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REVIEWS: CURRENT TOPICS

Effects of dietary fibers on disturbances clustered in the metabolic syndrome☆

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Abstract

Because of its growing prevalence in Western countries, the metabolic syndrome, a common metabolic disorder that clusters a constellation of abnormalities, including central obesity, hypertension, dyslipidemia and insulin resistance, is emerging as one of the most important public health problems in the world, taking into account that it is a major risk factor mainly for type 2 diabetes and cardiovascular diseases, and also for many types of cancer. Although the pathogenesis of this syndrome is complex and not fully understood, obesity and insulin resistance, accompanied by an altered profile of number of hormones and cytokines produced by the adipose tissue, seem to be the main causative agents. A prime therapeutic approach to the prevention and treatment of this syndrome involves lifestyle changes. Among dietary modifications, dietary fiber intake could play an interesting role in the management of metabolic syndrome through different mechanisms related to its dietary sources, specific chemical structure and physical properties, or fermentability in the gut. According to all of these variables, the different types of dietary fibers have been reported to take part in the control of body weight, glucose and lipid homeostasis, insulin sensitivity and in the regulation of many inflammation markers involved in the pathogenesis of metabolic syndrome, and which are also considered to be among its features.

Keywords: Dietary fiber; Metabolic syndrome; Cardiovascular disease; Type 2 diabetes; Obesity; Inflammatory markers

1. Introduction

Metabolic syndrome describes a cluster of metabolic abnormalities that co-occur in an individual and that are well documented as independent risk factors for cardiovascular disease. When grouped together in this syndrome, the risk of developing cardiovascular disease, as well as type 2 diabetes, is increased [1,2]. Prevalence of this syndrome is increasing dramatically throughout the world, not only in adult or older populations [3,4], but also in children and young people [5,6], running in parallel with the worldwide epidemic of obesity and diabetes [1]. Because of the elevated risk it presents of developing cardiovascular disease and type 2 diabetes, the metabolic syndrome has become an important public health problem that demands urgent therapeutic attention and interventional approaches. The essential emphasis in the management of metabolic syndrome *per se* is to mitigate modifiable risk factors such as obesity, physical inactivity and an inappropriate atherogenic diet through lifestyle changes [7]. Although the ideal dietary pattern for patients with metabolic syndrome is yet to be ascertained, there is a growing opinion among nutritionists and scientists about the benefits of an increased dietary intake of fruits, legumes, vegetables and cereals, which are considered as important sources of dietary fiber. Dietary fiber, an integral component of the diet, would appear to be particularly beneficial with regard to its putative role in the control of most of the metabolic disturbances clustered in the metabolic syndrome [8,9]. A large number of studies in humans and experimental models have evidenced the efficacy of dietary fiber in regulating body weight, food intake, glucose homeostasis, insulin sensitivity and other cardiovascular disease risk factors such as serum lipid profile, hypertension and systemic

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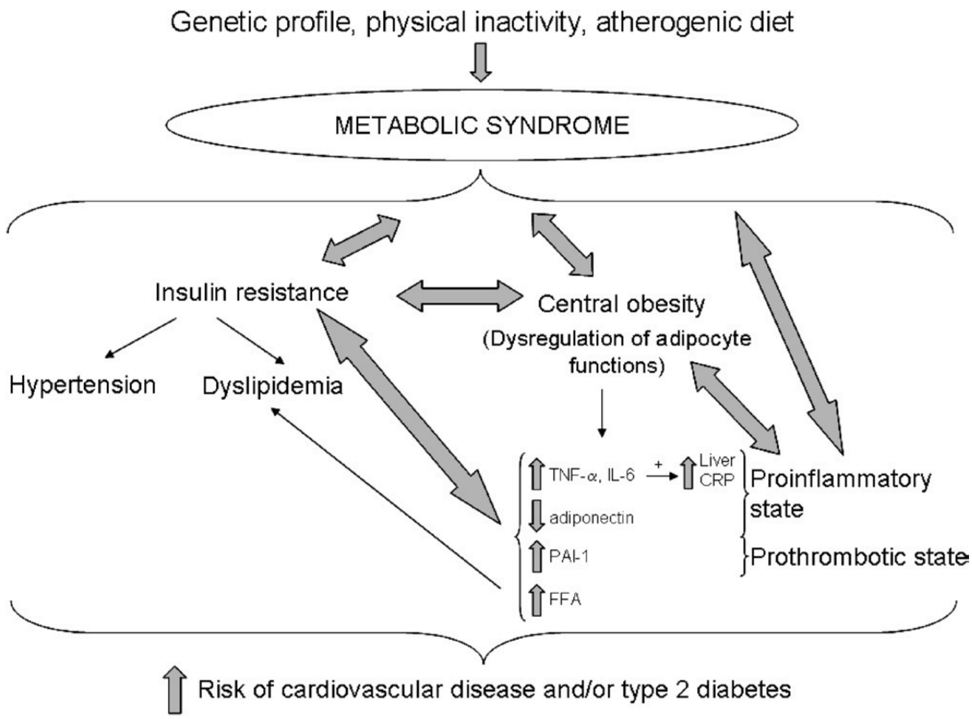

Fig. 1. Abnormalities clustered in the metabolic syndrome and pathophysiological main causal agents. FFA, free fatty acid.

inflammatory markers [8–10]. Moreover, a number of randomized studies have described the positive effects of foods rich in dietary fiber on obesity, cardiovascular diseases or type 2 diabetes, and recent ones refer specifically to their beneficial effects on most of the alterations present in individuals affected by the metabolic syndrome [11,12].

The purpose of the present review is to present an outcome of the main findings related to the effects of dietary fibers in the control of physiological and metabolic abnormalities clustered in the metabolic syndrome, resulting in a preventive action against the risk of developing mainly type 2 diabetes and cardiovascular diseases, and other important pathologies such as many kinds of cancer. An approach concerning the possible mechanisms of action of the different types of fiber on the core components of this syndrome is presented. Special mention is made of the effects of dietary fibers or high-fiber foods and the mechanisms by which they could regulate the production of inflammation markers involved in the pathogenic pathway of metabolic syndrome such as proinflammatory cytokines, acute-phase response markers and the anti-inflammatory adipocytokine adiponectin reported in recent studies.

2. Features of the metabolic syndrome

Since it was first described in the 1920s, the metabolic syndrome has appeared to be one of the most important problems of worldwide public health in the 21st century, taking into account its growing prevalence in developed and developing countries [2]. The metabolic syndrome, which clusters as the main metabolic abnormalities central obesity, low concentrations of plasma high-density lipoprotein (HDL) cholesterol, high levels of triglycerides, hypertension and hyperglycemia, together with insulin resistance [2,13], is associated with an increased risk of both cardiovascular disease [14,15] and type 2 diabetes [16]. Furthermore, several studies have indicated that it predicts future diabetes cases [17,18], and lately, other studies have also established that metabolic syndrome is a risk factor for different types of cancer such as colorectal and breast cancer [19,20].

The management of disorders clustered in this syndrome and in the mechanisms involved in its development is of great interest to prevent or reduce risk of all of these pathologies. Many definitions of this syndrome have been proposed by expert groups during all these years, and although they provide different clinical and epidemiological criteria to identify the components of the metabolic disturbances that are clustered in this syndrome, they agree on its core components: obesity, insulin resistance, dyslipidemia and hypertension [21–23]. Recently, following a workshop consensus statement from the International Diabetes Federation, a new worldwide definition of the metabolic syndrome has been afforded, and participants agreed to include the following as its general features: abnormal body fat distribution, insulin resistance, atherogenic dyslipidemia, elevated blood pressure, proinflammatory and prothrombotic states [24].

The pathogenesis of the metabolic syndrome is complex and not fully elucidated. Central obesity and adipose tissue disorders together with insulin resistance appear to stand out as the main potential etiologic factors [2,25,26], although other causes that play a main role in the development of metabolic syndrome include genetic profile and other acquired factors such as physical inactivity, ageing, proinflammatory and prothrombotic states and hormonal dysregulation [2,24,25,27] (Fig. 1).

Elevated levels of inflammatory markers and proinflammatory cytokines evidenced implication of an inflammatory state in the metabolic syndrome [28–31]. Among acute-phase response markers and inflammatory cytokines, interleukin (IL) 6, C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α) have been directly related to the metabolic syndrome and most of its features, i.e., obesity and insulin resistance [28–31]. A recent review established a hypothesis to explain metabolic syndrome pathogenesis from a proinflammatory state that induces insulin resistance and leads to clinical and biochemical manifestations of the metabolic syndrome. This resistance to insulin action promotes inflammation further through an increase in free fatty acid concentration and interference with the anti-inflammatory effect of insulin [29]. From another perspective, the pathway leading to this pathology would involve the abnormal production of hormones and cytokines from adipose tissue [30,31], namely, excessive production of IL-6, TNF-α and the prothrombotic agent plasminogen activator inhibitor type 1 (PAI-1) and low secretion of the protective adipocytokine adiponectin, a molecule that exerts anti-inflammatory, antiatherogenic and antidiabetic effects and whose production is down-regulated in individuals with metabolic syndrome [32]. In fact, hypoadiponectinemia has been demonstrated to be independently associated with the metabolic syndrome, indeed, more strongly than are any other inflammatory markers [33], and it seems to play an important role in the pathogenesis of metabolic syndrome [32]. On the other hand, IL-6 overproduction by adipose tissue in obesity may induce hepatic CRP synthesis and promote the onset of cardiovascular complications. In any case, proinflammatory/prothrombotic state, insulin resistance and central obesity are intimately associated, and all of these factors are related to the rest of abnormalities clustered in the metabolic syndrome.

3. Dietary fiber

It is important to consider that the definition of dietary fiber is complex and in continuous evolution [34]. According to the American Association of Cereal Chemists, dietary fiber consists of edible parts of plants or analogous carbohydrates that resist digestion and absorption in the small intestine, with complete or partial fermentation in the large intestine [35]. It is a very complex group of substances, and although opposing groups around the world argue about which substances should be classified as dietary fiber, most of them would agree that it includes the indigestible, nonstarch polysaccharides, cellulose and hemicellulose, oligosaccharides, pectins, gums and waxes [36]. On the basis of water solubility, dietary fiber can be divided into insoluble and soluble fiber. The former includes cellulose, many hemicelluloses and lignin. Among soluble fibers, we can consider pectins, gums, mucilages and storage polysaccharides. In the past decades, dietary fiber has been recognized to play an important role in a healthy diet; its benefits are not disputed and all dietary fibers are presumed to have a physiological effect [35,37]. Dietary fiber is considered as a useful functional food, i.e., a food with health benefits, in many situations: its benefits for health maintenance and disease prevention have been plainly demonstrated, and it figures as a main component in medical nutrition therapy. To consider the physiological properties of different dietary fibers, concepts others than their water solubility, such as their viscosity or capacity to form gels, or their fermentation capability in the lower part of the gut must be taken into account. In fact, consumption of dietary fibers that are viscous (mainly soluble fibers) lowers blood cholesterol levels and helps to normalize blood glucose and insulin levels, making these fibers part of the dietary plans used to treat or prevent cardiovascular disease and type 2 diabetes, while fibers that are incompletely or slowly fermented in the large intestine promote normal laxation and are integral components of diets used in the management of intestinal disorders, such as constipation, or in the prevention of the development of diverticulosis and diverticulitis [38]. Furthermore, many epidemiological studies have provided evidence that consumption of fiber-rich foods may reduce risk of certain types of cancer, namely, colon, rectum and breast cancers [39–41]. Nevertheless, an adequate diet rich in fiber also contains other micronutrients such as minerals, vitamins, phenols, phytoestrogens and unsaturated fatty acids, which can contribute to the dietary health properties.

Although it can be provided in the diet by natural sources such as cereals, fruits, vegetables or legumes or by supplement, except in certain therapeutic situations, dietary fiber should be obtained through consumption of foods [38]. In the daily diet, we usually ingest a mixture of soluble and insoluble dietary fiber, and it is difficult to separate their effects, as a balanced diet is composed of a combination of both. Furthermore, food rich in fiber may contain soluble and insoluble fiber in different quantities [42]. In general, although cereals are mainly considered a good source of insoluble fiber, as the majority of grains, including wheat, rice or rye contain a large amount of this type of dietary fiber, cereals usually contain a relatively low quantity (about 25%) of soluble fiber [42]. Exceptions are oats, a very good source of soluble fibers (about 50%). While legumes constitute important sources of both types of fiber, the fiber content of fruits and vegetables is generally lower than that of cereals and legumes and consists mainly of the soluble type [42].

3.1. Dietary fiber and obesity

Abdominal obesity and abnormal distribution of fat in the individual constitute the main abnormalities of the metabolic syndrome. This feature is highly related with insulin resistance [43] and may be particularly detrimental to the cardiovascular function. An interesting and effective strategy to improve the metabolic syndrome may be loss of weight and, more specifically, reduction of body fat [7,27,44]. Lifestyle changes, such as regular physical activity and nutrition improvement, are the basis for successful long-term weight loss and control of overweight and obesity [7,45]. Among dietary changes, indirect evidence from a number of epidemiological studies suggests a beneficial role of a high-fiber diet in weight control [46,47]. Dietary fiber supplementation has been shown to reduce body weight in several human trials [48,49]. Epidemiological or cross-sectional observational studies have shown that intake of dietary fiber is inversely correlated with body weight [50] and body fat [51]. A prospective cohort study (the Nurses' Health Study) established the association between changes in whole-grain consumption and weight gain over 12 years in a middle-aged female population [52]. In this study, the cross-sectional analysis at baseline showed that body weight gain was inversely associated with whole-grain intake but positively associated with refined-grain intake. Longitudinally, participants who had greater intake of whole grains tended to gain less weight than did those with greater intake of refined grains. Moreover, compared with women who had decreased intake of high-fiber or whole-grain products, those who had the greatest increase in intake of high fiber or whole grains (median intake 42.4 g/day) reduced by 49% the odds of becoming obese. In line with these findings, another study conducted over 8 years in 27,082 men aged 40–75 years also demonstrated a dose-related inverse association between an increase in whole-grain intake and long-term weight gain [53]. Moreover, other food sources of dietary fiber have been inversely linked to body weight. In support of the potential effect of soluble fiber sources, fruit fiber and apples have also been inversely associated with long-term weight gain. In a feeding study among overweight women aged 30–50 years, supplementation with apples and pears consumed three times a day for 12 weeks contributed to weight loss [54]. Furthermore, one of the prospective studies mentioned above also showed that increase in fruit fiber intake (predominantly accounted for by apples) reduced weight gain in a dose–response relation that was even stronger than that exhibited by cereal fiber [53]. Surprisingly, vegetable fiber did not appear to reduce long-term weight gain in this population [53].

Most evidence points to the effect of dietary fiber on hunger and satiety, based on different mechanisms, through its intrinsic effects and hormonal responses. Dietary fiber has consistently been shown to have a higher satiety value when compared with digestible complex carbohydrates and simple sugars [55,56]. High-fiber food may promote satiation (lower meal energy content) and satiety (longer duration between meals) due to its bulk [57] and relatively low energy density [56], leading to decreased energy intake. Most soluble fiber types result in highly viscous intestinal contents with gel-like properties that may delay gastric emptying and/or intestinal absorption [46]. In the small intestine, soluble fiber may blunt postprandial glycemic and insulinemic responses that are linked to reductions in the rate of return of hunger and subsequent energy intake [58]. Fiber may also affect secretion of gut hormones or peptides, such as cholecystokinin or the glucagon-like peptide-1 (GLP-1), independent of glycemic response, which may act as satiety factors or alter glucose homeostasis [56]. Some studies have shown prolonged increases in circulating cholecystokinin after ingestion of fiber-rich meals relative to energy-matched low-fiber meals [59,60]. Cholecystokinin is secreted from cells in the small intestine on ingestion of food, and functions in the stimulation of pancreatic secretion, regulation of gastric emptying and central inducement of satiety [61]. Experiments in rats have shown that the satiogenic effect of other soluble fibers such as oligofructose and other fructans has been associated with an important increase in circulating anorexigenic gut peptides such as GLP-1 and peptide YY, as well as with a reduction in serum ghrelin levels [62]. The peptide GLP-1 plays an interesting role in controlling appetite and food intake and, consequently, in the regulation of body weight.

In any case, controversial positions exist about how dietary fiber must be afforded to be efficient in preventing or treating obesity. Most studies support the view that dietary fiber should only be obtained through consumption of foods rich in fiber [38,52,53,63] and not by supplements. Although studies in both experimental models [64–66] and human trials [48,49] describe an important decrease in weight gain by using fiber supplements rich in soluble fiber such as psyllium, guar gum or glucomannan, after an exhaustive review and meta-analysis of most clinical trials, the evidence for most of these dietary supplements as aids in reducing body weight in humans is not definitely convincing [67,68].

3.2. Dietary fiber and insulin resistance/hyperglycemia

As another main component and causative factor of the metabolic syndrome, insulin resistance, accompanied or not by hyperglycemia, is an essential target in the therapeutic approach of this syndrome. Clinical trials and observational epidemiological studies (Table 1) demonstrate the importance of lifestyle changes to improve insulin sensitivity and glucose tolerance, and among these changes, the diet and specific nutrients, such as dietary fiber, play an important role in the management of insulin resistance and incidence of type 2 diabetes [69]. In this way, epidemiological studies have shown that diets rich in dietary fiber are associated with a reduced risk of diabetes and cardiovascular disease [70–72], and a cross-sectional analysis has revealed that the dietary intake of total as well as soluble and insoluble fiber is inversely associated with insulin resistance, supporting evidence that a high intake of dietary fiber is associated with enhanced insulin sensitivity [73].

Soluble dietary fiber has been reported to reduce postprandial glucose levels and to improve insulin sensitivity in both diabetic and nondiabetic persons [74–77]. It also favors increased glucose uptake into skeletal muscle and improves insulin sensitivity by increasing the viscosity of the stomach contents [78] and impeding digestion of carbohydrate and absorption of macronutrients [79]. However, the molecular basis for these effects of dietary fiber remains unclear. A study in stroke-prone spontaneously hypertensive rats suggests that psyllium supplementation effectively prevents insulin resistance by increasing skeletal muscle plasma membrane content of the insulin-responsive glucose transporter type 4 (GLUT-4), by a mechanism different from the activation of the phosphatidylinositol-3 kinase pathway [80]. A hypothesis highlighting this concern suggests that a series of fatty acids stimulate peroxisome proliferator-activated receptor (PPAR) γ, whose activation has been reported to increase GLUT-4 content in adipocytes [81]. Therefore, these authors speculate that it is likely that short-chain fatty acids (SCFAs), such as propionic and butyric acids, which result from anaerobic bacterial fermentation of soluble fermentable dietary fiber in the colon [82], increase muscle GLUT-4 via PPARγ [80].

However, the control of glycemia and insulin resistance cannot be attributed only to soluble dietary fiber. Although insoluble fibers are mainly nonviscous and have negligible effects on postprandial glucose responses and only small effects on macronutrient absorption [83], surprisingly, most epidemiological studies clearly show that increased consumption of mainly insoluble cereal fibers and whole grains has been recommended to improve insulin sensitivity and to lower serum insulin concentrations [73,84,85]. In the Framingham Offspring Study, it has been shown that not only total but also fruit and cereal fiber intakes were inversely related to insulin resistance [11], as determined by the homeostasis model assessment of insulin resistance (HOMA-IR). A previous study demonstrated that cereal fiber intake was favorably related to fasting insulin concentrations [86]. In fact, recently, a randomized, controlled, single-blind, crossover study performed in overweight or obese subjects with normal glucose metabolism showed that

Table 1
Effect of fiber intake on hyperglycemia and insulin resistance: clinical studies

Author [reference]	Study design	Major findings
Anderson et al. [75]	Randomized, double-blind, placebo-controlled parallel study in 34 men, aged 30–70 years, with type 2 diabetes and mild to moderate hypercholesterolemia. After a 2-week dietary-stabilization phase consuming a diet for diabetes, subjects followed an 8-week treatment phase consuming the diet and receiving either 5.1 g psyllium or cellulose placebo twice daily.	All-day and postlunch postprandial glucose concentrations were 11.0% (P<.05) and 19.2% (P<.01) lower in the psyllium than in the cellulose placebo group.
Sierra et al. [76]	Randomized and crossover analysis of the acute effects of soluble fibers ispaghula husk and guar gum on postprandial glucose and insulin concentrations in 10 healthy women aged 30–48 years. An oral glucose load (50 g) with and without fiber (10.5 g) was administered in the morning after an overnight fast.	Mean serum insulin concentrations decreased significantly in the presence of both soluble fibers. The insulin AUC was reduced by 36.1% for ispaghula husk and 39.4% for guar gum (differences were significant between both fibers and glucose alone; Wilcoxon's test). The glucose AUC was significantly reduced by 11.1% for ispaghula husk but not for guar gum (reduction 2.6%)
Sierra et al. [77]	Clinical study in three phases among 20 type 2 diabetic patients. Phase 1 (1 week), Phase 2 (treatment, 14 g of psyllium/day, 6 weeks) and Phase 3 (4 weeks). Phases 1 and 3: diet for diabetes plus sulfonylurea treatment.	The glucose AUC in the presence of fiber (Phase 2) was significantly lower (12.2% and 11.9%, respectively) than those obtained at the end of Phases 1 and 3. Insulin AUC decreased by 5% in Phase 2 compared with the value in Phase 1 and was 15% lower than in Phase 3, although no significant differences were observed.
Pereira et al. [84]	Randomized, nonblinded, crossover controlled feeding trial with two 6-week feeding periods in 11 overweight or obese hyperinsulinemic adults aged 25–56 years. Participants randomly received a whole-grain or a refined-grain diet during the first feeding period and then were fed the other diet for the second period.	Fasting insulin was lower (10%) following periods with the whole-grain (141 ± 3.9 pmol/L) than with the refined-grain (156 ± 3.9 pmol/L) diet (P=.03). The HOMA also showed that insulin resistance was lower with the whole-grain (5.4 ± 0.18 U) than with the refined-grain (6.2 ± 0.18 U) diet (P<.01). No significant differences were observed for fasting glucose or postprandial insulin.
Esposito et al. [85]	Randomized single-blind trial in 120 obese women aged 20–46 years, for 3 years. Intervention group diet: low-energy diet with foods rich in complex carbohydrates, monounsaturated fat and fiber (25 vs. 16 g/day in the control group).	After 2 years, women in the intervention group exhibited decreased body mass index (−4.2; P<.001), fasting insulin (−3 μU/ml; P= 009) and HOMA (−0.9; P=.008).
Weickert et al. [87]	Randomized, controlled, single-blind, crossover study among 17 overweight or obese subjects with normal glucose metabolism. Diet: three macronutrient-matched portions of fiber-enriched oat bread (white bread enriched with 31.2 g insoluble fiber/day) or control (white bread) over 72 h.	Intake of fiber-enriched bread significantly improved whole-body glucose disposal, equivalent to an 8% improvement of insulin sensitivity. Mean insulin concentrations were not significantly changed after fiber intake compared with control. Accordingly, mean insulin action was significantly enhanced by 12% after fiber intake.

AUC, area under the curve; HOMA, homeostasis model assessment of insulin sensitivity in the fasting state.

intake of cereal within the recommended daily range [38] for 3 days significantly improved whole-body insulin sensitivity [87]. Notably, associations between cereal fiber intake and reduced diabetes risk remain significant after correction for confounding factors, e.g., changes in body weight, age, exercise, intake of fat, smoking, alcohol intake or a family history of diabetes [88]. Although, to date, no obvious mechanism for the beneficial effects of cereal fiber has been described, consumption of purified insoluble fiber, which is the predominant fraction of cereal fiber, might improve whole-body insulin sensitivity [89]: the consumption of insoluble dietary fibers within the recommended daily fiber intake [38] significantly accelerated the early insulin response, an effect that was associated with an earlier increase of postprandial active values of the incretin hormone glucose-dependent insulinotropic polypeptide (GIP), whereas GLP-1 was unaffected. Although the effects of dietary fiber on postprandial GIP and GLP-1 responses have not yet been elicited, the results showed in this study by insoluble fiber on these hormones would not be the same as those produced by soluble dietary fibers such as oligofructose, which has been described to increase GIP secretion and augment GLP-1 concentration [62,90,91]. These short-term effects of cereal fiber do not seem to be influenced by colonic fermentation. In any case, larger and longer term well-controlled studies also including subjects with impaired glucose metabolism should be performed to confirm these findings, and other techniques using animal models should be used to elucidate the mechanisms involved in the effects of both soluble and insoluble fiber on insulin sensitivity and the role played by incretin hormones in such mechanisms.

3.3. Dietary fiber and dyslipidemia

Most individuals with metabolic syndrome show atherogenic dyslipidemia, characterized by low levels of HDL cholesterol and high concentration of triglycerides in plasma, a profile that constitutes an important risk factor for cardiovascular diseases. The influence of dietary fibers on blood lipids has been extensively documented in the last decades. Numerous clinical and animal studies have demonstrated the hypocholesterolemic properties of mainly soluble fibers [65,66,75,77,92]. Randomized controlled trials have shown that soluble fiber in oat products decreases blood concentration of cholesterol, especially low-density lipoprotein (LDL) cholesterol, among hypercholesterolemic patients [93]. In a meta-analysis, Brown et al. [94] evaluated the hypocholesterolemic effects of pectin, psyllium, oat bran and guar gum from 67 controlled trials. These authors concluded that all of those soluble fibers were equally effective in reducing plasma total and LDL cholesterol, while no significant changes were observed in plasma HDL cholesterol or triglyceride concentrations. In fact, this meta-analysis indicates that the effect of fiber by itself on plasma cholesterol is likely to be modest, although significant. However, when intact foods are considered as the source of fiber, the overall effect on disease risk appears to be greater. In any case, studies in healthy individuals cannot conclude that soluble fiber intake reduces total and LDL cholesterol, as results are modest in some cases and no effect is found in others [95,96]. Hypertriglyceridemia is also a main component of metabolic syndrome atherogenic dyslipidemia. Studies dealing with dietary fiber effects on plasma triglyceride are not conclusive. Most of these studies, performed in both healthy and hypercholesterolemic individuals, describe no effect of many dietary fibers on this lipid component [94–96]. However, in a randomized crossover study in subjects with type 2 diabetes, a population prone to hypertriglyceridemia, intake of a high-fiber diet particularly rich in soluble fiber (total fiber intake 50 g/day, of which 25 g/day was soluble fiber and 25 g/day insoluble fiber) for 6 weeks lowered triglyceride concentrations by 10.2% [97]. It should be noted that this quantity of dietary fiber was largely above the level recommended by the American Diabetes Association (total fiber intake 24 g/day, of which 8 g was soluble fiber and 16 g insoluble fiber) and was quite superior to those used in other studies.

Investigations in animal models also describe a significant decrease in hypercholesterolemia in long-term studies in guinea pigs, hamsters and obese diabetic Zucker rats fed diets with an increased content in soluble dietary fibers such as psyllium, pectin and guar gum [65,66,98–100]. Furthermore, many of these studies also show reduction of plasma triglyceride concentrations following a prolonged intake of diets with high dietary fiber contents. This evident reduction of hypertriglyceridemia has been observed in the metabolic syndrome experimental model of obese Zucker rats fed for 25 weeks with a diet supplemented with 3.5% husks of *Plantago ovata* [66] or an apple diet [101]. Goto Kakizaki rats, a model of type 2 diabetes, fed a barley diet having a high dietary fiber content for 16 weeks, also showed an important diminution of triglycerides at the end of the experimental period [102]. Another study in a different experimental model of obesity, diabetes and hypertriglyceridemia, the Otsuka Long–Evans Tokushima fatty (OLEFT) rats, revealed that fermented mushroom milk diet containing 3% dietary fiber also lowered triglyceride levels in this model [103]. Moreover, chronic oligofructose supplementation as a soluble dietary fiber has also been described to significantly decrease postprandial triglyceridemia in Wistar rats [90,91,104].

The mechanisms involved in the hypocholesterolemic effects of dietary fiber remain undefined. Satiation and satiety effects underlie the small cholesterol-lowering properties of insoluble dietary fibers with moderate or low bile acid binding capabilities [105]. The use of animal models has triggered major advances in mechanistic approaches that help clarify the role of soluble fiber in lowering plasma cholesterol [92,98–100]. The major mechanism could be the ability of soluble fiber to increase bile acid loss [106]. The physicochemical properties of soluble fiber in the intestinal lumen have a very significant repercussion on hepatic cholesterol metabolism and on the synthesis, processing in the intravascular compartment and catabolism of lipoproteins. The main outcome of fiber action is a lowering of hepatic cholesterol pools as a result of cholesterol being diverted to bile acid synthesis, and less cholesterol delivery to the liver through chylomicron remnants [92]. The combination of all of these mechanisms results in the consistent hypocholesterolemic effect induced by soluble fiber (see Ref. [92] for review). Concerning the hypotriglyceridemic effects of soluble fiber such as psyllium, although mechanisms are not fully explained, they are consistent with a possible delay in the absorption of triglycerides and sugars from the small intestine [107]. In addition, fiber effects in decreasing the glycemic index may also play a role in decreasing plasma lipid levels [108]. Furthermore, the hypotriglyceridemic effect of oligofructose results from the inhibition of hepatic lipogenesis through modulation of fatty acid synthase activity [104,109]. It has been suggested [90] that incretin hormones could be involved in this hypolipidemic effect due to the control they exert on glucose homeostasis and insulin secretion, since glucose levels regulate fatty acid synthase gene expression in the liver, and this effect is potentiated by insulin [110]. Nevertheless, further experiments should be performed to clarify these mechanisms.

3.4. Dietary fiber and hypertension

Hypertension is another core component of the metabolic syndrome and an important risk factor for coronary heart disease, stroke, and renal disease [111]. The effects of dietary fiber supplementation on blood pressure have been examined in different trials and animal models in the last decades. A study has suggested that a diet containing fiber-rich grain, fruit and vegetables significantly decreases the need for antihypertension medication and improves blood pressure control in individuals with hypertension [112], and a randomized crossover study in 68 hyperlipidemic adults has shown small reductions in blood pressure after intake of high-fiber diet containing β-glucan or psyllium (8 g/day more than unsupplemented food in the control diet) [113]. Investigations in experimental models using different types of dietary fiber have supplied interesting results about their effects on blood pressure. The lowering effect of a diet supplemented with psyllium on systolic blood pressure has been reported in spontaneously hypertensive rats [114] and obese diabetic Zucker rat [66]. Another study in Goto Kakizaki type 2 diabetic rats showed reduced systolic blood pressure following long-term consumption of cereal dietary fiber [102]. These studies suggest that a diet high in fiber decreases blood pressure in hypertensive, obese and diabetic rats. In fact, prospective observational studies that have analyzed the relation between dietary fiber intake and risk of developing hypertension have indicated that an increased consumption of dietary fiber intake is inversely related with blood pressure and may contribute to prevent hypertension. In a randomized, double-blind, placebo-controlled trial in 110 participants aged 30 to 65 years who had untreated but higher than optimal blood pressure or Stage 1 hypertension [115], the effects of supplemented soluble fiber intake from oat bran (mean dietary intake of total, soluble and insoluble fiber increased by 10.6, 5.8 and 4.9 g/day in the high-fiber group and −0.1, 0.2 and −0.5 g/day in the low-fiber group, respectively) on blood pressure for 12 weeks were analyzed; both systolic and diastolic blood pressure were significantly reduced in the study participants who consumed a high-fiber diet (mean reduction by 3.4 and 2.2 mmHg, respectively). In contrast, blood pressure reduction was not significant in those who consumed a low-fiber diet. Furthermore, a meta-analysis on the published randomized trials has been recently presented, indicating that increased dietary fiber consumption may provide a safe and acceptable means to reduce blood pressure in patients with hypertension [116].

Several mechanisms for a potential effect of dietary fiber intake on blood pressure have been hypothesized. Dietary fiber has numerous effects on the digestion and absorption of foods. Insulin resistance and its concomitant compensatory hyperinsulinemia have been suggested as major underlying pathogenetic mechanisms for the development of hypertension [117]. In this way, effectiveness of both soluble and insoluble fibers in reducing insulin resistance and insulin levels in both diabetic and healthy persons [86,118,119] would contribute to treating or preventing hypertension. Intake of dietary fiber has also been shown to efficiently reduce body weight [48,49] and weight gain [52,53]. Increased body weight is a strong risk factor for hypertension [120]. Weight loss makes an important contribution to the treatment of hypertension, and prevention of weight gain through a higher intake of dietary fiber would likely have a large impact on the burden of hypertension and, consequently, cardiovascular diseases in the general population.

3.5. Dietary fiber and prothrombotic state

Individuals with metabolic syndrome also present an abnormal prothrombotic state characterized by elevated plasma fibrinogen and factor VII coagulant activity levels and raised concentrations of PAI-1, the main inhibitor of endogenous fibrinolysis. These hemostatic anomalies, which contribute to increase risk of coronary heart disease, may be corrected with dietary treatment of the underlying clinical disorder [121]. Most cross-sectional analyses reported a negative association between cereal fiber intake and fibrinogen [122,123], whereas other investigations [124–126] found no effect of high fiber consumption on fibrinogen. A randomized clinical trial of 201 subjects [125] found no effect of fiber intake on fibrinogen after 4 weeks' consumption of a diet high in cereal fiber compared with a diet low in cereal fiber. Another randomized analysis of the National Heart, Lung, and

Blood Institute Family Heart Study, a multicenter population-based study including 883 men and 1116 women, did not show a significant association between fiber intake and fibrinogen [126]. The authors did not attribute this negative finding to the difference in the source of fiber consumed, given the heterogeneity of the dietary constituents in this later study population, thinking that the possible explanation might be the lack of causal relation between fiber intake and fibrinogen concentration. In any case, another interesting finding of this later study was an inverse relation between PAI-1 and age- and energy-adjusted indexes of fiber intake for both men and women. After adjustment for anthropometric, lifestyle and metabolic factors, lowest and highest quintiles of fiber intake (9.7±3.7 and 29.2±5.4 g/day, respectively) led to reductions of (ln)PAI-1 values of 0.21 and 0.32 pmol/L (*P* for trend=.009) in men, while in women, this reduction was less pronounced, with lowered values of (ln)PAI-1 of 0.08 and 0.20 pmol/L (*P* for trend=.037) corresponding to the lowest and highest quintiles of fiber intake (10.8±3.9 and 26.8±9.4 g/day). These results were in agreement with those of previous studies. A cross-sectional study of 260 subjects [127] reported an inverse dose–response association between fiber-rich food (fruit, vegetables and root vegetables) consumption and PAI-1 concentrations after adjusting for anthropometric and metabolic factors. Furthermore, Sundell and Ranby [128] also described an inverse relation between dietary fiber intake and PAI-1 activity in a study among 11 healthy subjects whose diets were supplemented with 10 g oat husk per day for 2 weeks. They observed that PAI-1 activity was decreased by 50% compared to the baseline ($P<.05$), but no effect in other thrombotic parameters such as factor VII coagulant blood activity was shown.

Mechanisms to explain an inverse relation between fiber intake and PAI-1 have not yet been elucidated. In the case of fermentable soluble fiber, the production of SCFAs such as acetic, propionic and butyric acids as a result of their fermentation in the colon could contribute to this effect, as these acids may inhibit the hepatic synthesis of coagulation factors through inhibition of fatty acid release [129]. If dietary fiber has some effects on hepatic PAI-1 synthesis, the most likely mechanism is its reducing effects on fat absorption [107,108] and on the flow of triacylglycerol-rich lipoproteins to the liver. In addition, SCFAs decrease serum fatty acids [129], leading to increased insulin sensitivity and, subsequently, to a decrease in PAI-1 concentration, given the positive correlation between hyperinsulinemia and PAI-1 [130].

In any case, dietary trials of diseased and healthy volunteers suggest that the optimal antithrombotic diet for individuals suffering from the metabolic syndrome is not just a diet leading to weight loss or reduction of plasma levels of insulin and triglycerides. It also has to have a low-fat diet with a high content of foods rich in complex carbohydrates and dietary fiber of mixed origin [121].

3.6. Dietary fiber and proinflammatory state

There are interesting reports about the effects of dietary fiber intake on the acute-phase response marker CRP and the inflammatory cytokines IL-6, IL-18 and TNF-α, whose levels are found abnormally elevated in the metabolic syndrome, and some studies suggest an association between consumption of dietary fiber and the anti−inflammatory adipocytokine adiponectin. Results from two epidemiological studies using cross-sectional data from the National Health and Nutrition Examination Surveys (NHANES) 1999–2000 and evaluating the relation between dietary fiber and CRP have demonstrated an inverse association between dietary fiber intake and serum concentrations of CRP [131,132] (Table 2). Another recent observational study using cross-sectional and longitudinal analysis [133] (Table 2) confirms these inverse associations between total dietary fiber, soluble fiber, insoluble fiber and CRP concentrations, and its results support the hypothesis that persons consuming higher amounts of dietary fiber would have lower concentrations of CRP. In addition, this study provides evidence that both soluble and insoluble dietary fibers are associated with CRP concentrations [133]. Recently, a study in diabetic women [134] indicated that after adjustment for age, body mass index (BMI), lifestyle and dietary covariates, intake of both whole grains and bran was associated with significantly decreasing trends of CRP and TNF-α receptor 2 (TNF-R2). High intake of cereal fiber was also inversely associated with the lower levels of these systemic inflammatory markers among women with type 2 diabetes. Furthermore, a study in people with hypertension, diabetes or obesity or presenting most of these high-risk conditions shows that increasing dietary fiber intake results in a reduction of plasma CRP, concluding that there is a significant inverse association between dietary fiber intake and levels of inflammatory markers in individuals with diabetes, hypertension or obesity, and an even stronger relationship among people with two or more of these conditions of metabolic syndrome [118].

As previously mentioned, other vascular inflammatory markers have been related to changes in diets and their fiber content. A study comparing the effect of three different meals on circulating concentrations of IL-18 and adiponectin in healthy and type 2 diabetic subjects after a single meal showed that while a high-fat meal acutely increased circulating IL-18 concentration and decreased that of adiponectin in both diabetic and nondiabetic subjects, the fiber content of carbohydrate meals influenced the serum concentrations of IL-18 and adiponectin, as IL-18 concentration decreased and adiponectin levels remained unaltered after consumption of the high-carbohydrate high-fiber meal (16.8 g fiber), while IL-18 concentration decreased and adiponectin levels were transiently reduced with the high-carbohydrate low-fiber meal (4.5 g fiber) in both groups [135]. A randomized trial conducted in 120 obese women

Table 2
Effect of fiber intake on proinflammatory state associated to abnormalities clustered in the metabolic syndrome: clinical studies

Author [reference]	Study design	Major findings
King et al. [131]	Epidemiological study using cross-sectional data from NHANES 1999–2000, among 4900 adults aged 40–65 years. Separate data on type of dietary fiber were not available, so associations by type of dietary fiber could not be assessed.	Inverse association between dietary fiber intake and serum concentrations of CRP. Median CRP was 23% lower in subjects in the highest quartile of fiber consumption (19.5 g/day) compared with the lowest one (8.4 g/day) (P<.05). Increased fiber was significantly associated with a lower likelihood of elevated CRP (P<.05). Each additional gram per day of fiber consumed was associated with a 2% lower risk of elevated CRP.
Ajani et al. [132]	Epidemiological study using cross-sectional data from NHANES 1999–2000, among 3920 subjects ≥20 years old. Dietary fiber intake was used as the independent variable and included as both a continuous and a categorized (quintiles) variable, comprising a median range of between 5.1 and 32.0 g/day.	Inverse association between dietary fiber intake and serum concentrations of CRP. Odds for high concentrations of CRP were reduced by 40% among participants with the highest intake of dietary fiber compared with those of the lowest quintile (P<.001).
Ma et al. 2006 [133]	Prospective observational study designed for cross-sectional and longitudinal analyses, evaluating the association between dietary fiber and CRP among 524 healthy subjects for 1 year. Mean total dietary fiber intake was 16.1 g/day (ranged from 2.6 to 51.0 g/day). Mean soluble fiber intake was 5.8 g/day, and mean insoluble fiber intake was 10.3 g/day.	Intake of total dietary fiber (separately for soluble and insoluble fiber) decreased CRP concentrations in both cross-sectional and longitudinal analyses. The likelihood of elevated CRP concentrations was 63% lower in participants in the highest quartile of total fiber intake than in participants in the lowest quartile.
Esposito et al. 2003 [85]	Randomized single-blind trial in 120 obese women aged 20–46 years, for 3 years. Intervention group diet: low-energy diet with foods rich in complex carbohydrates, monounsaturated fat and fiber (25 vs. 16 g/day in the control group).	After 2 years, women in the intervention group exhibited decreased concentrations of IL-6 (−1.1 pg/ml, P=.009), IL-18 (−57 pg/ml; P=.2) and CRP (−1.6 mg/ml; P=.008), while adiponectin levels increased (2.2 μg/ml; P=.02) with respect to the control group.
Weickert et al. [87]	Randomized, controlled, single-blind, crossover study among 17 overweight or obese subjects with normal glucose metabolism. Diet: three macronutrient-matched portions of fiber-enriched oat bread (white bread enriched with 31.2 g insoluble fiber per day) or control (white bread) over a period of 72 h.	No significant changes were observed in postabsorptive serum adiponectin and ghrelin after 72 h high-fiber consumption compared with the control group.
Qi et al. [119]	Cross-sectional analysis in 780 diabetic men from the Health Professionals' Follow-up Study. Dietary information was obtained in 1986, 1990 and 1994 using semiquantitative food frequency questionnaires.	Adiponectin levels were 19% higher in the highest quintile than in the lowest quintile of cereal fiber. There were no significant associations between intakes of total fiber, vegetable fiber and fruit fiber and plasma adiponectin levels.
Qi et al. [136]	Cross-sectional analysis in 902 women with type 2 diabetes from the Nurses' Health Study. Dietary information was obtained using semiquantitative food frequency questionnaires.	Intakes of cereal fiber and fruit fiber were significantly associated (P=.002 and .036, respectively) with an increasing trend of plasma adiponectin concentrations. Adiponectin concentrations were 24% higher in the highest compared with the lowest quintile of cereal fiber.

showed that after 2 years, women who consumed a low-energy Mediterranean-style diet including a higher intake of fiber (25 vs. 16 g/day in the control group) exhibited decreased BMI and serum concentrations of proinflammatory markers IL-6, IL-18 and CRP, while adiponectin levels were significantly increased compared with the control group [85] (Table 2). The effects of dietary fiber on adiponectin are not clear, as in a recent short-term randomized trial performed over 3 days in overweight and obese subjects, no differences in adiponectin levels were observed following increased insoluble dietary fiber intake [87] (Table 2). In addition, two cross-sectional analyses performed in both diabetic men and women to examine the associations of dietary fibers and glycemic load with plasma adiponectin have found that diets low in glycemic load/index and high in dietary cereal fiber are associated with increased circulating adiponectin concentrations [119,136] (Table 2). Investigations in the experimental model of metabolic syndrome of obese diabetic Zucker rat have demonstrated that consumption of a diet supplemented with husks of *P. ovata* rich in soluble fiber for 25 weeks significantly reduced plasma TNF-α concentration and increased adiponectin circulating levels [66]. Taking into account the few studies in human and animal models concerning plasma adiponectin concentration following intake of diets with high dietary fiber content, results are controversial, although different outcomes could be attributed to the duration of the studies, as long-term investigations have revealed a relationship between high fiber intake and adiponectin, while no effect has been observed in short-term studies. More trials considering different types of fiber without further lifestyle or diet changes, and for short and long periods, should be

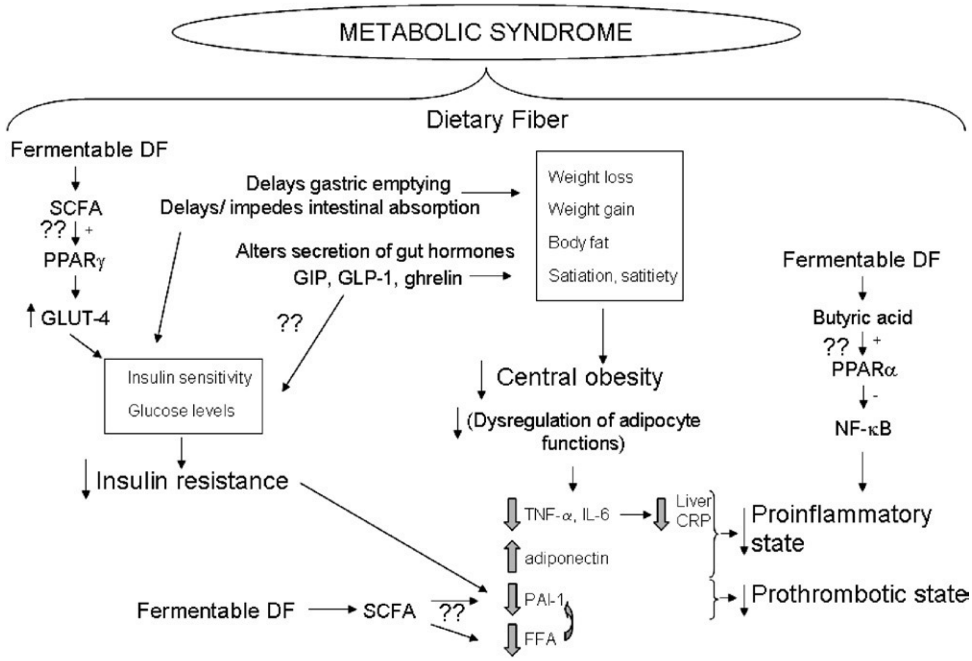

Fig. 2. Effects and possible mechanisms of dietary fiber on central obesity, insulin resistance, and proinflammatory and prothrombotic states involved in the metabolic syndrome. DF, dietary fiber; FFA, free fatty acid; NF-κB, nuclear factor-κB. ?? indicates mechanisms that have been proposed mainly in experimental models but that deserve further studies.

conducted to firmly clarify an association between dietary fiber intake and this anti-inflammatory adipocytokine that seems to play an important role in the pathogenesis of metabolic syndrome.

The mechanism of beneficial effects of dietary fiber on proinflammatory and anti-inflammatory cytokines and adipocytokines in adipose tissue is unclear. Its effect favoring weight loss could be involved, as most weight loss studies have shown that decreasing body weight was related to decreases in CRP [137] and in sera TNF-α of obese patients [138] and to increases in adiponectin circulating levels of obese women [85]. The hypoglycemic action of dietary fiber could also contribute to its anti-inflammatory effect. In a recent review article, King [139] suggested that dietary fiber decreases lipid oxidation, which in turn is associated with decreased inflammation. These anti-inflammatory effects of dietary fiber could also be attributed, in the case of fermentable fibers, to the production of butyrate. Clinical trials suggest that butyrate has anti-inflammatory properties in pathologies such as inflammatory bowel disease [140], and it has been described for anti-inflammatory activity in different human cellular types, such as macrophages and monocytes [141,142]. In a recent study, antiatherogenic properties have also been attributed to this molecule [143] in endothelial cells. Furthermore, this study suggests that the anti-inflammatory and perhaps antiatherogenic action of butyrate would be partly attributable to an inhibitory effect on the nuclear factor-κB activation through the activation of PPAR-α, and to the associated expression of VCAM-1 (vascular cell adhesion molecule-1) and ICAM-1 (intercellular adhesion molecule-1) [143], although this possibility deserves further studies.

4. Conclusion

Dietary fiber exerts clinical benefits on all the abnormalities clustered in the metabolic syndrome, since it has been shown to reduce body weight gain, dyslipidemia and hypertension and to improve insulin sensitivity in altered inflammatory markers associated with metabolic syndrome both in human studies and in experimental models. Considering the numerous types and sources of dietary fibers and their different physicochemical and physiological properties, it is extremely difficult to establish which mechanisms predominate in the beneficial effects exerted by dietary fibers on metabolic syndrome. While soluble gel-forming fibers regulate most of the metabolic disturbances clustered in this syndrome by different mechanisms linked to their gel-forming capability and their fermentability in the colon, nonviscous insoluble fibers contribute to ameliorate some of the same abnormalities by other not well known mechanisms. Both types of fiber are beneficial and probably complementary to reduce risk of cardiovascular disease and type 2 diabetes. A better understanding of the biochemical mechanisms by which each type of dietary fiber may regulate glucose and lipid metabolism and hormonal factors involved, such as the incretins GLP-1 and GIP, is decisive to reinforce nutritional strategies in the prevention and treatment of the constellation of disorders of the metabolic syndrome (a simplified schema of effects and possible mechanisms of dietary fiber on most of such disorders is represented in Fig. 2). An interesting but not yet well explored approach of the treatment of this syndrome deals with the effects of dietary fibers in the modulation of altered thrombotic and inflammatory markers and, although in the case of soluble fermentable fiber, SCFAs such as butyric acid seem to play a role, further investigations are needed to elucidate the mechanisms of these effects and those of insoluble fibers. In conclusion, this dietary strategy holds great promise and appears to be beneficial in some settings. Although more clinical studies are needed to firmly establish the relevance and involvement of dietary fibers in the prevention and treatment of metabolic syndrome components, recommendation of consumption of diets high in fiber for both healthy and risk group populations seems adequate and would represent a simple, noninvasive and socially acceptable method for reduction of metabolic risk factors that contribute to metabolic syndrome.

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