



TO THE QUESTION OF THE ROLE OF FREE FATTY ACIDS IN THE FORMATION OF INSULIN RESISTANCE AND METABOLIC SYNDROME.

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Article history:	Abstract:
Received: January 11 th 2022 Accepted: February 11 th 2022 Published: March 30 th 2022	This article provides information on obesity as one of the leading causes of metabolic syndrome (MS), insulin resistance (IR), type 2 diabetes (DM2) and consequent cardiovascular disease (CVD).
Keywords: Obesity, Metabolic Syndrome (MS), Insulin Resistance (IR), Diabetes Mellitus (DM2), Cardiovascular Disease, High Economic Situation, Psychological Stress.	

INTRODUCTION: Obesity is one of the main causes predisposing to the development of metabolic syndrome (MS), insulin resistance (IR), type 2 diabetes mellitus (DM2) and, as a result, to cardiovascular diseases (CVD) [1]. MS is sometimes referred to as the "plague of the 21st century". In the US, for example, MS is present in 22.8% of men and 22.6% of women. It could be assumed that MS develops in people with a relatively high economic status, which allows excessive food intake [1,8]. In fact, in the United States, a large-scale study (4978 men and 2035 women, aged 39 to 63 were examined) found an inverse relationship between a person's position on the socioeconomic ladder and the likelihood of having MS. And it was concluded that "the development of MS is a biological mechanism that leads to "social inequality" in the distribution of coronary risk among people." As is known, in persons with a high socioeconomic status, such a risk, according to statistics, is much lower [13].

Psychological stress can also lead to MS and DM 2, when high levels of FFA are associated with increased formation of reactive oxygen species in mitochondria, which, in turn, activate various intracellular reactions, which disrupts the normal pathways of regulatory signals (for example, due to impaired activity of t .n "stress-sensitive kinases"). This leads to a decrease in the ability of cells to adequately respond to the action of insulin and IR develops [14].

The ability of skeletal muscles to adjust their metabolism to the currently dominant substrate is commonly referred to as good "metabolic health" or "metabolic flexibility". It is clear that good "metabolic health" is associated with normal insulin sensitivity. But there is one tissue that "works" for FFA both day and night - this is the myocardium. For the myocardium, FFAs are the main metabolic resource, and FFAs are rapidly metabolized due to β -oxidation in

mitochondria and provide the heart with 65 to 70% of ATP. The remaining 20–25% of ATP is obtained by the myocardium through glycolysis [11].

With an excess amount of adipose tissues, their excessive lipolysis occurs. Normally, the release of FFAs from adipose tissues is tightly regulated, which provides other tissues with a well-balanced amount of FFAs necessary to adequately meet their energy needs. However, in obesity, pathologically increased amounts of signaling molecules enter the bloodstream, which leads to disruption of metabolic homeostasis [15].

Thus, the earliest events leading to disruption of the mechanism of insulin action and the onset of IR occur precisely in adipose cells and long before the onset of impaired glucose tolerance. It is adipose tissues that are currently considered as the site of the initial emergence and development of IR.

It is believed that in overweight individuals with normal glucose tolerance (and no genetic predisposition to diabetes), IR caused by elevated FFA levels is fully compensated by increased insulin secretion caused by high FFA levels. These individuals develop hyperinsulinemia but not hyperglycemia. This explains why more than half of obese individuals with elevated plasma FFA do not develop DM [5,6].

However, at FFA levels above their physiological range, the picture is quite different. An increase in the rate of FFA oxidation leads to an increase in O₂ consumption by the myocardium and to the accumulation of intracellular intermediates, which leads to pathological consequences [9]. These consequences include disruption of the ATP-dependent ion pump and mobilization of intracellular calcium cations, leading to myocardial calcium overload and impaired relaxation resulting in diabetic cardiomyopathy or dilated lipotoxic cardiomyopathy (dilated lipotoxic cardiomyopathy), as with excessive FFA levels in plasma, lipids in the myocardium "are



transformed from an energy source into a source of toxins" [12].

In individuals with T2DM, adipose cells tend to increase in size. These enlarged cells are resistant to the anti-lipolytic action of insulin, which leads to an increase in FFA throughout the day and a decrease in the ability to store triglycerides. As a result, lipids no longer "retained" by adipose tissues enter the bloodstream and "overwhelm" the muscles, liver, kidneys, and pancreatic β -cells. Moreover, dysfunctional adipose cells begin to secrete excessive amounts of factors that provoke the development of IR, inflammatory processes in the walls of blood vessels, and atherosclerosis [7].

Chronically elevated levels of FFA are toxic to pancreatic β -cells. This phenomenon has been called the "lipotoxic effect" [4]. Elevated levels of FFA can have not only suppressive, but also detrimental effects on β -cells, first leading to desensitization and suppression of insulin secretion, and then to apoptosis [12]. Apoptosis is a genetically programmed cell death process that can be triggered by various stimuli.

However, lipotoxicity does not only affect β -cells. Excess FFA is accompanied by the accumulation of triglycerides in the parenchymal cells of many tissues, namely in skeletal and cardiac myocytes and in hepatocytes, which leads to their damage and chronic dysfunction. In the kidneys, FFA infiltration aggravates tubular damage and inflammation, leading to the progression of nephropathy [9].

An increased flow of FFAs to the liver due to lipolysis of visceral fat leads to an increase in endogenous glucose synthesis in the liver, which increases hyperglycemia. It is believed that the "glucolipototoxicity" of excess FFA causes endoplasmic reticulum stress, leading to IR and, again, to the death of β -cells [11].

Thus, an increased flow of FFA from a large mass of adipose cells, as well as disturbances in the mechanisms of storage of triglycerides and in the mechanisms of lipolysis in tissues that are initially normally insulin sensitive, seem to be the earliest manifestations of anomalies leading to IR.

Accumulation of FFAs in non-adipose tissues (primarily skeletal muscle and liver) leads to their abnormal metabolism. As a result, intermediates of fat metabolism, such as ceramides, diacylglycerol and triglycerides, accumulate at the sites of improper storage of FFAs, which leads to disruption of the insulin signal transduction pathway and, thereby, glucose transport. In particular, increased levels of ceramide formed with excess FFA in skeletal muscles "erroneously" activate the regulatory cascade of cerin kinases, which disrupts the insulin signal transduction pathway.

Ceramide is an important lipid component of the cell membrane. It is a second messenger in the sphingomyelin signaling pathway and is involved in the regulation of cellular processes such as cell differentiation, cell proliferation, and apoptosis.

Sphingolipids are an essential component of all eukaryotic cells. They are precursors of active metabolites that play an essential role in tissue development, oncogenesis, cell growth and differentiation [10].

Elevated ceramide levels, resulting from excess amounts of FFA, TNF- α , or glucocorticoids, impair insulin signaling by inhibiting phosphorylation in the Akt/PKB system. Indeed, in obese individuals with IR, ceramide levels in skeletal muscle are increased 2-fold and this increase is associated with increased plasma FFA concentrations.

Another "culprit" of IR is diacylglycerol - DAG (diacylglycerol - DAG). Its elevated levels, as well as high levels of FFA, are associated with the severity of type 2 diabetes, and it also impairs the insulin signaling pathway [8].

Thus, the mechanism of IR development at excessive concentrations of FFA is realized due to:

1. increased glucose levels; chronically high levels of FFA have a "lipotoxic" effect on pancreatic β -cells;
2. increased flow of FFAs to the liver, especially due to lipolysis of visceral fat, increases endogenous glucose synthesis in the liver;
3. elevated levels of ceramides, diacyltriglyceryl and triacylglycerol inhibit the insulin signal transduction pathway in skeletal muscle;
4. excessive amounts of adipocytokines disrupt glucose homeostasis, synthesize increased amounts of pro-inflammatory cytokines, which leads to a chronic inflammatory process that disrupts the insulin signal transduction pathway. IL-6 and TNF- α secreted by fat cells increase IR, while secreted angiotensin II increases blood pressure and contributes to the development of atherosclerosis [14].

As you know, insulin is a pleiotropic hormone, the main function of which is to stimulate the consumption of glucose by skeletal muscles and myocardium, to suppress the synthesis of glucose and VLDL-C in the liver. Another important function of insulin is suppression of FFA secretion by adipose tissues [7]. In IR, this function of insulin is impaired. It was found that insulin-resistant adipose cells secrete elevated levels of FFA, which actually allows



us to consider elevated levels of FFA as a marker of IR.

Elevated levels of FFA impair cholesterol metabolism and lead to atherogenesis. The mechanism of this process is as follows:

1. At high levels of triglycerides in the liver, large amounts of VLDL cholesterol are secreted from it into the blood plasma;
2. In plasma, due to lipolysis from VLDL-C, FFA and highly atherogenic remnant lipoprotein particles rich in triglycerides are formed;
3. From the plasma, FFA and remnant particles are reabsorbed by the liver, which further increases the level of FFA in hepatocytes and further stimulates the synthesis of VLDL cholesterol;
4. In the liver, with a high level of VLDL cholesterol and a normal level of cholesterol ester transfer protein (cholesteryl ester transfer protein - CETP) - triglycerides from VLDL cholesterol pass into HDL cholesterol, and cholesterol from HDL cholesterol passes into VLDL cholesterol. As a result, the following are formed: cholesterol-rich, very atherogenic remnant particles of HSLPONP and HDL cholesterol, containing many triglycerides and little cholesterol;
5. Such HDL-C particles lose apolipoprotein A by A1 triglycerides (due to hepatic lipase activity). As a result, the level of antitherogenic HDL cholesterol decreases;
6. At high levels of VLDL-C (rich in triglycerides), CETP protein transfers triglycerides from VLDL-C to LDL-C and transfers cholesterol from LDL-C to VLDL-C.
7. Triglyceride-rich LDL cholesterol due to the activity of hepatic lipase or lipoprotein lipase lose triglycerides, decrease in size and become very atherogenic small dense particles of LDL cholesterol [6].

Thus, elevated levels of FFA lead to a decrease in the level of "antatherogenic" HDL-C and to the formation of extremely atherogenic small dense particles of LDL-C, to an increase in plasma levels of triglycerides. But there is another way that high levels of FFA induce atherogenesis.

Elevated levels of FFA cause oxidative stress [9]. FFA cause oversynthesis of reactive oxygen species in the mitochondria of macrovascular endothelial cells, which leads to the oxidation of LDL cholesterol and to the modification of HDL cholesterol, this induces an inflammatory process in the walls of blood vessels, endothelial dysfunction and leads to the formation and accumulation of cholesterol plaques, and then to ischemia [9].

An increase in the concentration of FFA during ischemia due to their "incomplete combustion" further aggravates the pathological situation, which is accompanied by an increase in oxygen demand, a violation of calcium homeostasis, and a decrease in

heart contraction. Glucose oxidation is suppressed, further exacerbating the oxygen deficiency caused by elevated FFA levels.

This activates the apoptosis enzymes. During ischemia, FFA metabolism becomes pathological, lactate and hydrogen ions are formed inside ischemic cells, which leads to degradation of myocardial contractility, diastolic dysfunction, and a decrease in the arrhythmogenic threshold of cardiomyocytes [13].

Elevated levels of FFA lead to left ventricular dysfunction. Patients with signs and symptoms of heart failure (HF) and with preserved LV systolic function have been shown to have significant abnormalities in diastolic function. This condition is called diastolic heart failure (DHF) and occurs in 40% of patients with chronic heart failure (CHF). DM is one of the biggest risk factors for DHF. DHF occurs in 40% of diabetic patients and correlates with poor glycemic control. The proposed mechanisms of diastolic dysfunction of the "diabetic heart" are: abnormalities in the metabolism of macroergic phosphates, impaired calcium transport, interstitial accumulation of glycosylation end products, imbalance in the synthesis and degradation of collagen, abnormal microvascular functions, activation of the cardiac renin-angiotensin system, a decrease in the level of adiponectin and disorders of FFA and glucose metabolism [9].

Elevated FFA is the earliest marker of ischemia. In a prospective study, 2103 men who initially did not have coronary artery disease were followed up for 5 years. During this period, 144 of them developed CAD. As it turned out, elevated fasting FFA levels were associated with a 2-fold increase in the risk of coronary artery disease [12]. In another study, 30 patients admitted to the emergency department with ACS (heart pain for 12 hours) had troponin I and FFA levels measured. 9 persons were diagnosed with MI. Within 24 hours of admission, all 9 patients with MI had elevated TnI levels. At the same time, in each of 9 cases of increased TnI, FFA levels were also elevated. Upon admission, high concentrations of FFA were in 28 out of 30 patients (93%) [2].

During ischemia, the concentration of FFA increases and has a proarrhythmic effect, causing tachyarrhythmia (rapid non-rhythmic contractions of the ventricles).

The fact that IR disrupts the process of fibrinolysis, which leads to increased thrombus formation, is a well-known fact. The prothrombotic state is believed to be the result of the direct action of hyperinsulinemia and its associated metabolic pathologies: postprandial hyperglycemia, hypertriglyceridemia, and elevated FFA levels. One of the most important reasons for this is that a large mass of adipose cells synthesize large



amounts of plasminogen activator inhibitor 1 (PAI-1), which reduces fibrinolysis [11].

The first reports that high concentrations of FFAs can reduce fibrinolysis in vitro appeared as early as 1974. Then, in experiments in vitro, it was shown that in a suspension of homogenized clots, FFAs inhibit plasmin activity. Elevated FFA levels are a target for therapy. If elevated levels of FFA cause such severe and potentially fatal pathologies, in particular ischemia, could the development and use of drugs that reduce the concentration of FFA or block its pathological action really be a lifesaver? A large number of original studies have been devoted to solving this problem. It is believed that the most promising drugs for this may be: drugs that reduce the level of FFA, lipids, TG and drugs that control ischemia.

Thus, an increase in the level of FFA draws the patient into a spiral of pathological events:

1. FFA accumulate in adipose tissues, the concentration of FFA in the blood increases;
2. Accumulation of FFA in skeletal muscles not intended for FFA deposition leads to pathological metabolism of FFA, the intermediates of which cause IR;
3. Large amounts of adipocytokines secreted by a large mass of adipose cells disrupt glucose homeostasis;
4. IR further increases the concentration of FFA in the blood and in the liver;
5. Increasing the concentration of FFA disrupts the metabolism of cholesterol in the liver, leading to oxidative stress in the vascular system and endothelial dysfunction, which ultimately leads to IR, MS and CHD with all the consequences.

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