

REVIEW

# Trans Fats and Metabolic Syndrome

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Two issues affecting health today are metabolic syndrome and trans fats. Metabolic syndrome is a common condition that has no single known cause. Trans fats are fatty acids that can be artificially made and added to food, or can naturally occur in ruminant-derived foods. There has been speculation that metabolic syndrome and trans fats are correlated. Studies indicate both positive and negative correlations between metabolic syndrome and the consumption of trans fats.

Trans fats are isomers of polyunsaturated fatty acids which have at least one double bond in the *trans* configuration, rather than the *cis* configuration typically found in nature (1). There are two major types of trans fats: ruminant-derived and industrially-produced. Industrially-produced trans fats (ITFs) are made via the partial hydrogenation of liquid plant oils in the presence of a metal catalyst, high heat and vacuum. Heating food oil results in oxidation, hydrolysis, isomerization and polymerization, which transform the *cis* bonds into *trans* bonds. Trans fats are thereby incorporated into the food (2). Through this method, even simply heating food oil through cooking can result in the creation of trans fats. Ruminant-derived trans fats (RTFs) occur naturally in animals such as cattle. They are present in the meat and dairy products of ruminant animals. Although located throughout the body, prions are most prevalent in the nervous system, and this is primarily where disease prions do harm. Amyloid precursor proteins (APP) and tau are also located throughout the body but primarily in the nervous system, the location where the disease forms of these proteins primarily do harm (1,2).

Since RTFs are naturally occurring, they are difficult to avoid in omnivorous diets. Two similar studies performed by Mohankumar et al. and Wang et al. have shown that increased consumption of RTFs can help ease the effects of, or even reverse, metabolic syndrome. ITFs have been shown to cause or worsen the effects of metabolic syndrome (3, 4). Both types of trans fats are linked to coronary heart disease (CHD). Trans fats have been associated with both positive and negative

health effects. ITFs were first used in the 1950s to improve the taste, texture and shelf life of processed foods (5). ITFs were originally believed to be a healthy alternative to saturated fats. While saturated fats contribute roughly 10% of the total energy in the North American diet, trans fats constitute roughly 1-2% of the total energy (1). Association of trans fats with adverse health effects was discovered as early as 1957 (5). The major health problem associated with trans fats was CHD, which is the leading cause of death in the United States. In addition to CHD, trans fats are linked to cancer, particularly colon and breast cancers (1).

A minimal amount of trans fat is produced in the gut by gut flora. In one study, these gut-produced trans fats were shown to reduce carcinogenesis, atherosclerosis and overall body fat. These health benefits are conditional; the trans fats must be conjugated. These trans fats could be considered a health benefit. However, the amount of trans fat produced in the gut is trace, so overall benefit is minimal (4).

## Metabolic Syndrome

Metabolic syndrome, also known as metabolic X syndrome, MetS or MetX, is a condition marked by the presence of several other conditions. Metabolic syndrome was recognized as a condition in 1998 (6). Major indications of metabolic syndrome are increased belly fat, type 2 diabetes, high cholesterol and hypertension. Inflammation has also been linked to metabolic syndrome (7). Insulin sensitivity has been linked to hepatic conditions such as nonalcoholic fatty liver disease, thereby also linking it with metabolic syndrome. A possible primary cause of metabolic syndrome is insulin resistance. Other possible causes are

obesity and sedentary lifestyle, suggesting that a functional cure for metabolic syndrome might be achieved through better diet and exercise. However, unlike a pill or injection, this would not be a fast cure. Metabolic syndrome is a serious health concern today, as it leads to a 46% greater chance of mortality (2). Although the cause(s) for metabolic syndrome may be mostly unknown, it has been demonstrated that trans fats are a possible cause, or contributor, to the syndrome.

## Correlations between Trans Fats and Metabolic Syndrome

There have been several studies on correlations between metabolic syndrome and trans fats. There are both positive correlations (in which trans fats exacerbate metabolic syndrome) and negative correlations (in which trans fats help prevent or halt the progress of metabolic syndrome). These are dependent upon the type of trans fat consumed. In a study conducted by Mazidi, high trans fatty acid intake was linked with metabolic syndrome (8).

Trans fat intake has been positively linked to type 2 diabetes (9). As a potential key cause of metabolic syndrome, type 2 diabetes is associated with a decrease in insulin sensitivity. In one study, conducted by Kimokoti and Brown, rodents were fed a diet low in fat but high in trans fats (2). The diet led to a series of conditions including increased body fat (particularly around the belly/midsection), increased weight, higher blood sugar due to insulin sensitivity and fatty liver, all of which are indicative of metabolic syndrome. In the same study, short term consumption was not shown to be a leading cause of metabolic syndrome (2).

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Trans fats have been shown to be associated with oxidative stress, elevated pro-inflammatory cytokines, insulin resistance and metabolic programming. These are all linked with metabolic syndrome. Mother mice fed diets of increased trans fats and overall greater fatty acids during pregnancy and lactation were shown to have offspring who were predisposed to metabolic syndrome due to problems with mitochondrial bioenergetics and lipid metabolism (7).

An experiment conducted by Zhao et al. showed that fatty acid consumption caused obesity, insulin resistance and liver problems in mice, all signs of metabolic syndrome (10). Feeding mice elaidic acid, an ITF, also led to insulin resistance (11).

A possible mechanism of insulin resistance is the reduction of glucose transporter type 4 (GLUT4) expression, which may decrease the binding of insulin to adipocytes (12). GLUT4 is an insulin-regulated glucose transport mechanism protein. It is found primarily in adipose tissue and striated muscle tissue. In the GLUT4 study, trans fats were found to adversely affect high density lipoprotein cholesterol and oppose the effect of insulin, the latter of which is a possible cause of metabolic syndrome (12).

In human subjects, trans fat consumption was associated with dyslipidemia, diabetes, allergic disease and metabolic syndrome. Of 902 patients in one study conducted by Mori et al., 318 had metabolic syndrome (13). Fasting serum trans fat levels were higher in patients with metabolic syndrome and/or cardiovascular disease. In another human study conducted by Giugliano et al., a diet low in trans fats and rich in polyunsaturated fatty acids, such as omega-3 fatty acids, was shown to reduce inflammation, which in turn reduces atherosclerosis (7). Atherosclerosis leading to cardiac arrest and other fatal conditions is the leading cause of mortality due to metabolic syndrome (7). The research associates metabolic syndrome with inflammation.

A high plasma level of trans fats has been associated with unfavorable changes in glucose metabolism and cardiometabolic parameters, suggesting metabolic

syndrome (14). A higher intake of trans fats and fatty acids in general has been shown to lead to a higher incidence of metabolic syndrome (15). In another study by Maximino et al., there was a positive correlation between plasma trans fatty acids and metabolic syndrome (16).

Another indication of the positive link between ITF consumption and metabolic syndrome is the increased amount of cases in the developing world, where there are limited restrictions on using ITFs in foods. Increased trans fats consumption in India has been shown to cause an increase in cases of metabolic syndrome, especially in older, well-fed individuals (17).

Short term consumption of trans fat was not shown to be a significant cause of metabolic syndrome (18). In one study, a short-term diet containing 5-9% trans fats, which is much greater than average, was shown to have no adverse effects on insulin sensitivity and glucose metabolism, both key contributors to metabolic syndrome.

Many of the above studies only involved ITFs. However, RTFs have also been shown to be negatively correlated with metabolic syndrome. In a study conducted by Wu et al., RTFs were shown to lower insulin resistance, thus preventing type 2 diabetes (6). They were also shown to lower blood pressure and reduce hypertension. Both conditions are indications of metabolic syndrome (6).

Overall, it has been shown that the two major types of trans fats have markedly different correlations to metabolic syndrome. ITFs have a positive link, while RTFs have a negative link. There is no easy cure yet, and simply cutting ITFs out of a diet will most likely not cure metabolic syndrome, as consuming more RTFs will may not stave off the ITF effects. There have been cases where a decline in trans fats consumption alone did not halt the progression of metabolic syndrome (16). Trans fats, particularly RTFs and ITFs, which can be generated by cooking, are not easy to eliminate from the diet. Hence, trans fats are a dietary issue that is likely to persist.

#### Linoleic Acid and Other Fatty Acids

Several types of fatty acids have important nutritional value. Linoleic acid

is a polyunsaturated fatty acid in the *cis* conformation. It is found in vegetable oils and is vital to proper health. Linolenic acid, or  $\alpha$ -linolenic acid, is an omega-3 fatty acid, while  $\gamma$ -linoleic acid is an omega-6 fatty acid. Both types of fatty acids are found in vegetable oils. While omega-3 fatty acids have health benefits, they can become trans fats when heated. In studies conducted by Mohankumar et al. and Wang et al., there were no links between metabolic syndrome and linoleic acid (3, 4). However, *trans*-11 vaccenic acid and conjugated linoleic acid helped ease the symptoms of metabolic syndrome (3).

#### Hepatic Links to Metabolic Syndrome

Nonalcoholic fatty liver disease is also linked to insulin resistance, suggesting that metabolic syndrome may be affected by liver function (5). Although the molecular and cellular mechanisms for insulin resistance remain unclear, it has been shown that unsaturated fats, such as trans fats, have more of an effect on insulin resistance and/or insulin sensitivity than saturated fats (16).

It was demonstrated that a deficiency in or inhibition of 11 $\beta$ -HSD1 (cortisone reductase) can possibly give resistance to both metabolic syndrome and nonalcoholic fatty liver disease, which are related due to hepatic metabolism (19). Cortisone reductase is an enzyme that reduces cortisone in tissues, thereby activating related glucocorticoid receptors. This enzyme could be explored as a possible treatment for both conditions. Supplying 11 $\beta$ -HSD1 in some way, either pharmaceutically or through gene therapy, might be a treatment for metabolic syndrome, nonalcoholic fatty liver disease and other hepatic conditions (19).

#### Trans Fats and Metabolic Syndrome Worldwide

Metabolic syndrome may have been present in the developed world since before the official discovery of it in 1998, due to excess nutrition and sedentary lifestyles. Cases of metabolic syndrome are also showing up in the developing world, due to increased urbanization, more access to food, and increased lifespans (17). In developing nations such

as India, being obese can be a sign of status. Hence, obesity caused by metabolic syndrome may be looked upon favorably. Approximately 1.5 billion people throughout the world are obese. With belly fat a key symptom of metabolic syndrome, increasingly prevalent obesity could be associated with an increase in the prevalence of metabolic syndrome and related conditions (18). In Latin America, metabolic syndrome affects approximately 24.9% of the population (16).

The dangers posed by trans fats consumption, particularly ITFs, have been well documented, leading to a 2015 US government ban on added trans fats (5). This is not characteristic of the developing world, where starvation and malnutrition have been prevalent until relatively recently. A trend in the developing world is to have a diet more like the one in the industrialized world, consisting of mainly processed and fast foods rather than a simpler agrarian home cooked diet (20).

India is home to over a billion people. As in other developing nations, there is an increased demand for fats, oils and processed foods, resulting in increased consumption of trans fats. Vanaspati is a popular type of cooking oil in northern India consisting of approximately 53% trans fats (17). Many other foods in India have well over 40% trans fats (18). In decreasing order, the foods that tend to have the highest amount of trans fats are baked goods, animal products, margarine, french fries, snack chips, shortening, breakfast cereals and candies (20). In one Indian study, trans fat consumption led to female infertility, compromised fetal development, and an overall cognitive decline (21). Cases of metabolic syndrome are on the rise in India (21). Type 2 diabetes, CHD and hypertension, all indicative of metabolic syndrome, are all becoming more prevalent throughout India (21).

Trans fats are also prevalent in foods in Mexico and other parts of Latin America (16, 22). Cases of metabolic syndrome are also on the rise in Latin America. Metabolic syndrome has even been recorded among children in Mexico (22). Trans fats are also similarly present in foods, as is the case in India. In one study

conducted in Latin America, greater consumption of fatty acids in general, such as trans fats, led to a greater incidence of metabolic syndrome (16).

The new appearance of problems associated with the consumption of trans fats and metabolic syndrome are not limited to the developing world. A regression in diet and lifestyle, such as choosing junk foods over healthier alternatives and forgoing physical activity, can lead to a reoccurrence of metabolic syndrome. This may be the case in Japan, a modern industrial nation. In a study there, excessive consumption of trans fats led to systemic inflammation and endothelial dysfunction (14). These problems were not just limited to older people. The young population was also prone to effects if they excessively consumed trans fats (14).

In another study conducted by Yamada et al., involving young women in Japan, a diet rich in processed foods, which include trans fats, increased the risk of metabolic syndrome (22). The fat intake in Japan has been very low until recently. This study indicated a positive link between trans fat intake and metabolic syndrome. The authors stated that further studies are needed.

As in many industrialized Western nations, metabolic syndrome is an issue in Japan, where a study in 2000 surveyed 3264 people of varying ages and backgrounds (23). The overall incidence of metabolic syndrome was 7.8%. Men in the survey had a much greater incidence of metabolic syndrome at 12.8%, with onset generally around the age of 30, versus 1.7% of women with onset around the age of 50 (23).

Metabolic syndrome is a problem throughout the world, as is consumption of trans fats. To its detriment, the developing world is catching up to the industrialized world in these aspects rather than learning from the dietary and lifestyle mistakes previously made by their industrial counterparts.

Trans fats have been highly regulated since the discovery of the negative health effects and have been banned throughout the world. The dangers of trans fats were confirmed by 1990s studies which led to the United States ban on the addition of trans fats to foods (5). Although many

other developed nations followed, an average person in the developed world still takes in roughly 30 grams of trans fats daily. Better economic conditions and increased urbanization have led to increased demand for trans fats-based foods (17).

Trans fats in foods are a persistent widespread issue. They are naturally present in some foods and, while the addition of trans fats has been eliminated via legislation in much of the developed world, there are no such laws in the developing world. Increased communication regarding trans fat issues may help spread positive dietary information throughout the world.

### Usage and Replacement of Trans Fats

There is a link between ITFs and insulin resistance, which has been associated with metabolic syndrome. There is also an association with type 2 diabetes, a trademark condition of metabolic syndrome. One approach toward a functional cure in some cases may be to replace trans fats with other types of foods (2). A possible replacement for ITFs is the saturated fatty acid stearic acid (24, 25). Stearic acid is readily available in various foods, such as milk fat, lard, cocoa butter and shea butter. Mammals can also synthesize stearic acid from acetyl-CoA molecules. Stearic acid is absorbed much less efficiently than other saturated fatty acids and can be excreted (24, 25). Stearic acid also doesn't cause insulin resistance, which has been shown to be a contributing factor to metabolic syndrome (6). In general, saturated fatty acids have a less clear effect on insulin resistance than trans fats. The upper limit of dietary saturated fats is suggested at 5-10% of total energy intake due to negative effects on cardiovascular health (14).

### TLR-4 and MyD88

Insulin resistance has been shown to be induced by the activation of toll-like receptor 4 (TLR-4) in the liver (3). Increasing dietary fats can interfere with toll-like receptor 4. TLR-4 transcriptionally activates ceramide synthesis, which leads to inhibition of insulin signaling. The purpose of a study by Mohankumar et al. was to show that fatty acids, such as trans fats, did not directly

control insulin resistance (3). MyD88 protein is involved in signaling within immune cells where it plays a role in insulin signaling and insulin resistance. While fatty acid intake did result in the impairment of insulin signaling (and thus insulin resistance), hepatic ceramides were not increased, bringing into question the roles of TLR-4 and MyD88 (3).

Other data suggest that insulin resistance is not dependent on TLR-4 or ceramide synthesis, and a knockdown of TLR-4 or the protein MyD88 prevents fatty liver in rats (28). While the cellular and molecular mechanisms for insulin resistance currently remain unknown, the TLR-4 pathway has been shown to have effects on appetite. In addition, TLR-4 deficient mice developed hepatic insulin resistance when fed a diet rich in both saturated and unsaturated fats such as trans fats (28).

### Possible Cures for Metabolic Syndrome

Metabolic syndrome, which was only recognized as a definitive condition in 1998, currently has no known single cause (6). The main factors associated with metabolic syndrome include sedentary living and poor diet (2). There may be additional unknown causes yet to be discovered.

For example, cigarette smoking was shown to be positively linked to metabolic syndrome (15). Cigarette smoking decreases lung and heart capacity, thus limiting physical activity. The health dangers of cigarette smoking, and tobacco usage in general, have been well documented. There are many methods by which a person can cease using tobacco products, potentially alleviating one possible cause of metabolic syndrome (15).

Proper nutrition is another key component in the onset of metabolic syndrome. Foods leading to a caloric excess, such as carbohydrates, sugars and fatty acids, play a definite role in metabolic syndrome. In one experiment led by Dorfman, rodents fed a high caloric diet all had significant weight gain, body fat, higher blood sugar, fat accumulation in the tissues and signs of insulin resistance, all signs of metabolic syndrome (26). Rodents that were fed

omega 3 fatty acids, such as those found in fish oil, had less insulin resistance than those that did not (10). Salmon oil was also used in another study, with similar results (17). This study, conducted by Misra et al., also noted a negative link between omega 3 consumption and metabolic syndrome.

Trans fats, particularly RTFs, have been explored as a possible cure for metabolic syndrome. The RTF vaccenic acid was shown to have beneficial effects on cardiovascular disease when fed to rats (27). The rats in the study also had stimulated mitochondrial fatty acid oxidation, which could lead to improvements in liver and adipose tissue metabolism and reduction in dyslipidemia and hepatic steatosis (27). RTFs such as *trans*-11-vaccenic acid and conjugated linoleic acid were shown to ease the symptoms of metabolic syndrome (27). In another study, vaccenic acid was again shown to improve blood lipids and metabolic disorders such as metabolic syndrome (4).

Disease forms are promoted with increases in cholesterol.

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