down the speed of digestion in the digestive tract, stabilizing blood glucose and insulin levels. The ideal amount of fiber required for NAFLD treatment has yet to be defined, but according to the American Diabetes Association (2004), the recommended total daily fiber intake is 25–30 g, of which 20–30% should come from soluble fiber.

Recently, the effects of high-fiber and low-glycemic index carbohydrates on glycemia and lipid profile were described in a meta-analysis (Anderson et al., 2004). In this manner, the choice of healthy sources of carbohydrate might be responsible for the beneficial effects on NAFLD and MS patients (Esposito et al., 2004).

8.2.5.1.3 Protein
There is little information on the effect of protein quantity, quality, and compositi on the pathophysiology of NAFLD and NASH. However, it is known that protein deficiency or malnutrition can cause steatosis. A normoproteic diet, representing 15–20% of total energy intake, is therefore recommended (Zivkovic et al., 2007).

8.2.5.1.4 Saturated Fat
High saturated fat intake is associated with liver dysfunction caused by an increase production of reactive oxygen species, which leads to damage in the mitochond rion of hepatocytes. In fact, lipotoxicity caused by long-chain fatty acids has been implicated in the development of numerous obesity-related diseases including NAFLD. Indeed, high saturated fat intake (more than 10% of total energy) promotes insulin resistance, which plays a key role in the NAFLD genesis. Therefore, these data suggest that saturated fat intake must be limited in NAFLD patients (Cave et al., 200).

However, the literature is rather unclear about the exact minimum amount of saturated fat intake that should be recommended to promote beneficial effects. Clinical evidence suggesting that this nutrient intake should be ≤7% of total energy and >10% of energy may be suboptimal for NAFLD patients (German and Dillard, 2004).

8.2.5.1.5 Monounsaturated Fatty Acids
Oleaginous, olive oil, nuts, and avocado are good sources of monounsaturated fatty acids (MUFA). Studies have demonstrated their beneficial effects on cardiovascular disease risk factors and blood lipid profiles. In patients with type 2 diabetes, this type of fatty acids reduces VLDL-c and triacylglycerol without reducing high-density lipoprotein cholesterol (HDL-c), suggesting that an MUFA-rich diet could bring benefits to NAFLD patients (Rodriguez-Villar et al., 2004).

8.2.5.1.6 Polyunsaturated Fatty Acids
Low hepatic n-6 and n-3 polyunsaturated fatty acids (PUFAs) may contribute to steatosis and steatohepatitis and can be affected by diet and oxidative stress (Alles et al., 2008).

The two series of PUFAs, n-3 and n-6, and their derived products are provided in cis-linoleic and linolenic acids, respectively. The main compounds of PUFA: arachidonic acids derived from n-6, and docosahexaenoic acids and eicosapentaenoic acids derived from n-3. These nutrients present an anti-inflammatory action by decreasing the inflammatory mediators (Martin et al., 2006).
The ratio of n-6 to n-3 fatty acids seems to be important in determining the effect of PUFAs on various lipid and nonlipid indexes. The main sources of n-3 are fish oil and fish oil/day supplementation promotes decreased blood triacylglycerol, hepatic enzyme fasting glucose, TNF-α, and steatosis regression in NAFLD patients (Capanni et al., 2006; Spadaro et al., 2006). These data suggest that consumption of n-3 fatty acids found in fish oils and walnuts is likely to improve blood lipid profiles and

### TABLE 8.5

**Different Dietetic Plans for NAFLD Control and Their Effectiveness in Some Clinical Parameters**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Diet</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamamoto et al. (2007)</td>
<td>126 kJ/kg/day of energy, a fat energy fraction of 20%, ≤6 mg/day iron, and 1.1–1.2 g/kg/day of protein</td>
<td>↓ ALT, AST, ferritin, body weight BMI</td>
</tr>
<tr>
<td>Capanni et al. (2006)</td>
<td>1 g fish oil/day supplementation for 12 months</td>
<td>↓ blood triacylglycerol concentrations, hepatic enzymes, fasting glucose, and steatosis in NAFLD</td>
</tr>
<tr>
<td>Spadaro et al. (2006)</td>
<td>2 g fish oil/day supplementation for 6 months</td>
<td>↓ blood triacylglycerol concentrations, hepatic enzymes, TNF-α, and steatosis regression</td>
</tr>
<tr>
<td>McAnley et al. (2005)</td>
<td>&lt;20% carbohydrate, 25–30% protein, 55–65% fat, 20% saturated, 10% MUFAs, 300–600 cholesterol</td>
<td>↓ body weight, waist circumference, insulin sensitivity, triacylglycerol, and ↑ steatosis, total cholesterol, and LDL Histological improvement in 60% of NASH patients</td>
</tr>
<tr>
<td>Huang et al. (2005)</td>
<td>40–45% from carbohydrates, with emphasis on complex carbohydrates with fiber; 35–40% from fat with emphasis on monounsaturated and polyunsaturated fats; 15–20% from protein for 12 months</td>
<td>↓ ALT and serum insulin ↓ Body weight, BMI waist circumference, inflammatory markers, glucose, total cholesterol triacylglycerol, and insulin resistance, as well as improving endothelial function and ↑ HDL-c concentrations</td>
</tr>
<tr>
<td>Daubiou et al. (2005)</td>
<td>Oligofructose given for eight weeks 50–60% carbohydrates, 15–20% protein, and total fat = 30%</td>
<td>Higher odds of inflammation</td>
</tr>
<tr>
<td>Esposito et al. (2004)</td>
<td>Diet with higher carbohydrate intake</td>
<td>Higher odds of inflammation</td>
</tr>
</tbody>
</table>

*Note:* Clinical results from different dietetic plans.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; TNF-α, tumor necrosis factor α; NASH, nonalcoholic steatohepatitis.
Nutritional and Clinical Strategies on Prevention and Treatment of NAFLD

reduce inflammation, steatosis, and liver damage in NAFLD patients (Zivkovic et al., 2007).

8.2.5.1.7 Trans Fatty Acids

Trans fatty acids can be naturally found in dairy products as a result of bacterial metabolism in ruminant animals and industrialized foods—margarines, biscuits, creams, some breads, fried potatoes (fast food), cake shops, cakes—as a result of hydrogenation (Chiara et al., 2003).

It is essential to note that the trans fatty acids used in food processing act as

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| TABLE 8.7 |
| Five Essential Recommendations for Prevention and Treatment of NAFLD and MS |
| Nutritional Strategies and Recommendations on Treatment and Prevention of NAFLD |
| Individual nutritional plan to promote gradual weight loss and maintenance of ideal weight |
| Changes in inadequate food habits |
| Reduction of simple carbohydrate intake and with high glycemic index, substituting them with complex carbohydrates, mainly with low glycemic index and load (Table 8.4) |
| Incorporation of fibers in the daily menu, such as fruits, vegetables, oats, mainly soluble fibers that slow down the gastric emptying, promoting a maintenance of glycemic rate |
| Reduction of saturated and trans fatty acids, substituting with monounsaturated and polyunsaturated fatty acids, which decrease the risk of heart disease and improve insulin sensitivity |

8.2.6 Practical Applications

It is important to note that, based on our understanding of the disease pathogenesis, it seems logical that a multidisciplinary approach addressing the underlying MS and obesity is required to effectively treat patients with NAFLD and serve as a potent weapon in our line of defense against correlated diseases.

8.3 Summary Points, Policy Makers, and Future Research

- NAFLD should be recognized as part of the MS and should be managed by a multidisciplinary approach addressing liver disease in the context of risk factors for diabetes and premature cardiovascular disease.
- Lifestyle changes are the first line and mainstay of management. The basal universal approach consists of clinical, nutritional, exercise, and psychological counseling.
- It is important to identify the cutoff points of visceral fat on NAFLD and MS development as well as the relation with proinflammatory cytokines, with the aim of creating new clinical and nutritional strategies in the prevention and treatment of these diseases and their comorbidities.
- Future research is needed to discover possible specific liver drugs and deal with NAFLD and comorbidities related to obesity, MS, and associated chronic diseases, especially during the early stages of life.

References


Nutritional and Clinical Strategies on Prevention and Treatment of NAFLD


Anexo 7.

Capítulo de Livro Internacional:
Bioactive Foods, Nutrients and Herbs in Prevention and Treatment of Heart Disease

The effects of a fermented soy product and isoflavones in Metabolic Syndrome Control

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tmello@psicobio.epm.br
1. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL-c</td>
<td>very low density lipoprotein cholesterol</td>
</tr>
<tr>
<td>LDL-c</td>
<td>low density lipoprotein cholesterol</td>
</tr>
<tr>
<td>HDL-c</td>
<td>high density lipoprotein cholesterol</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drugs Administration</td>
</tr>
<tr>
<td>USDA</td>
<td>United States Department of Agriculture</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>NAFLD</td>
<td>non-alcoholic fatty liver disease</td>
</tr>
<tr>
<td>PPARs</td>
<td>peroxisome proliferator-activated receptors</td>
</tr>
<tr>
<td>SREBP</td>
<td>sterol regulatory element-binding protein</td>
</tr>
<tr>
<td>BW</td>
<td>body weight</td>
</tr>
<tr>
<td>ERRs</td>
<td>estrogen-related receptors</td>
</tr>
<tr>
<td>ApoB-100</td>
<td>Apolipoprotein B-100</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>Homeostasis Model Assessment Insulin Resistance</td>
</tr>
<tr>
<td>mg</td>
<td>micrograms</td>
</tr>
<tr>
<td>cAMP</td>
<td>Adenosine Monophosphate cyclical</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>calcium</td>
</tr>
<tr>
<td>GI</td>
<td>glycemic index</td>
</tr>
<tr>
<td>CPT-1</td>
<td>carnitine–palmitoyl transferase 1</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
</tbody>
</table>

2. Abstract

Metabolic syndrome is a constellation of medical disorders that increase the risk for cardiovascular disease and Type II diabetes, which involves a complex interaction of genetics, diet, and lifestyle. At present, scientific evidence has shown that isoflavones may influence chronic disease control. This chapter will review the effects of a fermented soy product and isoflavones in the treatment and prevention of all Metabolic syndrome components.
3. Introduction

Obesity increases the risk for a number of disorders such as metabolic syndrome, diabetes, and cardiovascular disease. Metabolic syndrome is a combination of medical disorders that increase the risk for cardiovascular diseases and Type II diabetes. Obesity may lead to metabolic syndrome because it increases the prevalence of visceral obesity, insulin resistance, very low-density lipoprotein cholesterol (VLDL-c) and low-density lipoprotein cholesterol (LDL-c), decreased high-density lipoprotein cholesterol (HDL-c), elevated triglycerides, hypertension (high blood pressure), and fatty liver, which are important factors of metabolic syndrome. During the last few decades, several studies were developed to examine the role of nutritional factors in the prevention and treatment of obesity (ØRGAARD et al, 2008).

Scientific evidence has shown that isoflavones may influence the control of chronic diseases such as cancer, diabetes mellitus, cardiovascular diseases, and dislipidemias, which are considered co-morbidities of obesity (Figure 1). These compounds are widely found in beans, particularly in soybeans (Glycine max). In addition to their anti-estrogen activity, they have biological properties that may impact many biochemical and physiological processes. Evidence that isoflavones protect against chronic diseases is based on experimental and epidemiological studies. In humans, epidemiological studies clearly show a higher incidence of some kinds of cancers and cardiovascular diseases in western people that are exposed to limited amounts of soy isoflavones, such as daidzein and genistein, in their diets. Additional evidence, such as the effects of genistein on insulin release, has also been observed in experimental animal models. It seems that their mechanisms of action depend on
their estrogen agonist-antagonist properties and other biochemical properties such as enzymatic activity inhibition and antioxidant effects (Steves & Monteiro, 2001).

According to the FDA, 40-60 mg/day of isoflavone are suggested to obtain beneficial effects. The isoflavone concentration in soy products can vary depending on range of grains, soil, climate, was area of cultivation, and, especially, processing. World soy consumption is estimated at around 239.4 million tons. The USDA in the USA estimates a production of 84.5 million tons and a consumption of approximately 54.7 million tons. The USA is the main world producer of soy, corresponding to 35% of total production. After the USA, Brazil is responsible to 26.5% of world soy production. Due to its cholesterol-lowering effect, soy protein has been studied exhaustively around the world for mechanism and clinical proof. In 1994, the Ministry of Health and Welfare in Japan approved soy protein as a food for special health use (FOSHU), and in 1999 the FDA approved a similar designation and labeling of soy protein (Takamatsu et al, 2004).

The daily consumption of soy has been associated with prevention and treatment of several diseases, making soy considered a functional food. Its bioactive components are amino acids, peptides, fiber, and isoflavones. The soy grain presents a higher nutritional value, containing more proteins, vitamins, and minerals than other grains. The quality of soy protein is not totally equal to animal protein; therefore, soy protein needs to be combined with other vegetable proteins to be effective. It is important to note that the quantity of lipid in soy grain is superior to that of other grains; however, these lipids do not promote cholesterol. Soy grain is also rich in fibers, being suggested for use in weight loss diets, diabetics, and other co-morbidities. Consumption is recommended in lactose intolerance; however, the calcium quantity of soy is negligible compared to that observed in animal milk. Whole
soy grain contains 8% of iron; however, this iron is not as well absorbed as the iron in red meat (Embrapa, 2010). See Tables 1 and 2 for soy-grain composition:

**Table 1. Mineral composition of soy grain (100g)**

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Milligrams (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>230</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>580</td>
</tr>
<tr>
<td>Iron</td>
<td>9.4</td>
</tr>
<tr>
<td>Sodium</td>
<td>1</td>
</tr>
<tr>
<td>Potassium</td>
<td>1.900</td>
</tr>
<tr>
<td>Magnesium</td>
<td>220</td>
</tr>
</tbody>
</table>

Source: Embrapa, 2010

**Table 2. Amount of Isoflavones in different soy products**

<table>
<thead>
<tr>
<th>Food</th>
<th>Amount of Isoflavones (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>½ cup soy flour, fat free</td>
<td>257</td>
</tr>
<tr>
<td>½ cup soy flour, raw</td>
<td>210</td>
</tr>
<tr>
<td>½ cup soy grain</td>
<td>216</td>
</tr>
<tr>
<td>½ cup tofu</td>
<td>76</td>
</tr>
<tr>
<td>1 cup soy milk</td>
<td>48</td>
</tr>
<tr>
<td>90mg soy hamburguer</td>
<td>8</td>
</tr>
<tr>
<td>1 tablespoon soy sauce</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Source: Embrapa, 2010

The term "probiotic" refers to live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (WHO, 2002). Probiotic bacteria have been the focus of much scientific and commercial interest due to a range of possible health effects of these bacteria on processes such as lipid metabolism (Klein et al., 2008; Park et al 2008). The most widely studied probiotic bacteria are *Lactobacillus GG, Lactobacillus acidophilus, Bifidobacterium bifidum,* and *Enterococcus faecium* (Klein et al., 2008; Park et al., 2008; Ross et al., 2000). Probiotic dairy products are considered to have functional properties because the probiotic bacteria added to the regular fermentation cultures provide therapeutic benefits such as modification of the immune system, reduction in cholesterol,
alleviation of lactose intolerance, and faster relief from diarrhea (Hekmat et al., 2006). In normocholesterolemic women and men, fermented milk with a bacteria culture containing Enterococcus faecium initially promoted a rapid reduction of LDL-cholesterol but over a long-term period of intake (6 months), the reduction of LDL-cholesterol was similar to that from the placebo product (Richelsen et al., 1996). Today, the soybean is another alimentary source that gets attention from the scientific community. Some studies in human subjects have shown a significant hypocholesterolemic effect of soy protein in hypercholesterolemic subjects (Gaddi et al., 1987; Widhalm et al., 1993; Potter et al., 2004; Anthony et al, 1998). However, the hypocholesterolemic effect of soy protein also has been shown to be minimal or negligible in normocholesterolemic subgroups (Cheik et al., 2008).

During the past few years, we have dedicated our research to studying the role of a fermented soy product in the control of obesity and dyslipidemia. It was demonstrated in hypercholesterolemic male adult rats that, over an 8-week period, a dose of 1ml/rat/day of a soy fermented product enriched with Enterococcus faecium and Lactobacillus Jugurti improved lipid metabolism and reduced visceral and central adipose tissue, suggesting a correlation to protecting against both obesity and dyslipidemia (Cheik et al., 2008). Moreover, Manzoni et al. (2005) reported that administration of the same fermented soy product supplemented with isoflavones had beneficial effects on the white adipose tissue of juvenile male rats, leading to a decrease in adipocyte size. Therefore, this chapter is dedicated to reviewing the role of soy products as functional foods and their bioactive components as effective controls of obesity, dyslipidemia, and NAFLD (a constellation of metabolic abnormalities included in metabolic syndrome); and considering the relevance of soy in nutritional strategies to prevent these diseases and improve the human health.
Fermented Soy product and Isoflavones in Adipose Tissue Metabolism

The metabolism of adipose tissue is regulated by lipolysis, lipogenesis, and lipid accumulated from the diet (Oyama & do Nascimento, 2009). Previous studies developed by our group showed that a fermented soy product effectively reduced rates of lipogenesis and lipid absorption from the diet (Cheik et al., 2008; Guerra et al., 2007). On the other hand, soy products stimulate an increase in lipolysis, leading to a significant reduction in central and visceral adipose tissue areas. Moreover, these effects were observed to be more accentuated when the soy product was associated with chronic exercise training (Cheik et al., 2008; Guerra et al., 2007). Indeed, increasing evidence from animal studies has suggested that soy components may regulate lipid metabolism by modulating the activities of key transcription factors and thereby changing the downstream gene expression involved in lipogenesis or lipolysis (Xiao et al., 2008).

As mentioned above, the intake of soy protein has been associated with improvements in lipid metabolism, with much attention being focused on the serum cholesterol-lowering properties of soy. The components of soy that are responsible for improvements in lipid metabolism have been investigated and their specific actions debated. One component, isoflavones, has been shown to have weak estrogenic activity, and recently, several research groups have suggested that isoflavones activate peroxisome proliferator-activated receptors (PPARs) (Mezei et al., 2006). Results of in vitro studies have demonstrated that soy isoflavones, particularly genistein and daidzein, were able to activate both peroxisome proliferator-activated receptors (PPARs) and PPARα-mediated gene expression. In vivo studies have also
demonstrated the effects of isoflavone intake on physiological parameters such as glucose tolerance (Mezei et al., 2003). Furthermore, the soy isoflavone genistein has been identified as a ligand of the PPAR-α receptor (Dang et al., 2003). Gene profiling suggests that genistein regulates gene expression through PPAR, which acts to stimulate mitochondrial fatty acid oxidation (Kim et al., 2004). The three different isoforms of PPARs (α,γ,δ) have overlapping tissue distributions and functions associated with lipid metabolism. Isoflavone acting through both PPAR-α independent and PPAR-α dependent pathway. One possible explanation is again the isoflavones activation of PPAR-γ since increased adipocyte differentiation and tissue lipid accumulation result in initially decreased serum triglycerides (Ye et al., 2001). Alternatively, the PPAR-α independent pathway of isoflavone regulation may occur via the activation of sterol regulatory element-binding protein (SREBP) pathways. It was previously shown that exposure to isoflavones induces SREBP processing in an in vitro model (Mullen et al, 2009).

Further work suggests a possible action of isoflavones similar to the nonestrogenic ligands that bind estrogen-related receptors (ERRs). Recently, these receptors have been demonstrated to contribute to lipolytic processes. Finally, evaluation of receptor activation studies suggests that thyroid receptor activation may provide additional clues explaining the metabolic action of isoflavones. The recent advances in the discovery and evaluation of the promiscuous nuclear receptors that bind many different chemical ligands should prove helpful in explaining some of the biological effects of soy isoflavones and other phytochemicals in the regulation of adipose tissue metabolism (Ricketts et al., 2005).

The role of genistein in adipogenesis in vitro has been studied in multipotent stem cells and preadipocyte cells. The volume of an adipocyte varies in accordance
with the balance of lipogenesis and lipolysis. Lipogenesis involves the incorporation of free fatty acids into adipocytes for storage as triglycerides. Lipolysis describes the process that triglycerides stored in adipocytes to hydrolyze into free fatty acids and glycerol. Different from estrogen, which mainly inhibits lipogenesis, genistein regulates both lipogenesis and lipolysis in vitro. An experimental study with genistein supplementation showed a decrease in lipogenesis and an increase in lipolysis, confirming that genistein regulates adipogenesis and the process of triglyceride storage, leading to changes in the number and volume of adipocytes (Dang, 2009). The relationship between these mechanisms of soy compounds in the regulation of adipose tissue metabolism in experimental research needs to be confirmed and further explored in human studies.

Sites et al., (2007) reported a significant effect of soy on total abdominal fat and subcutaneous abdominal fat in postmenopausal women. Although a 5-fold reduction in visceral fat gain with soy compared to a placebo was noted, this did not reach significance. After adjusting for total body fat, however, there was a strong trend toward a correlation between soy and the prevention of visceral fat accumulation. The greater effect on subcutaneous versus visceral fat partly may be explained by the greater absolute amount of subcutaneous fat and the fact that total abdominal fat is the summation of subcutaneous and visceral abdominal fat. However, Anwar et al., (2001) showed differential regulations of ERα and ERβ in the subcutaneous and visceral fat of postmenopausal women. Specifically, estradiol stimulation increased ERβ expression but decreased ERα expression in subcutaneous adipocytes but not in visceral adipocytes in vitro (Anwar et al., 2001). Thus, soy isoflavones that stimulate primarily ERβ may have a greater effect on subcutaneous than visceral adipocytes.
Soy and Isoflavones in Weight loss

In a prospective randomized, controlled trial, 14 women with overweight/obesity were randomly assigned to 720 mL of soy milk or an equivalent volume of skim milk daily for 8 weeks. It was shown that 720 mL soy milk or an equivalent volume of skim milk, both of equal protein content, promoted statistically equivalent losses in weight, body fat, and abdominal circumference while preserving fat free mass. The results of this study are promising to vegans and other individuals who restrict dairy products due to food allergies or intolerance. Indeed, soy milk ingestion promoted additional benefits, mainly in post-menopausal women and in metabolic syndrome control. These findings support the contention that individuals attempting to lose weight should be encouraged to maintain high dietary calcium intake either by consuming 720 mL soy milk or skim milk daily to optimize weight loss (Lukaszuk et al., 2007).

A recent clinical trial with 180 postmenopausal Chinese women reported a mild but significant favorable effect of soy protein with isoflavones on changes in body weight (BW), body mass index, and body fat percentage relative to isoflavone extracts and milk protein after a 6-month supplementation (Liu et al., 2010).

Soy and Isoflavones in cardiovascular diseases and Dislipidemias

Cardiovascular diseases include stroke and atherosclerosis, which causes vascular problems that range from diseases of the arteries, veins, and lymph vessels to blood disorders that affect circulation. Like the blood vessels of the heart, the
peripheral arteries also may develop atherosclerosis, a build-up of fat and cholesterol deposits called plaque, on the inside walls. Over time, this build-up narrows the artery. Eventually, the narrowed artery causes less blood to flow, and a condition called ischemia can occur. Ischemia refers to an inadequate blood flow to the body's tissue. A high cholesterol-serum concentration is considered one of the main factors that cause the occurrence of these pathologies, once it is one of the precursors in the development of atheroma (Steves & Monteiro, 2001).

Soy consumption has been associated with cardiovascular illness reduction, especially of atherosclerosis in animal models. Indeed, epidemiological evidence suggests that populations that eat diets rich in soy and soy products present minor rates of mortality from these diseases (Lichtenstein, 1998). In spite of the fact that studies in animals have suggested that soy protein reduces blood cholesterol, similar studies in human have presented less consistent results. The presence or absence of isoflavones can be a factor in this confusion. These isoflavones, mainly genistein and daidzein, have presented a hypocholesterolemic effect in both animals and human.

Animal studies have demonstrated that isoflavones are essential to decreasing blood cholesterol levels. Additional studies have shown that isoflavones do not just perform an important role in lipoprotein regulation, reducing LDL-c and increasing HDL-c, but also in protecting against the development of atheroma (Anthony et al., 1998).

A study in postmenopausal women with metabolic syndrome revealed that both soy nuts and soy protein had beneficial effects on serum concentrations of total cholesterol, LDL-c, triacylglycerol, and apoB-100 (Azadbakht et al., 2007). Beneficial effects of soy consumption on blood lipids were the most consistently reported findings. In a meta-analysis of 38 controlled clinical trials, Anderson et al. (18)
demonstrated significant reductions in total cholesterol (9%), LDL-c (13%), and triacylglycerols (11%) with the consumption, on average, of 47 g soyprotein/d. Two recent meta-analyses concluded that the isoflavone content of soy may be responsible for its lipid-lowering effects (Zhan et al., 2005; Zhuo et al., 2004). Controversy still exists regarding the contribution of potential mechanisms of action in soy protein, isoflavones, and other soy components on blood lipids and lipoproteins (Azadbakht et al., 2007).

Mechanisms of action are typically based on the connection between isoflavones and estrogen receptors inside cells—similar to the connection between these cells and estradiol— influencing cholesterol and lipoprotein metabolism. In addition, isoflavones would be able to act like antioxidants, inhibiting the thrombotic process and blocking the proliferation of smooth-muscle cells in artery walls (Cavallini et al., 2009). On the other hand, a high consumption of soy products can promote a reduced consumption of foods rich in saturated fats and cholesterol, exerting an indirect effect on the blood cholesterol decrease. It seems that LDL oxidation occurs inside arteries when these particles become isolated from hydro-soluble antioxidants. Some authors hypothesize that isoflavones could be incorporated in the lipoproteins and could protect against oxidation (Cavallini et al., 2009).

**Soy and Isoflavones in Glycemic Control**

Metabolic syndrome is a clustering of metabolic abnormalities that occurs in individuals with impaired insulin sensitivity. Foods that improve insulin sensitivity might also modulate the metabolic abnormalities linked with insulin resistance. Soy consumption could reduce the risk of metabolic syndrome through its beneficial
components, including complex carbohydrates, unsaturated fatty acids, vegetable protein, soluble fiber, oligosaccharides, vitamins, and minerals, inositol-derived substances such as lipintol and pinitol, and phytoestrogens—particularly the isoflavones genistein, diadzein, and glycitein.

It was observed that soy consumption improved glycemic control. HOMA-IR decreased significantly during a soy nut diet. This finding may support a direct pharmacologic effect of soy constituents. The hypothesis that soy isoflavones modulate glycemic control is not proven yet.

Diabetes Mellitus is characterized as a metabolic disorder associated with an absolute or relative deficiency of insulin, presenting metabolic alterations and vascular and neuropathic problems as clinical consequences (Rolim et al., 2008).

Insulin is the main regulatory hormone of glucose metabolism. This hormone activates glucose and amino acid transportation, glycogen and lipidic metabolism, proteic syntheses, and specific gene transcriptions. The biological actions of insulin are initiated by the connection of this hormone to specific receptors located in the plasmatic membranes of responsive cells. It has been emphasis how the initial sign promoted by the connection of insulin to the receptor is converted to the final effects of this hormone on growth and metabolism and how this signalization is altered in states of insulin resistance, such as in the DM type 2 (Esteves et al, 2001).

In the cells, insulin receptors are enzymes stimulated by itself, with protein tirosina quinase activity. The general mechanism of insulin action initiates with the connection of this hormone to the tirosina quinase receptors in the cellular membrane. This connection is dependent on plasmatic glucose concentrations and triggers a series of intracellular reactions that lead to insulin secretion. This process is also mediated by intermedial signals such as calcium levels and AMP cycles (cAMP).
Studies have shown that intracellular calcium (Ca\(^{2+}\)) is strictly related to insulin secretion. The key effect of Ca\(^{2+}\) in insulin secretion involves the acceleration of a protein kinase that is dependent on Ca\(^{2+}\)/calmodulin (Esteves et al., 2001).

Due to the inhibitory effect of the tirosin kinase protein, genistein has been studied as a regulator component of insulin secretion, a secretion that is controlled by the complex cellular signaling mechanisms of this receptor. It was observed in animal studies that genistein produced beneficial effects in diabetes treatment (Esteves et al., 2001).

The mechanisms that isoflavones, especially genistein, use to exert this effect still are not well elucidated. It is known that genistein has the potential to inhibit tirosin kinase proteins and that the action in the protein receptors promotes increased insulin secretion. Research has shown that genistein activates the receptors, creating an accumulation of cAMP and intracellular calcium. Thus, we can infer that a possible action mechanism composed of these elements would be caused by the activation of kinase proteins (A and C). Quinases A and C activate the protein phosphorylation, which culminates with the gene transcription for insulin that increases the secretion of this hormone. In contrast, these kinase proteins are activated by membrane receptors connected to the G protein and not by tirosin kinase receptors. The tirosin kinase receptor deactivation by genistein would promote the activation of kinase proteins A and C by the dependent mechanisms of calcium and cAMP. In addition, it has been observed that daidzein promotes a proportional increase in insulin secretion to genistein, and daidzein is not an inhibitor of tirosin kinases, suggesting again that the mechanism that leads to increased insulin secretion involves much more than tirosin kinase receptor inactivation (Figure 2).
The glycemic index (GI) describes different effects on the body by ranking carbohydrates according to their impact on blood-glucose levels. Choosing low-glycemic index carbohydrates, which produce small fluctuations in blood glucose and insulin levels, is an important co-adjuvant tool to long-term health, reducing the risk of Non Alcoholic Fatty Liver Disease (NAFLD), promoting better glycemic control, and improving some parameters of Metabolic Syndrome (Dâmaso et al., 2009). This way, foods with a low GI may provide a variety of health benefits. Blair et al. (2006) measured the GIs and insulin indexes (II) of select soy foods, and they observed that soy food products generally have low GI values and low to medium GL values. Improvements in ingredient selection and usage may further improve glycemic responses to soy foods. The low GI of soy foods appears to be an additional benefit of soy for human health and suggests that soy foods are an appropriate part of diet plans intended to improve control over blood glucose and insulin levels (Blair et al., 2006).

In 32 postmenopausal women with diet-controlled type 2 diabetes, it was verified that dietary supplementation with soy phytoestrogens favorably altered insulin resistance, glycemic control, and serum lipoproteins, thereby improving their cardiovascular risk profiles (Jayagopal, 2002).

**Soy and Isoflavones in NAFLD**

The term “non-alcoholic fatty liver disease” (NAFLD) has been used to describe a larger spectrum of steatosis liver diseases commonly associated with the metabolic syndrome (MS) that represents a constellation of related health diseases. However, obesity-associated NAFLD was first described nearly 50 years ago but only recently
has been confirmed to be partially caused by the complexity of the biochemical machine that plays an important intermediary role between inflammatory processes and cellular mechanisms of NAFLD-related diseases (Zivkovic et al., 2007).

NAFLD is considered the hepatic manifestation of metabolic syndrome, including multifactorial diseases that involve complex interactions of genetics, diet, and lifestyle and are defined as the accumulation of lipids, primarily in the form of triacilglycerol, in individuals who do not consume significant amounts of alcohol (20g ethanol/d) (de Piano et al., 2007). Given the close relationship between obesity, metabolic syndrome, and the development of NAFLD, it is not surprising that many NAFLD patients present multiple components of metabolic syndrome. Therefore, the management strategies for such patients need to be predominantly supported by diet therapy to promote weight loss as well as improve related co-morbidities; however, multidisciplinary approaches, including clinical examinations, exercise, and psychological counselling are recommended for long-term success.

Prevention of hyperinsulinemia may ameliorate metabolic abnormalities that occur in the liver as a consequence of obesity. There is evidence that type of dietary protein could play an important role in the secretion of insulin by the pancreas and in the regulation of hepatic lipogenesis mediated by sterol regulatory element binding protein-1 (SREBP-1) (Torre-Villalvazo et al, 2008).

The induction by insulin of SREBP-1 in the liver is a rapid process (Azzout-Marniche et al., 2000). In fasting rats, after the consumption of a casein diet, their serum insulin concentrations rose rapidly, reaching maximal concentration after 1 h. In these animals, hepatic SREBP-1 mRNA concentrations increased in proportion to serum insulin levels. Interestingly, when casein was replaced with soy protein, there was a 36% reduction in insulin concentration, which in turn reduced SREBP-1 mRNA
levels in the liver by approximately 54% (Ascencio et al., 2004). Recent results have shown that repression of SREBP-1 expression by soy protein is also due to an increase in serum glucagon concentration, decreasing the insulin:glucagon ratio (unpublished results). As a consequence, the reduction of SREBP-1 by soy protein intake also reduced gene expression of enzymes involved in fatty acid biosynthesis (Torres et al., 2006) (Figure 3).

The primary event in the progression of NAFLD constitutes the deposition of triglycerides in the cytoplasm of hepatocytes (Unger, 2002). It has been shown that excess triglycerides may cause fibrosis in nonadipocyte cells. Hepatic fibrosis is a common finding in obese, nonalcoholic patients with excessive hepatic triglyceride depositions (Browning et al., 2004). Soy protein consumption prevents triglyceride accumulation in the liver, decreasing the deleterious effects of lipotoxicity (Ascencio et al., 2004). The mechanisms by which soy protein prevents triglyceride accumulation is by reducing hepatic fatty acid and triglyceride biosyntheses and by increasing fatty acid oxidation through the activation of the transcription factor peroxisome proliferator-activated receptor α (PPARα) (Tovar et al., 2005). PPARα is a ligand-dependent transcription factor of the nuclear receptor superfamily (Mehendale, 2000).

It controls fatty acid oxidative metabolism through the transcriptional induction of carnitine–palmitoyl transferase 1 (CPT-1) and several enzymes for h-oxidation (Ip et al., 003). A soy protein diet up-regulates PPAR-α gene expression in the liver and is associated with a higher content of CPT-1 mRNA, with respect to rats fed with casein (Tovar et al., 2005). This pattern of gene expression is associated with an increased carbohydrate and lipid oxidation and energy expenditure as seen in Type 2 diabetic mice (Ishihara et al., 2003).

Although some reports have suggested that soy protein changes in expression of
the genes is related to lipid metabolism in liver and in adipose tissue, there are few reports concerned with the comprehensive influence of the intake of soy protein on gene expression (Takamatsu et al., 2004).

3. Summary Points

- Metabolic syndrome is a constellation of medical disorders managed in a multidisciplinary approach that leads to risk factors for diabetes and premature cardiovascular disease.
- Lifestyle changes are the first line and mainstay of management. The basal universal approach consists in the clinical examinations, nutrition, exercise, and psychological counselling.
- It is important to identify new nutritional strategies including daily soy consumption, in the prevention and treatment of obesity and related co-morbidities, since we could verify beneficial actions of soy in several metabolic syndrome components.
- Future research is needed to discover other benefits offered by soy and soy products on metabolic syndrome control and on the co-morbidities related to obesity.
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Figure 1. Functions of Isoflavone in Metabolic Syndrome parameters
**Figure 2.** Possible mechanisms of isoflavones action in the insulin secretion control.
**Figure 3.** Mechanism of action of soy protein.

Soy protein consumption decreases the insulin/glucagon ratio and reduces the expression of SREBP-1, which in turn decreases the expression of lipogenic genes. Isoflavones stimulate SREBP-2, increasing serum cholesterol clearance. Low hepatic cholesterol reduces oxysterol concentrations, preventing the stimulation of LXR-a, which additionally reduces SREBP-1 expression. As a consequence of soy protein consumption, there is a low concentration of VLDL particles. In addition, low serum cholesterol levels observed with soy protein diets prevent kidney damage, decreasing inflammatory response and increasing NO production.