnia, palpitations, and increased blood pressure. Fenfluramine and its isomer dexfenfluramine, the serotonergic drugs that suppress the appetite, have been withdrawn by the FDA in 1997 due to heart valve damage in women taking the therapy. Sibutramine was approved in 1997; however, it showed adverse effects such as headache, dry mouth, insomnia, and constipation. It has also been found to increase heart rate and blood pressure. In long term treatment, Sibutramine also increased the risk of non-fatal myocardial infarction as well as stroke; and therefore, it has been withdrawn by the FDA in 2010. Rimonabant, a suppressor of the endocannabinoid system blocks the cannabinoid type 1 receptor ($CB_1$), which induces anorexigenic and thermogenic effects. It was approved by EMA in 2006; however, psychiatric adverse effects such as anxiety, depression and suicidal attempts have occurred, and therefore, the suspension of Rimonabant by EMA has been recommended in 2008. It has never been approved by the FDA as well. Orlistat has common side effects such as flatulence, diarrhea, bloating, and abdominal pain. It also interferes with the absorption of the fat-soluble vitamin (A, D, E, K). Orlistat was approved without a conduction of long-term trial on safety. The FDA has been notified of certain liver injuries reported; however, the FDA regarded the risk as low, and allowed the continuation of Orlistat (Cheung et al., 2013).
Pharmacological approaches are usually considered when the risk factors are not reduced with the preventative measures and other non-pharmacological approaches (Kaur, 2014). First line pharmacological therapy for cardiovascular heart diseases influencing metabolic syndrome includes hypolipidemic treatment, hypertension treatment, and type II diabetes mellitus treatment.

## i. Hypolipidemic Treatment

The primary goal in hypolipidemic treatment is reducing the LDL cholesterol levels; however, if triglycerides level is higher than 28 mmol/L (500 mg dL), then lowering TG levels takes priority over LDL lowering. After both levels are maintained, increasing HDL cholesterol levels is the next target. HDL levels are increased by weight loss and physical activity.

### a. Statins

One of the main recommended drugs for LDL lowering are statins, also known as hydroxymethyl glutaryl coenzyme A reductase inhibitors. HMG-CoA reductase is the key enzyme in the cholesterol synthesis that helps in the conversion of HMG-CoA to Mevalonate; which is an early step in cholesterol biosynthesis. Therefore, inhibition of HMG-CoA reductase by statins lowers the cholesterol levels in the blood, as well as lipoproteins containing Apo-B in hypercholesterolemic patients. Statins influence the secretion of both LDL and VLDL levels in hyperlipidemic patients, as well as decreasing triglycerides levels by inhibiting intracellular cholesterol biosynthesis. Atorvastatin has been shown to decrease LDL levels, as well as improve hepatic lipoprotein production. Simvastatin, another member of the statins, has been shown to decrease LDL levels, and raise HDL plasma concentration in the long term (Binesh Marvasti and Adeli, 2010). In hypercholesterolemia, HDL was found to be raised approximately 4-10%. Although the changes in levels are not dose-related, the increase in HDL was found to be proportional to the reduction in Apo-B lipoproteins (McTaggart and Jones, 2008). Simvastatin and Rosuvastatin were found to increase HDL concentrations compared to Atorvastatin; however, the HDL increase was independent of the LDL decrease effects of statins (Barter et al., 2010). Rosuvastatin is a new statin member with high efficacy in reducing LDL levels compared to other statins, due to its high binding ability to HMG-CoA reductase. This high binding of Rosuvastatin causes a stronger inhibition of the enzyme, which leads to a higher therapeutic effect. Rosuvastatin also has a longer half-life compared to the other statins, with a higher selectivity for hepatic cells; as they are the main site of cholesterol synthesis. Statins are also used in primary and secondary prevention of other cardiovascular diseases. (Binesh Marvasti and Adeli, 2010) Rhabdomyolysis is the most serious adverse effect occurring from the use of

statins; however, it occurs very rarely (about 0.1% or less). Other adverse effects may include derangement in liver functions, and diabetogenic potential. They also interact with drugs with have an influence on cytochrome P450 group. Therefore, statins are considered a safe group for therapy for most patients; however, patients with co-morbidities, polypharmacy, or alcohol abuse are at an increased risk of severe side effects from the long-term use of statins. (Ramkumar et al., 2016)

### b. Cholesterol Absorption Inhibitors

Another group of hypolipidemic agents are cholesterol absorption inhibitors; which are a class of drugs that decrease the absorption of cholesterol from the small intestine, and therefore decrease the cholesterol reaching the liver; which allows more cholesterol to be removed from the blood. (Binesh Marvasti and Adeli, 2010) Cholesterol absorption inhibitor, Ezetimibe, targets the uptake at the jejunum enterocytes. It primarily targets the Nieman Pick C1 like 1 transport protein. However, Ezetimibe has not shown to have an effect on triglycerides or fat-soluble vitamins. It is metabolized through glucoronidation in the liver, then it is excreted into the bile back to the intestinal lumen, finally, it is excreted into the feces. Because Ezetimibe undergoes enterohepatic circulation, it has a long half-life of 22 hours. Ezetimibe is not metabolized by Cytochrome P450, and therefore, does not interact with other medications such as statins, fibrates, amiodarone, or amlodipine. (Phan et al., 2012) At a given dose of 10 mg/day, studies have shown a reduction in LDL cholesterol levels by 20-25%; either by monotherapy of Ezetimibe, or in combination with statins. It is advised to use when a statin is insufficient to reach LDL level of 5 mmol/L (100 mg/dL), Ezetimibe should be added to the therapy alongside the statin. Ezetimibe, however, was not shown to have similar effects as statins on atherosclerotic risk factors; such as anti-inflammatory, antioxidant, and effects on nitric oxide bioavailability, yet it is still prescribed alongside Statins, in the treatment of hypercholesterolemia. (Binesh Marvasti and Adeli, 2010)

### c. Fibrates

Fibrates are another type of hypolipidemics for reduction of triglycerides, VLDL, as well as increasing HDL. They bind and activate Peroxisome Proliferator-Activated Receptor α (PPARα), regulating gene expression, and therefore influencing the metabolism of fatty acids and lipoproteins in the liver, muscles, and kidneys. (Shipman et al., 2016) The activation of PPARα leads to increased lipolysis, as well as increased plasma clearance of atherogenic triglyceride lipoproteins. The activation, as well, increases synthesis of ApoAI and ApoAII, which are major proteins in HDL. Treatment with gemfibrozil leads to an increase in LDL size, and decrease in LDL by 5%, while increasing HDL by 10%; similarly, treatment with finofibrate, ciprofibrate, and bezafibrate have shown equal effects on LDL levels.

There are common side effects associated with fibrates therapy; including gastrointestinal adverse effects, flatulence, nausea, diarrhea, constipation, dermatological effects such as pruritus, and urticaria. Musculoskeletal adverse effects such as pain and cramps, as well as neurological effects such as headache and dizziness, are less common. (Goldenberg et al., 2008) Adjusting the dose is recommended in renal insufficiency, and they are contraindicated in liver and gallbladder diseases. If fibrates are used alongside statins, Fenofibrate is the recommended fibrate to use, as gemfibrozil has a higher risk of myositis. Fenofibrate binds to proteins and may interact with Warfarin, and therefore, levels should be closely monitored.

### d. Omega-3 Fatty Acids

Omega-3 fatty acids are also FDA approved for treatment of severe hypertriglyceridemia, greater than 1000 mg/dL, and LDL levels are lowered by 20%-50%. The triglyceride lowering is usually dose related in the case of omega-3 fatty acids supplements, with a required dose of 3-4 grams per day. Side effects to such supplements may occur with high doses, such as gastrointestinal discomfort.

### e. Niacin

Niacin is also used in the treatment of lipid and lipoprotein abnormalities. It reduces triglycerides by 15%-40%, by reducing triglyceride synthesis. (Karanchi and Wyne, 2019) Several adverse effects have been reported with the use of Niacin; these include, nausea and vomiting, flushing, epigastric burning, and jaundice. (RIVIN, 1962) Flushing was found to be reduced by using aspirin and starting with a low dose. Crystalline, immediate-release (IR) niacin is absorbed rapidly by the body, reaching peak levels in 30-60 minutes, causing immediate flushing to the patients. Sustained-release niacin formulations are new formulations intended to reduce the flushing, due to the delay niacin absorption during treatment. However, sustained-release niacin has been found to cause hepatotoxicity. Another newer extended-release niacin formulation has shown to reduce flushing side effects. It could also be safely combined with statins to lower LDL and TGs, with no risk of flushing as a side effect (Kamanna et al., 2009). Niacin is also contraindicated in patients with peptic ulcer. (Karanchi and Wyne, 2019)

## ii. Hypertension Treatment

Hypertension occurs when systolic blood pressure is ≥140 mmHg and diastolic blood pressure is ≥90 mmHg. It is considered a strong risk factor for major cardiovascular diseases, and usually it is asymptomatic, which increases exposure time to the disease, leading to more cardiovascular complications. Hypertensive therapy reduces the complications of cardiovascular diseases such as heart attack, stroke, and heart failure (Freeman et al., 2017).

### a. ACE Inhibitors

The renin-angiotensin system (RAS) is known for regulation of cardiovascular functions, as well as hydromineral balance. Overactivity of the RAS has been found in obese patients, as well as in hypertensive patients. Therefore, drugs that have an effect on Angiotensin II synthesis-also known as angiotensin converting enzyme inhibitors, or angiotensin II receptor blockers-have shown to be effective in treatment of hypertension. After synthesis of Angiotensin-II, it either binds to receptors in the target areas, such as muscles, kidneys, adrenal cortex, and brain,

or it is degraded to yield further products, such as Angiotensin III and Angiotensin IV, which have an effect on memory and learning (de Kloet et al., 2010).

In the below figure, Figure 4, the renin-angiotensin system pathway is explained (Perlot and Penninger, 2013).

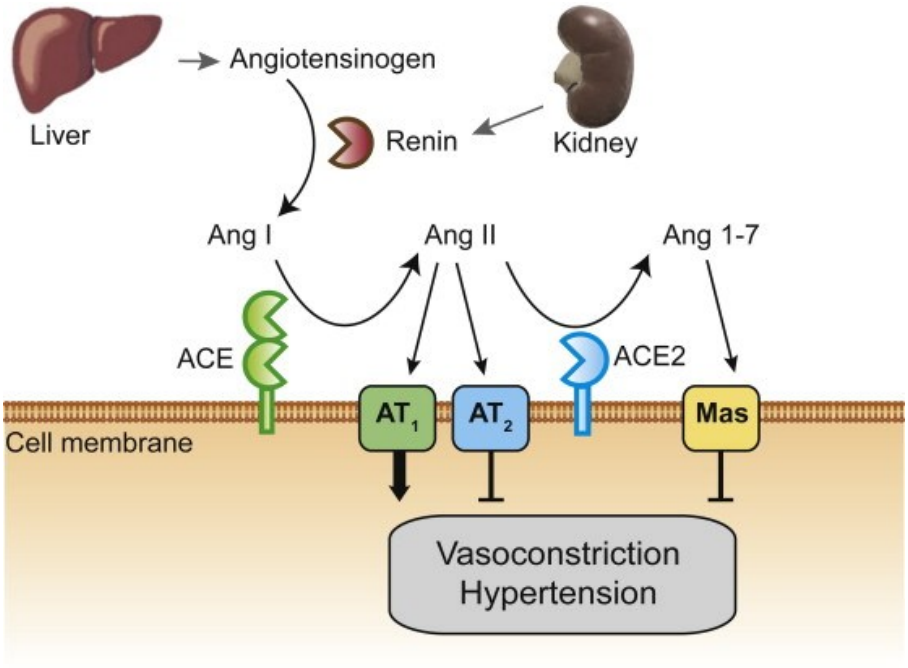


Figure 4. The classical renin-angiotensin system.

Source: https://www.sciencedirect.com/science/article/pii/S128645791300155X

Common generic names for ACE inhibitors are Captopril, Perindopril, Ramipril, Enalapril, and Lisinopril, and for ARBs –also known as sartans – are Candesartan, Valsartan, Telmisartan, and Losartan. (*[Table], Common Generic and Brand Names for ACE Inhibitors and ARBs, 2010*)

All the ACE inhibitors are administered per oral, except for Enalapril, which is given intravenously. In patients with heart failure, salt-depleted patients, and renal impaired patients, the dose should be decreased. Almost all the ACE inhibitors are prodrugs, which are activated in the body after ingestion, except Lisinopril and Captopril, which are not prodrugs, and do not require activation. The activation of the prodrugs usually occurs in the liver, therefore, when a patient has hepatic insufficiency, a non-prodrug ACE inhibitor is recommended to prescribe.

Adverse effects may occur in patients on ACE inhibitors therapy, they may include dry cough – in which the patient decides if they can tolerate it – since there is no treatment for the cough.

Another significant adverse effect to occur is angioedema; it can occur anywhere in the body including the tongue, glottis and larynx, which may compromise the patient's ability to breathe, due to the airway obstruction. In this case, diphenhydramine or methylprednisolone may be used until the edema effect subsides.

Renal failure has also been reported in patients taking ACE inhibitors; patients with already renal insufficiency are susceptible to worsening of their renal function, and therefore, constant renal function monitoring is required.

Another common adverse effect to any hypertensive medication is hypotension. Patients at risk of hypotension are patients with heart failure, ischemic heart disease, hyponatremia, and renal dialysis.

Hypokalemia is another common adverse effect that occurs due to the use of ACE inhibitors; patients at risk are patients with renal insufficiency, as well as potassium-sparing diuretics users. Usually the treatment should depend on the level of potassium, and on the kidney functions.

ACE inhibitors are contraindicated in patients with history of angioedema or previous hypersensitivity related to ACE inhibitors. They should as well not be given in pregnancy, as they may cause deformities. (Herman and Bashir, 2019)

**b. β-blockers**

β- Blockers have been used in hypertension for many years. Studies have shown that the use of β-blockers reduced cardiovascular mortality, and they are recommended as first line and second line antihypertensives.

Propranolol, a first generation β-blocker, blocks both β1- and β2 – receptors. By blocking β1- receptors, there is an inhibitory effect on myocardial contractions, causing a negative

chronotropic, dromotropic and inotropic effect. By blocking β2-receptors, there is a contraction of smooth muscles, causing bronchospasm. Second generation blockers, such as Atenolol, Metoprolol, and others, have high β1-receptor sensitivity, and are usually preferred in patients with chronic lung diseases, as well as smokers. Furthermore, Carvedilol, a third-generation agent has additional vasodilatory properties due to the α-adrenergic blockage.

The half-life of β-blockers varies from 9 minutes, such as Esmolol, to 24 hours, such as Nadolol and Penbutolol. Longer half-life drugs lead to longer action, which increases medication adherence; and therefore they are more preferred in hypertension. (Stafylas and Sarafidis, 2008)

Common adverse effects of β-blockers, specifically cardio-selective β-blockers include bradycardia, hypotension, lower exercise potential, and atrioventricular nodal block. There are other side effects that include nausea, vomiting, dizziness, headache, discomfort, fatigue, and dry mouth. There is a risk of β1-blockers administration in diabetic patients due to their ability to mask hypoglycemia induced tachycardia, which is a warning symptom for patients suffering from hypoglycemia. β- Blockers also interact with several drugs causing adverse effects; these drugs include nitrates, ACE inhibitors, and other hypertensive drugs.

β1 blockers are usually contraindicated in patients with chronic obstructive pulmonary disease and asthma. They also should not be administered to patients with fluid retention, as well as patients with heart block. (Tucker and Theetha Kariyanna, 2019)

### c. Calcium Channel Blockers

Calcium channel blockers, another type of antihypertensives, inhibit the L-gated calcium channels, and also cause vasodilation; they are being used as first and second line therapy. Calcium channel blockers are categorized into 3 categories according to their chemical structures; benzothiazepines (Diltiazem), phenylalkylamines (Verapamil), and dihydropyridines (Nifedipine, Felodipine, Amlodipine, and others). They bind to the α1 subunit, inhibiting cell excitability, and blocking calcium influx. They also have negative inotropic and chronotropic effects. (Ozawa et al., 2006)

Adverse effects may occur with calcium channel blockers usage. Constipation and bradycardia are common with Diltiazem and Verapamil, while dihydropyridines may cause lightheadedness, peripheral edema, and headache. Diltiazem and Verapamil are therefore contraindicated in patients with heart failure, because of the possibility of bradycardia and worsening cardiac output. (McKeever and Hamilton, 2019)

**d. Diuretics**

Diuretics are another class of anti-hypertensives that have been used mainly for primary, uncomplicated hypertension, as well as controlling edema. Diuretics reduce sodium reabsorption in renal tubules, which leads to an increase in sodium and water excretion. Sodium reabsorption occurs in different parts of the kidneys. The thick ascending part in Loop of Henle reabsorbs about 25% of the sodium, while the distal convoluted tubule reabsorbs about 5%. Loop diuretics (Furosemide) act on the thick ascending part in the Loop of Henle, therefore, they can inhibit the largest amount of sodium. Furosemide's bioavailability can vary; it should be taken on an empty stomach to increase absorption. It is highly bound to plasma proteins (~95%). Almost half of furosemide administered is excreted into the urine, while the rest gets metabolized in the kidneys into glucuronide. Patients with renal dysfunction show an increase in the plasma half-life of furosemide, due to low excretion. Common adverse effects of Furosemide include hypovolemia, due to electrolyte imbalance, ototoxicity, and hypersensitivity. These adverse effects are higher and more potent in cardiovascular disease patients, in patients taking non-steroidal anti-inflammatory drugs, and in the elderly. If Furosemide is administered during Warfarin treatment, Warfarin dose must be reduced due to the displacement action of Furosemide on the plasma proteins. (Oh and Han, 2015)

Thiazides are another type of diuretics which act on the distal convoluted tubule by inhibiting the sodium chloride ($Na^+/Cl^-$) co-transporter, which decrease sodium reabsorption. Consequently, the fluid loss is increased in the urine, which decreases plasma volume and extracellular fluid. The volume loss leads to decreased cardiac output, as well as decreased blood pressure. Thiazides are associated with hyperlipidemia, hyperglycemia, hypokalemia, hyperuricemia, as well as stimulation of the renin-angiotensin system. (Duarte and Cooper-DeHoff, 2010) Chlorthalidone has a longer half-life than Hydrochlorothiazide, and was found to

decrease blood pressure better, especially at nighttime. Hydrochlorothiazide, however, is available in different combination preparations, which may support adherence in certain patients.(Allan et al., 2012) Indapamide is also another thiazide diuretic with possible calcium antagonist-like activities, which may contribute to the reduction in blood pressure. (Duarte and Cooper-DeHoff, 2010) Higher doses of thiazides tend to cause more adverse effects, such as hypokalemia; however, they tend to show more reduction in blood pressure. Patients taking diuretics should be aware of sodium intake, which should not exceed 1500mg/d. (Allan et al., 2012)

## iii. Insulin Resistance, Type II Diabetes Treatment

Insulin resistance is characterized by poor response to endogenous or exogenous insulin. Some patients require insulin of >1 unit/kg/day, which are considered insulin resistant; while patients who require >2 units/kg/day are considered severely resistant patients. The causes of insulin resistance vary; they include medications such as glucocorticoids and antipsychotics use, some endocrine disorders such as acromegaly and thyrotoxicosis, and physiological causes such as stress or pregnancy. (Church and Haines, 2016)

Type II diabetes mellitus is associated with insulin resistance; it is a chronic metabolic disorder that has become an epidemic in some countries. Lifestyle and diet modifications reduce the incidence of type II diabetes mellitus, as well as maintaining a BMI of 25 $kg/m^2$.

Certain pharmacological agents have been used for the treatment of both insulin resistance, as well as diabetes mellitus type II.

### a. Biguanides

Biguanides are a group of anti-diabetics, where Metformin is the most commonly used drug, especially in overweight and obese patients. It increases insulin sensitivity, suppresses the hepatic production of glucose, as well as decreasing glucose absorption from the gastrointestinal tract. Metformin has a low incidence of developing hypoglycemia, compared to other anti-diabetics. There is, however, a risk of development of lactate acidosis with the administration of Metformin; and therefore, it should be used cautiously in elderly, and in renal impaired patients.

### b. Sulfonylureas

Sulfonylureas are other pharmacological agents used in the treatment of both insulin resistance and type II diabetes mellitus. They are a well-tolerated group of drugs; however, they stimulate the secretion of endogenous insulin, thus, hypoglycemia is a risk, especially in the elderly, with a 36% risk compared to younger patients. Glyburide, a long acting sulfonylurea, is usually avoided in elderly patients, due to the higher risk of developing hypoglycemia. On the other hand, Glipizide, a short acting sulfonylurea, is preferred in elderly.

### c. Meglitinides

Meglitinides are secretagogues, similar in action to sulfonylureas – by stimulating endogenous insulin; however, their binding sites are different. Meglitinides act on the ATP-dependent potassium channels in the pancreatic β-cells, thus stimulating insulin secretion from the β-cells. Meglitinides have a lower risk of hypoglycemia due to their rapid onset and short duration of action. They are usually given prior meals for post-prandial glucose control. Repaglinide is metabolized by the liver, thus, dose adjustment is not important in patients with renal insufficiency, as only minimal amount is excreted via the kidneys.

### d. Thiazolidinediones

Thiazolidinedione is an insulin sensitizer, consisting only of Pioglitazone now. Pioglitazone does not cause hypoglycemia and could also be used in renal impaired patients; it is also well tolerated in elderly. However, peripheral edema and fluid retention may occur, and therefore Pioglitazone should be avoided in elderly with congestive heart failure.

### e. Alpha-glucosidase Inhibitors

Alpha-glucosidase inhibitors, such as Acarbose, have not been widely used; yet, they are safe and effective. They are effective for postprandial hyperglycemia; however, they should not

be administered to patients with renal impairment. Adverse effects such as diarrhea and flatulence may occur, and thus, limit its administration.

**f. GLP-1**

Glucagon-like peptide 1 (GLP-1), such as Liraglutide and Exenatide, which are incretin-based therapy, are targeted to improve body weight control, as well as glycemic control. They could be used as monotherapy, as well as in combination with other oral hypoglycemic agents. There is no hypoglycemic risk; they may also have an effect on inflammation, sleep, and cardiovascular health.

**g. DPP-IV**

Dipeptidyl-peptidase IV (DPP IV) inhibitors inhibit the dipeptidyl peptidase enzyme, which inactivates GLP-1, increasing its active levels, and therefore improves the function and glycemic control in type II diabetes mellitus. They can be used as monotherapy, as well as in combination with other anti-diabetogenic agents such as Metformin or Insulin. They are usually well tolerated with low risk of hypoglycemia; however, they are an expensive therapy alternative.

**h. Human Insulin**

Insulin could be used as monotherapy or in combination. It comes in many injectable forms, such as short-acting, intermediate acting, or long-acting. Long-acting forms are better due to lower risk of hypoglycemia, compared to the short-acting analogues. Therapy with basal insulin could be useful in case some beta cells function still remains. (Olokoba et al., 2012) Insulin was used as the ideal therapy for insulin resistance; however, some patients could not reach the glycemic control, where others were intolerant of the adverse effects such as hypoglycemia and weight gain, and therefore, other pharmacological agents are recommended. (Church and Haines, 2016)

Type II diabetes mellitus could be prevented by lifestyle modification as well as diet control. Since there is no cure for the disease, management of diabetes should be chosen accordingly to the lifestyle of the patient. (Olokoba et al., 2012)

## VII. Latest new approaches for Metabolic Syndrome Treatment

Current therapy for metabolic syndrome is effective and shows good therapeutic results; however, there is always a need for novel techniques and approaches towards the risk factors associated with the syndrome.

### a. Ketanserin

Several new approaches have been found for treatment of hypertension. Ketanserin is a specific 5-Hyroxytryptamine (5-$HT_2$) receptor antagonist. 5-HT has a direct smooth muscle action and causes vasoconstriction, as well as stimulating the vasoactive properties of noradrenaline and angiotensin. 5-$HT_2$ subtype is specific to the vasoconstrictive action. Ketanserin has been shown to reduce blood pressure in animals and has shown efficacy when used acutely in humans (Hedner et al.). Ketanserin has also been shown to have α-adrenergic blocking effect, as well as CNS inhibitory effect and interference with the renin-angiotensin-aldosterone system; however, the antihypertensive effect of Ketanserin is not fully based on the α-adrenergic blockage. In comparison with the classic $\alpha_1$-adrenergic blocking agent, Prazosin, Ketanserin was shown to reduce the blood pressure similarly; however, there was no first dose effect of postural hypotension, tachycardia, or increased catecholamines that are usually present with Prazosin first dose administration. Moreover, in the long term therapy of Prazosin, there were no changes in the heart rate, but with Ketanserin long term therapy, heart rate was reduced. However, prolongation of the QT interval during chronic treatment of Ketanserin has been recorded; causing clinical complications due to the possible development of ventricular arrhythmias (Donnelly et al.).

According to a study of patients with mild to moderate hypertension, the blood pressure and heart rates in both standing and lying down patients have shown to decrease after Ketanserin

treatment of 40mg daily for 1 week. The patients tested did not complain of any serious adverse effects; however, some symptoms of dizziness, fatigue and lightheadedness were recorded. These symptoms usually appeared 1-2 hours after administration and were gone after continued treatment. Therefore, there has been shown significant reduction in blood pressure after administration of Ketanserin (Hedner et al.).

**b. Cromakalim**

Another novel therapy for hypertension is Cromakalim (BRL 34915); a smooth muscle relaxant that works by enhancing the potassium efflux from the cells, causing hyperpolarization of the cell membrane. Due to its vaso-relaxant effect, it has shown a decrease in blood pressure in laboratory animals. It has also been found; according to a study that Cromakalim has an inhibitory effect on the histamine induced vasoconstriction, and could be used as a bronchodilator in asthma (Arch J.R.S, et al.). According to a study, Cromakalim was compared to Nifedipine, a $Ca^{2+}$ blocking agent, and was found to inhibit the noradrenaline-induced contractions in aorta's of rabbits, in comparison with Nifedipine. The effects of Cromakalim could be antagonized by glibenclamide, an oral anti-diabetic drug, or by increasing the extracellular $Ca^{2+}$. Cromakalim was also effective in $Ca^{2+}$ - free physiological salt solution by the inhibition of $Ca^{2+}$ refilling and release from the noradrenaline-releasable $Ca^{2+}$ stores; however, Nifedipine was found ineffective (Bray et al.).

**c. Tesofensine**

A new therapy for obesity is the novel drug Tesofensine, which is a serotonin noradrenaline dopamine reuptake inhibitor. It is currently still under development, it completed Phase I and II from clinical trials. The mechanism of action is mainly due to the appetite suppression effect, as well as increasing the resting energy expenditure. According to Phase II trials, it showed weight loss effects compared to other anti-obesity drugs. It is currently in Phase III of clinical trials; however, the adverse effects may be a drawback. These include dry mouth, headache, insomnia, gastrointestinal effects, and an increase in blood pressure and heart rate.

Another emerging therapy for obesity is the focus on receptor-interacting-protein 140 (RIP140); which is a nuclear hormone co-repressor that regulates fat accumulation. It interacts with other nuclear receptors such as estrogen, thyroid hormone and retinoic acid receptors. Silencing the RIP140 in animals results in long lasting weight loss, as well as increased metabolic rate. It is still being developed for treatment against obesity and type II diabetes mellitus.

**d. CDDO-Imidazole**

In addition to the previous emerging therapies, there is an inhibitor of adipogenesis; CDDO-Imidazole, which is currently still in clinical trials. It activates the nuclear factor (erythroid-derived 2) - like 2 (NFE2L2); which is a transcription factor that regulates the expression of antioxidant proteins to protect again oxidative damage. Activating the NFE2L2 results in increased mitochondrial biogenesis, reduced adipogenesis, as well as increased energy metabolism. This drug, in rodents, has been shown to reduce body weight and body fat, as well as diminishing hepatic lipid accumulation. (Martin et al., 2015)

**e. Technosphere Insulin**

There are a few new approaches to the treatment of insulin resistance, and type II diabetes. Technosphere insulin; a novel formulation of regular human insulin, is designed for pulmonary administration of insulin through inhalation. Technosphere is prepared by loading human insulin onto micro particles of fumaryl diketopiperazine (FDKP), which is a new excipient. (Rave et al., 2008) the Technosphere particles have high porosity, as well as high surface area for adsorption of other drugs; the Technosphere insulin powder is made of insulin that is adsorbed onto the Technosphere particle with a size suitable for deep lung delivery. FDKP drives the diffusion across the pulmonary membranes after the Technosphere particles dissolve and cause a high concentration of insulin. FDKP may also act as a penetration enhancer by dilating the tight junctions and opening up paracellular pathways between cells to enhance absorption. (Angelo et al.. 2009)

Technosphere insulin has been compared with subcutaneous regular human insulin, which showed a rapid onset of action, and short duration of the inhaled form. The maximum

serum insulin concentration occurred after almost 10-14 minutes of inhalation, and the major glucose-lowering effect occurred after almost 3 hours of administration. Variability in the insulin effect depends on the variability of the pharmacokinetics (absorption rate) and pharmacodynamics (metabolic response) of the insulin. The subcutaneous insulin absorption depends on many factors such as blood flow at the area of injection, the injection site, the depth of the injection, fat and other connective tissue present at the injection site, temperature affecting blood flow, and the physicochemical properties of the insulin injected. However, the inhaled insulin has decreased the insulin variability; as insulin is easily and faster absorbed from the pulmonary tissues. The blood flow in the lung's epithelium is more homogenous, in comparison to the subcutaneous tissue, which allows faster absorption of the insulin. There has been no severe adverse effects reported; most patients, however, complained of cough, which is a common phenomenon with most of inhaled drugs. (Rave et al., 2008)

### f. Insulin-chitosan Complex

Another new strategy towards oral insulin is the insulin-chitosan complex; which is based on a nanolayer encapsulation of insulin in chitosan. The aim of this new strategy is based on the unpredictable release and burst of insulin in the intestine, from the ordinary oral formulation, which increases hypoglycemia risk. The chitosan/heparin multilayer coatings are deposited onto the insulin-chitosan nanoparticle complex; in the presence of polyethylene glycol (PEG), which prevents insulin particles from being partially dissolved during the layer deposition, as well as promoting the retention of the precipitated insulin; increasing the capsule loading capacity. This leads to a sustained-release formulation, where the nanolayer encapsulation leads to increased stability, and decreased solubility at acidic pH. Chitosan is a naturally occurring polysaccharide, which enhances bioadhesive properties, as well as transmucosal absorption of insulin. The mucoadhesive property of chitosan extends the contact time and promotes cellular permeability. In the figure below, Figure 5, the chitosan/heparin coating is explained.

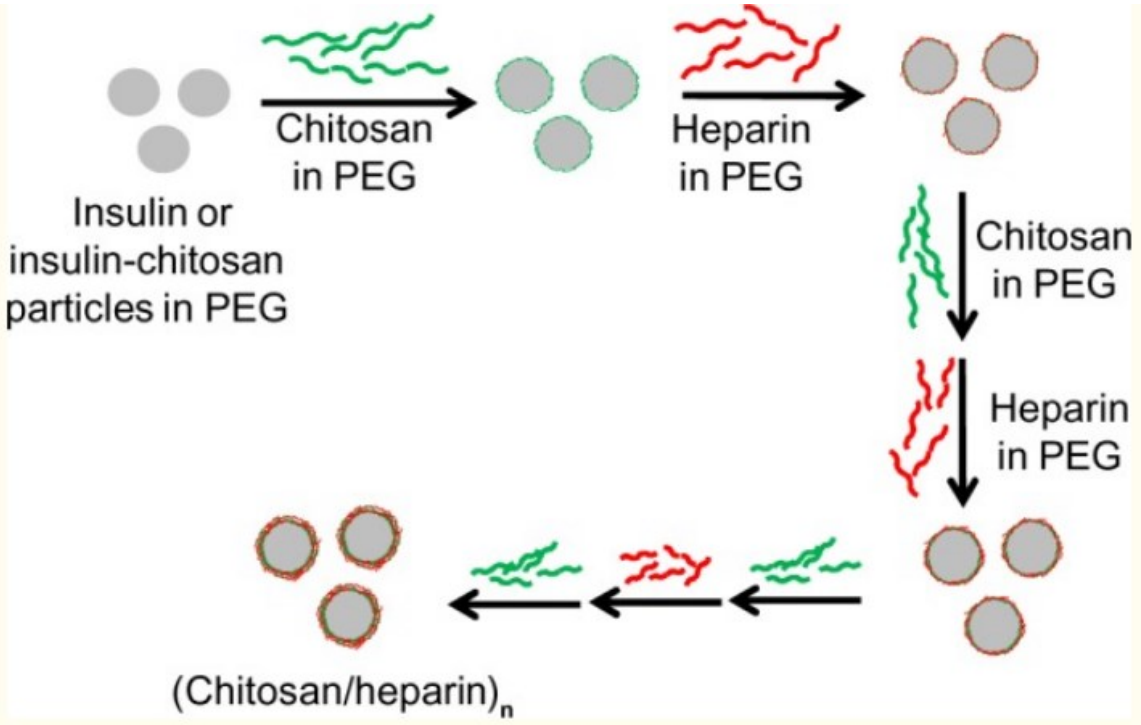


Figure 5. Scheme of nanocoating of insulin or insulin-chitosan micoparticles in the nonengineered polysaccharide capsules.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4014370/

In the typical release experiment, the insulin-chitosan is coated seven times by the chitosan/heparin layers, with chitosan as the outermost layer. The diameter of the insulin-chitosan microparticle was almost 1µm, which showed no difference compared to the nonencapsulated insulin; however, the insulin-chitosan microparticles were more solid with a crystal-like appearance, compared to the insulin particles which are loosely formed. The nanolayer encapsulation is a novel strategy, which helps the fast reduction of blood glucose, preventing sudden hypoglycemia, and making the formulation safer for oral administration. This strategy increases the intestinal absorption of the insulin; however, more extensive clinical testing is required for clinical development. (Song et al., 2014)

Imeglimin, from the family of Glimins, a tetrahydrotriazene compound, is a drug still in development for the treatment of type II diabetes mellitus. It is shown to act on the three main physiological components of type II diabetes; impaired glucose uptake by muscle tissue, excessive glucogenesis by the hepatic cells, and an increase in the apoptosis of the β-cells. (Marín-Peñalver et al., 2016) After review of the agents used to treat type II diabetes mellitus, Imeglimin was found to be the only agent targeting the three main defects in this disease. In

animals' studies, it has been shown to reduce fasting plasma glucose levels, as well as inhibiting hepatic glucose production, similar to Metformin mechanism. It has also been found to stimulate glucose uptake by skeletal muscles, and also reduce liver steatosis. Moreover, it has been found to have a similar mechanism to that of DPP IV inhibitors, with the glucose-dependent insulin secretion mechanism. This therapy is still under development, where further evidence is needed for FDA approval, however, it is hoped to be used either as an alternative therapy to type II diabetes, or in combination with other known therapies. (Vuylsteke et al., 2015)

**g. PPARs**

Peroxisome proliferator-activated receptors (PPARs) are responsible in the metabolic regulation of triglycerides, blood glucose, and abdominal obesity; therefore, they may play a role in therapeutic approaches to metabolic syndrome. PPAR-α, a type of PPARs which is predominately found in the liver, and also in the muscles and heart, are effective in lowering triglycerides levels by affecting triglycerides catabolism. Fibrates and omega 3 fatty acids are types of PPAR-α agonists. (Botta et al., 2018) The activation of PPAR-α occurs in the liver under energy deprivation, with the main use of increasing ATP production from β-oxidative phosphorylation. PPAR-α has also been found to have anti-inflammatory properties; which suggests that activation of PPAR-α improves both insulin resistance and obesity. Treatment with PPAR-α agonists has been shown to increase the expression of adiponectin, as well as tumor necrosis factor α. PPAR-β/δ, another type of PPARs, has also been found to have anti-inflammatory properties, where it reduces the proinflammatory markers, such as nuclear factor kappa B, in adipocytes and macrophages. (Corrales et al., 2018) It is the least characterized PPAR, yet it is expressed the most in skeletal muscles during fasting; studies have suggested it is tightly related to physical exercise. (Botta et al., 2018) PPAR-γ, the third type of PPARs, is expressed mostly in adipose tissues, both brown and white; playing a role in adipogenesis, thermogenesis, and in facilitating fat storage. It is important in the regulation of fat storage as triglycerides, as well as energy homeostasis; any alterations in the expression increases susceptibility to lipodystrophy, type II diabetes mellitus, and insulin resistance. There are 2 types of PPAR- γ, which are predominant in adipose tissues; PPAR- γ1, which is distributed the most, has a metabolic role in intestines, liver, macrophages, pancreatic β-cells, and adipose tissues,

while PPAR- γ2 is induced in the liver and skeletal muscles in conditions such as long-term obesity and overnutrition. (Corrales et al., 2018) Bone loss and high bone marrow adiposity occur due to the upregulation of PPAR- γ. Thiazolidinediones, agonists of PPAR-γ, have hypoglycemic effects, as well as improving insulin resistance in obesity; they also have anti-inflammatory effects on adipose tissues. However, they made lead to weight gain, as well as other adverse effects such as increase in plasma creatinine levels, formation of gallstones, myopathy, and some drug-drug interactions – such as Gemfibrozil. (Botta et al., 2018)

### h. Cholesteryl Esterase Transfer Protein Inhibitors

Cholesteryl ester transfer protein (CETP) mediates the transfer of cholesteryl esters from HDL to LDL and VLDL; thus, increasing LDL and VLDL levels while decreasing HDL levels. A deficiency in CETP leads to an increase in HDL, while in some pathological states, such as atherosclerosis, are associated with an increase in CETP. CETP inhibitors, in comparison with statins, not only increase HDL levels, but also reduce LDL levels, which is absent in the statins treatment. There are two developed compounds, Torcetrapib and Dalcetrapib, that were discontinued due to off-target effects of Torcetrapib, by stimulation of aldosterone system; leading to an increase in blood pressure, or in the case of Dalcetrapib, due to the cardiovascular harm. There are other CETP inhibitors, such as Anacetrapib and Evacetrapib that show promising results (Remaley et al., 2014). Anacetrapib was shown to have significant improvement in lipids profile and a decrease in the cardiovascular risk in statin-treated patients. This could be proof that Anacetrapib is the optimal therapeutic alternative for hypolipidemic treatment in high-risk patients on statin treatment, if the trials show positive results on the cardiovascular effects (Filippatos et al., 2017).

### i. Apo-AI Inducers

Apo-AI, also called preβ-HDL, is a lipid-poor, main constituent of HDL. It promotes cholesterol efflux from the cell membrane, which then matures to HDL. The induction of Apo-AI increases HDL, which is a mechanism similar to fibrates and nicotinic acid. A novel compound, RVX-208, has been found to induce Apo-AI as well. However, the primary outcome of the drug on atheroma volume in statin-treated patients failed, and therefore, the data from the

clinical trials were not published yet to determine whether it is a viable drug for pharmacological use in raising HDL (Remaley et al., 2014).

### j. PCSK9 Inhibitors

Despite the widely available treatments for LDL lowering, patients who are intolerant to statins develop CVD risks, or suffer hypercholesterolemia. Thus, the FDA has approved two novel therapies, Evolocumab and Alirocumab, which inactivate the proprotein convertase subtilsin-kexin type 9 (PCSK9), which is a hepatic protease that attaches to the LDL receptors and promotes its metabolism and degradation; this could lower LDL levels 50%-60% compared to statins therapy. Alirocumab had undergone three phase I trials; and it was observed that Alirocumab, in comparison with statins, remained effective for a longer period of time. Some adverse effects were reported with the use of Alirocumab, the most common were allergic reactions and elevated liver enzymes. Other adverse effects such as injection site reactions (itching and swelling), urinary tract infections, and diarrhea occurred as well. In Evolocumab administration, similar side effects were reported as Alirocumab; however, some adverse effects lead to the discontinuation of the drug, such as myalgia, dizziness, and nausea. Palpitations and angina pectoris were associated with Evolocumab as well. Despite the adverse drug effects occurring from the novel therapy of PCSK9 inhibitors, they show a promising future for patients who are intolerant to statins therapy (Chaudhary et al., 2017).

### k. Polypills

There is an emerging concept of the use of “polypills” in the treatment of metabolic syndrome; which is a pill consisting of more than one active ingredient that would target different cardiovascular diseases. There was a study regarding a “polypill” that consisted of combining aspirin, a β-blocker, an ACE inhibitor, a diuretic, and a folic acid; all contained in one tablet. The concept of polypill may be beneficial in improving adherence in patients taking more than one medication for the treatment of metabolic syndrome, as well as other cardiovascular diseases, which leads to the reduction of polypharmacy in such patients. Another advantage to the polypill is the decreased cost for both the patient and the society. Currently there are a few polypills under development, one of which consists of aspirin, statin, β-blocker, and ACE inhibitor. According to a study, patients with cardiovascular risk factors received Polycap, which

is a pill consisting of hydrochlorothiazide 12.5 mg, atenolol 50 mg, Ramipril 5mg, simvastatin 5mg, and aspirin 100mg. The Polycap was shown to reduce blood pressure, similarly to the antihypertensives taken separately; however, the reduction in cholesterol was less than patients who received simvastatin alone. There appeared to be no drug-drug interactions, and no serious adverse effects were seen. The concept of Polypill seems to be developing as it is an attractive therapy for patients, as well as pharmaceutical companies. (Matfin, 2010)

# VIII. Conclusion

Metabolic syndrome, also known as insulin resistance syndrome, is a cluster of diseases including; central obesity, insulin resistance, atherogenic dyslipidemia, elevated blood pressure, and prothrombic inflammatory states. There are several risk factors for the development of the syndrome and associated diseases; non-modifiable factors include environmental and genetics, while other modifiable risk factors include diet, smoking, and lack of exercise. The main therapeutic approach towards the disease is the targeting of the risk factors associated with the syndrome, such as the treatment and management of the blood pressure and blood glucose levels, the control of the body weight, and other general therapy such as diet and exercise. Despite the general, already known therapy for the treatment of risk factors associated with metabolic syndrome; there are emerging new therapies still under development. Some therapies have shown effective, while others are still undergoing clinical trials.

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