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Invited Review

The toxicity of dietary trans fats

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ABSTRACT

Cardiovascular disease remains the leading cause of death today. Trans fatty acids have been identified as an important cause of cardiovascular disease and the resulting clinical end points such as strokes and heart attacks. Although legislative efforts have limited the trans fats in our diet, significant amounts remain. Understanding the impact trans fats have on our body, therefore, remains a critical focus of study. In addition, paradoxically, recent research has now identified an important cardioprotective role for a subcategory of trans fats, the ruminant trans fats. Learning more about the mechanisms responsible for not only the toxic actions of trans fats but also their potential as beneficial compounds within our diet is essential to modulate cardiovascular disease today.

1. The chemistry and dietary nature of trans fatty acids (TFAs)

TFAs are commonly thought to be of only one particular category; industrially produced trans fats (iTFAs). However, TFAs are found naturally in foods as well. These are commonly known as ruminant trans fats (rTFAs) (Ganguly et al., 2013) and will be discussed separately below.

1.1. Industrially produced trans fats

The creation of TFAs began with the process of hydrogenation in the 1890s. The process of hydrogenation requires the addition of hydrogen atoms to a particular organic compound. If scientists bubble hydrogen gas through vegetable oils in the presence of a nickel catalyst, this will reduce and saturate the fatty acids within the oil. In this way, polyunsaturated fatty acids (PUFAs) can be converted to monounsaturated fatty acids (MUFAs) or saturated fatty acids (SFAs) (Wang et al., 2012). However, while the original approach largely focused on the effects of hydrogenation in vapors, Wilhelm Norman took the procedure and successfully caused liquid oils to become solids which led to the creation of shortenings, butters and margarines. Margarines are created by a process known as partial hydrogenation. During partial hydrogenation, some of the *cis* isomers found in the aliphatic chain become *trans* isomers as the hydrogenation process leaves the double bond intact. Therefore, the aliphatic tail is no longer kinked causing distinct conformational changes. Partial hydrogenation is mainly used to remove unstable fatty acids. MUFAs and PUFAs are generally unstable. When partially hydrogenated, these fatty acids are no longer unstable. Partial hydrogenation increases the shelf life of food products such as margarine. The process of partial hydrogenation is, therefore, a hallmark identifier for iTFAs. Fried foods, fast foods, pastries, margarines, shortenings, cake mixes and many frozen dinners and packaged foods contain industrially produced trans fats. iTFAs are found primarily as elaidic acid (18:1 trans-9). Oleic acid (18:1) is a naturally occurring fatty acid found in many vegetable oils. Upon partial hydrogenation, it becomes elaidic acid and changes conformation. Although elaidic acid is the primary form of iTFAs, 18:2, 18:3 and 16:2 fatty acid moieties can also be found in a *trans* form in industrially produced food products. North Americans consumed between 5 and 10 g/day of iTFAs daily (Enig et al., 1990) with an upper limit of 20 g/day (Bassett et al., 2009; Enig et al., 1990). Five to ten grams of iTFA/day constitutes approximately 2–5% of total energy within our diets (Allison et al., 1999).

Abbreviations: iTFAs, industrially produced trans fats; rTFAs, ruminant trans fats; TFAs, trans fatty acids; PUFAs, polyunsaturated fatty acids; MUFAs, monounsaturated fatty acids (SFAs); SFAs, saturated fatty acids; cLAs, conjugated linoleic acids; CVD, cardiovascular disease; WHO, World Health Organization; HCM, hypertrophic cardiomyopathy; LDL, low density lipoprotein; HDL, high density lipoprotein; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intracellular cell adhesion molecule-1; Bcl-2, B-cell lymphoma-2; Bax, Bcl-2 associated X protein; Bak, Bcl-2 homologous antagonist/killer; Bad, Bcl-2-associated death promoter; Noxa, phorbol-12-myristate-13-acetate-induced protein; Puma, p53 upregulated modulator of apoptosis; PI3K, phosphoinositide 3 kinase; ATG-6, autophagy related gene (also known as beclin-1); LC3-I, microtubule-associated protein 1A/1B-light chain 3; hsc-70, heat shock chaperone-8.

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1.2. Ruminant trans fats

Ruminant TFAs are often overlooked due to the abundance of literature focusing on the effects of industrially produced trans fats in different diseases. However, typically we consume 2–9% of our total fatty acid content as rTFAs (Bassett et al., 2010). Furthermore, the TRANSFAIR study estimated that as much as half of all trans fats consumed in specialty diets like the Mediterranean diet will be in the form of rTFAs (van de Vijver et al., 2000). Ruminant TFAs are found in grass grazing sheep and cattle. Therefore, sheep and cattle meats as well as dairy products (cheese, milk and butter) contain rTFAs. The major contributor within the category of rTFAs is vaccenic acid. Vaccenic acid (18:1 trans-11) constitutes 50–80% of all ruminant derived trans fats (Field et al., 2009). Conjugated linoleic acids (cLAs) complete the rest of the category. Briefly, cLAs are also found in ruminant products and are identified by two double bonds within the aliphatic chain that are separated by a single bond in between. Rumenic acid (c9t11-CLA) is an example of conjugated linoleic acids. Vaccenic acid consists of only one double bond. It is the isomer of oleic acid (18:1 trans-11) and although similar to elaidic acid, the position of the double bond in vaccenic acid (position 11 vs. position 9 in elaidic acid) plays an integral role in determining the differences between the two fatty acids. Vaccenic acid is derived from incomplete biohydrogenation of the PUFAs, linoleic acid and linolenic acid, within the gut of the ruminant animals. Specialized gut microflora known as *Roseburia hominis A2-183T*, *Roseburia inulinivorans A2-192T* and *Ruminococcus obeum-like strain A2-162* produce vaccenic acid from these sources. It is therefore imperative that the differences between iTFAs and rTFAs are recognized in terms of their detrimental or positive health effects.

2. Cardiovascular disease overview

Cardiovascular disease (CVD) is a term that broadly defines diseases which affect the heart and vessels surrounding the heart. CVD leads to compromises in heart function including inadequate function of the pump and decreasing blood supply to surrounding organs. CVD is becoming an increasing problem worldwide. For example, in 2008, it was estimated that 29% of all deaths in Canada were attributed to CVD. Recent statistics also suggest that 1.3 million Canadians suffer from CVD over the age of 12 (Heart and Stroke Statistics, 2014). The World Health Organization (WHO) reports that CVD is the number one killer globally (World Health Organization, 2014). In 2008, it was estimated that 17.8 million people died from CVD around the world (World Health Organization, 2014). It is, therefore, essential that researchers and medical practitioners continue the search for preventative and treatment strategies for this significant disease.

3. Cardiovascular disease risk factors

CVD can be characterized by two major risk factors: modifiable and non-modifiable. Non-modifiable risk factors include genetic predisposition to CVD and family history (Camm et al., 2009). Hypertrophic cardiomyopathy (HCM) is an excellent example of a genetic predisposition to CVD. In hypertrophic cardiomyopathy, the myocardium is thickened creating disproportioned chambers. Most prominently, HCM affects the left ventricle. When HCM is present in the absence of risk factors such as aortic stenosis or hypertension, it is thought to have a genetic pre-disposition (Camm et al., 2009). Disruptions in sarcomeric proteins create a basis for genetic predisposition to HCM (Camm et al., 2009). These genes include beta-myosin heavy genes (such as MYH7) and alpha tropomyosin genes (TPM1). Genetic basis for other CVDs such as dilated cardiomyopathy and arrhythmias are currently under investigation (Camm et al., 2009). Sex, age, race and being post-menopausal are also non-modifiable risk factors for CVD (Camm et al., 2009).

CVD can also be caused by modifiable risk factors. These are associated with lifestyle choices. These include but are not limited to increased smoking, high blood cholesterol (specifically high low density lipoprotein (LDL) vs. high density lipoprotein (HDL)), hypertension, obesity, physical inactivity, diabetes and stress. Diet has also been associated with heart disease. This is particularly relevant to the types of fat consumed within a diet including saturated fats, MUFAs, PUFAs and trans fats. Risk of CVD and consumption of trans fats or PUFAs will be discussed in the following sections.

CVD disease encapsulates a wide range of different pathologies. In the following section, we will discuss atherosclerosis and ischemic heart disease as the predominant forms of CVD and the role that trans fats may play in their pathologies.

4. Atherosclerosis

Atherosclerosis is a sub-type of arteriosclerosis. Arteriosclerosis is the term used to describe thickening or hardening of the arteries. This includes general stiffening of the arteries as an adult begins to age. The hardening of the artery is derived from factors such as cholesterol, calcium, fibrin or cellular waste products. Atherosclerosis can be attributed to risk factors such as high cholesterol and triglycerides, smoking and high blood pressure.

The development of atherosclerosis is still incompletely understood. To date, atherosclerosis is dependent on LDL accumulation and inflammatory responses within the vessel wall. Atherogenesis describes the progression of atheromatous plaques. Atheromatous plaques develop from fatty streaks within the vessels. Age contributes to increased fatty streaks within the arteries. However, early atherogenesis develops when monocytes adhere to the endothelium and migrate to the sub-endothelial space within the vessel. This migration increases monocyte-derived macrophage activation. LDL can then invade the endothelium and ultimately the vascular wall where it becomes oxidized further contributing to increased inflammatory response and an increase in the size of the atheroma. An increased blood pressure, infections and other known risk factors can contribute to injuring the endothelial layer of vessels. These injuries can become sites of inflammation and atheroma development. Over time, as atheromas grow they can harden or calcify. On their own, atheromas may not contribute to the increased risk of CVD. However, if the atheromas grow to eventually block or hinder blood flow within the arteries of the heart or throughout the body, severe complications can occur. These include heart attacks, strokes and organ failure. Furthermore, if the atheroma becomes dislodged, it can travel throughout the body and block blood flow. This often occurs within the brain to induce a stroke.

Atherosclerosis is a complicated, serious disease with a variety of risk factors. Although the exact mechanism is unclear, decreasing risk factors such as smoking and cholesterol levels have been associated with a decreased risk of atherosclerosis progression and its subsequent complications (Kapourchali et al., 2014).

5. Trans fats and atherosclerotic heart disease

The association of circulating cholesterol or LDL with atherosclerosis and coronary artery disease is well documented (Kapourchali et al., 2014). Therefore, the potential for dietary TFAs to alter or promote this relationship was immediately identified as a possible mechanism for the deleterious effects of TFAs on the cardiovascular system. A positive association between elevated circulating LDL levels and TFA intake has been shown in epidemiological studies (Benesch et al., 2014; Vineis and Wild, 2014). A significant decrease in LDL cholesterol was observed in a recent meta-