

Metabolic Alterations Present in Obesity and Correlation with Non-Alcoholic Fatty Liver Disease (NAFLD)

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ABSTRACT

Currently in the world, thousands of people are somewhat overweight. Obesity, mainly characterized by the accumulation of fat in adipose tissue can cause various damages in the body, including Metabolic Syndrome. There is a high correlation between patients with this syndrome and those with Non-Alcoholic Fatty Liver Disease (NAFLD), being defined as the increase of the deposition of lipids in the liver in the absence of excessive consumption of alcohol. Excess intake of saturated fatty acids, increased free fatty acids derived from white adipose tissue lipolysis, reduced β -oxidation along with an increase in de novo lipogenesis and decreased synthesis or secretion of VLDL in hepatocytes contribute to the Hepatic steatosis. The treatment for these pathologies is initially based on diet changes and

physical activity practice. In addition, there are still some classes of medicines available to treat the accumulation of fat in the liver as well as decrease insulin resistance. Studies still seek to find specific medicines for the treatment of NAFLD, therefore, the most effective method continues to be prevention, through an improvement in the quality of life, related to a balanced diet and the practice of regular physical activity.

Key words: Obesity; Adipose tissue; Diabetes; Non-Alcoholic Fatty Liver Disease

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INTRODUCTION

Currently in the world, thousands of people are somewhat overweight. Obesity, mainly characterized by the accumulation of fat in the adipose tissue can cause various damages in the body, mainly due to obese patients have a high prevalence in presenting a condition known as Metabolic Syndrome (MS). This Syndrome is characterized as a complex disorder represented by a set of metabolic disorders that are commonly associated with obesity, hypertension, dyslipidemia, hyperglycemia and hyperinsulinemia^[1].

The treatment strategy for pathologies associated with metabolic disorders is initially based on diet changes and physical activity practice. In addition, there are still some classes of drugs available to treat fat accumulation and improve insulin resistance^[2]. With this, the aim of this study was to gather the pathophysiological characteristics related to obesity, as well as its relationship with Non Alcoholic Fatty Liver Disease (NAFLD).

OBESITY AND METABOLIC SYNDROME

The number of people affected by various metabolic disorders has increased steadily in recent decades. Among these changes,

overweight and obesity have taken on alarming proportions. Studies published in 2016 revealed that the number of obese people in the world has grown six times more in the last four decades, rising from 105 million people overweight in 1975 to 641 million in 2014. It is also worth mentioning the number of overweight children: Between 1980 by 2013, the prevalence of overweight children and adolescents increased by almost 50%. The study also shows that the proportion of obese men rose from 3.2% to 10.8%, and that the share of women in the same condition jumped from 6.4% to 14.9%^[3]. The number of obese people has increased since the 1980s, being more accelerated between 1992-2002. However, in the more developed countries, there was a decrease in 2006. In developing countries, where almost two-thirds of the obese people in the world lives today, the increase tends to continue^[4]. In Brazil, a survey by the Ministry of Health published in 2014 revealed that overweight is present in 17.9% of the population, and in those older than 18 years this rate rises to an incredible 52.5%^[5].

Excess intake of fats, carbohydrates, soft drinks, and fast-food, associated with a generally sedentary population (in addition to genetic predisposition), are all factors that contribute greatly to the large number of overweight people. These factors make obesity a major public health problem. In addition, it is also a determining factor for the establishment of what we call today the metabolic syndrome, characterized as a complex disorder represented by a set of metabolic disorders that are commonly associated with obesity, hypertension, dyslipidemia, hyperglycemia and hyperinsulinemia^[1].

In addition to the excess of stored lipids, obesity is currently seen as a low-grade inflammatory process. Adipose tissue is able to release cytokines (TNF- α and interleukin-6, for example) which are known to interfere with organic homeostasis. For example, these cytokines may interfere with insulin action and trigger pathologies such as insulin resistance, diabetes mellitus (DM), and non-alcoholic fatty liver disease (NAFLD)^[6].

DIABETES MELLITUS

DM is a chronic disease characterized by hyperglycemia, resulting from altered carbohydrate metabolism due to an absolute or partial lack of insulin^[7]. It is the most common metabolic disease in the world, reaching about 381.8 million adults in 2013 and projected to rise to 591.9 million in 2035^[8]. In healthy individuals the release of insulin leads to suppression of hepatic glycogenolysis and stimulates the uptake of glucose into muscle, liver and adipose tissue cells. The rate of absorption of these cells depends on the action of insulin on the glucose transporter called GLUT 4 in muscle and adipose tissue. However, in the liver, its GLUT 2 transporter acts independently of the action of insulin^[9].

Diabetes is divided into two types: Type 1, in which pancreatic β cells are destroyed by autoantibodies, which leads to absolute insulin deficiency and type 2 (most cases of diabetes), in which different degrees of resistance to diabetes exist, as well as insulin uptake. In the first type the initial clinical symptoms usually appear around puberty when there is a loss of the production of this hormone and the administration of insulin is completely necessary for maintenance of life, so called insulin-dependent. In the second type, insulin is produced by pancreatic β cells, but its action is compromised, characterizing a state of insulin resistance leading to an increase in the production of this hormone as a alternative to try to keep glucose at normal levels. When this is no longer possible, diabetes arises. The onset of the condition is slower and the symptoms - thirst, increased diuresis, leg pains, visual changes, and others - may take several years to occur^[10].

Treatment is usually based on a change in lifestyle, including exercises and improved eating habits. In addition, administration of drugs aimed at improving the receptor/insulin interaction is essential. Metformin, for example, has the ability to increase the uptake of glucose present in the blood. Thiazolidinediones improve insulin sensitivity while sulfonyleureas stimulate the secretion of this hormone^[11]. In contrast, incretins (hormones produced by the gastrointestinal tract and released into the gut in response to food intake) also potentiate insulin secretion and sensitivity in their target tissues by playing an important role in pancreatic β -cell modulation^[12]. However, this hormone is rapidly degraded by an enzyme called Dipeptidyl Peptidase (DPP4). One form of treatment, therefore, has been to increase the half-life of incretins by creating analogs of this hormone resistant to DPP4 or enzyme inhibitors^[13]. An example of an enzyme inhibitor drug already available is Sitagliptin^[14]. It is worth mentioning that in specific cases the administration of insulin may also occur. Without a proper treatment, this pathology can trigger other pathologies such as hypertension, renal failure, retinopathies, among others^[15].

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Physiopathological characteristics

As stated before, Metabolic Syndrome may compromise the entire functioning of the body. An example of this is the high relationship found between patients with MS and presenting with NAFLD. This pathology is defined as the increase in the deposition of lipids in the liver in the absence of excessive alcohol consumption. These lipids are present within the hepatocyte cytoplasm and when they are present in more than 5% of the total body weight the disease can already be diagnosed^[16].

Excess intake of saturated fatty acids, increase of free fatty acids derived from lipolysis of white adipose tissue, reduction of β -oxidation together with an increase in de novo lipogenesis and decrease in the synthesis or secretion of VLDL (Very Low Density Lipoprotein) in hepatocytes contribute to hepatic steatosis. In addition, foods with a high fructose concentration also contribute to an increase in NAFLD. It is estimated that about a single meal consisting of approximately 80% carbohydrates is able to stimulate three times as much lipogenesis again compared to a fasting state. Other conditions related to insulin resistance and oxidative stress induce a lipotoxic environment within the liver causing inflammation and liver damage that may lead to the development of fibrosis^[17].

Epidemiological studies show that approximately 30% of the world population has some degree of NAFLD, and among the obese, this prevalence increases to up to 80%^[18]. This pathology has been associated with several factors, such as genetic alteration, excessive consumption of high-fat foods, hormonal and immune dysregulation, as well as being a developmental factor for insulin resistance^[19].

Diagnosis

In general, NAFLD is an asymptomatic condition in most cases. Only some vague symptoms such as fatigue and abdominal discomfort are reported^[20]. Regarding the laboratory diagnosis of this pathology, what is known is that it is quite unspecific, with exceptions excepted. A frequently performed test is the analysis of alanine aminotransferase (ALT/TGP) and aspartate aminotransferase (AST/TGO) levels, which may indicate the presence of a liver injury. It is important to rule out common causes of these lesions thus, it is requested complementary tests of some enzymes, proteins and antigens present in the liver. More specifically, NAFLD can be diagnosed by imaging

methods such as ultrasonography, magnetic resonance imaging, and computed tomography. Ultrasonography, which is based on the measurement of liver stiffness, even though it is widely available and without contraindications, uses subjective and poorly reproducible criteria that do not allow a reliable quantification of steatosis. Resonance has been considered a more effective noninvasive method, however, it is an expensive procedure and still not very accessible. Therefore, the most commonly used method for diagnosis of abdominal diseases is tomography^[21]. In addition to these methods, hepatic biopsy can also be done and in this way there are several levels of liver involvement in NAFLD^[22].

Treatments and importance of physical activity

Whereas patients with NAFLD are more likely to develop cardiovascular disease and when not treated the liver may meet total failure, effective treatments should be started as soon as the diagnosis has been made. However, there are only palliative treatments that begin with diet re-education and physical activity stimulation, in addition to drugs that can improve insulin resistance and consequently improve the pathological state of the liver. Medications used to control type 2 diabetes (such as Metformin and Thiazolidinediones) and weight loss (Orlistat) are well indicated^[23]. There are also indications for supplementation with antioxidants, vitamins, caffeine and omega-3 fatty acid in addition to the use of preventive vaccines against hepatitis A and B, which are recommended in order to avoid aggravation of the organ^[24]. Finally, statins may also be prescribed, as they promote the reduction of liver enzymes, as well as a 68% reduction in the chance of an adverse cardiovascular event^[25]. In some cases, the indication of bariatric surgery can also be evaluated since it is observed a significant decrease in hepatic steatosis, although it is a very invasive procedure and requires a good follow-up of the patient^[26].

It is noteworthy that in addition to the above mentioned drugs not being specific for the treatment of NAFLD, some of them can also cause worrying side effects. Metformin, for example, may lead to some unpleasant digestive reactions such as nausea, vomiting, diarrhea, and even hepatic impairment^[27].

As previously mentioned, physical exercise is recommended for the treatment of NAFLD. One of the actions of physical activity is to ease the metabolic activity of the liver, caused by a decrease of glycogen in liver tissue and skeletal muscle. This is due to an increased need for glucose by the body, caused by increased energy expenditure during exercise, causing glycogen to be rapidly broken down into glucose molecules. In addition, physical exercise also ends up providing a metabolic pathway to metabolize excess circulating glucose, which instead of being converted by the liver into triglycerides, will be stored as hepatic and muscular glycogen during a post-activity period. An important highlight is the fact that the liver is the organ responsible for providing glucose (present as glycogen) for the maintenance of the glycemic homeostasis during physical activity, providing a reduction in its carbohydrate stores. As a consequence, there is a decrease in the synthesis and storage of lipids in the liver^[28].

Moreover, new studies have shown that exercise is changing the fat, and as a result of that change, the fat releases beneficial proteins into the bloodstream, such as transforming growth factor beta 2 (TG-F-beta 2), an adipokine released from adipose tissue in response to exercise that actually improves glucose tolerance and increase fatty acid uptake for oxidation in the liver, suggesting a potential therapy for treatment of high blood sugar, and eventually a potential therapy for type 2 diabetes^[29].

Physical activity is an auxiliary treatment that must be aligned with the drugs currently available for reducing body weight, since there

are still compounds that act directly to the treatment of this disease. A regular physical activity is able to act on the fat mass deposited in the liver, mainly due to the stimulus of a greater energetic expenditure by the organism^[30].

CONCLUSION

The present study showed that has been a great increase of obese people in the World, a fact that is mainly due to the sedentary lifestyle of the population. According to data, this statistic should increase further in the coming years. Several pathologies are triggered by obesity, among them diabetes and the accumulation of fat in the liver. Studies still seek to find specific medicines for the treatment of NAFLD, so the most effective method continues to be prevention, through an improvement in the quality of life, related, mainly, to a balanced diet and the practice of regular physical activity.

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