

Fatty acids and their role in type-2 diabetes (Review)

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Abstract. Age, lifestyle and diet are major risk factors for the onset of type 2 diabetes mellitus (T2DM). Insulin resistance (IR) and β -cell dysfunction underlie the pathophysiology of T2DM. Diabetic populations are also prone to lipid and lipoprotein abnormalities as an indirect effect of IR on key metabolic enzymes. However, recent studies suggested that lipid changes may not only be a consequence of impaired glucose metabolism but also a causative factor. Fatty acids (FAs) influence translocation of glucose transporters and insulin receptor binding and signalling, in addition to cell membrane fluidity and permeability. It is thus suggested that FAs may have an essential role in the development of IR and T2DM. Specific combinations of FAs within phospholipids and triglycerides were indicated to exhibit the strongest associations with the risk of T2DM. The aim of the present review was to investigate the role of FAs in the pathogenesis of T2DM, as it has yet to be fully elucidated.

Contents

1. Introduction
2. FAs
3. n-3 and n-6 PUFA bioactive mediators
4. FAs and T2DM
5. Conclusion

1. Introduction

Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance (IR). Improved risk prediction and understanding of the pathogenesis underlying IR are crucial for the management of T2DM. The aetiology of IR is multifactorial. Genetic background and environmental factors, such as age, lifestyle and

diet, are two classifiable disease risk factors and the interaction between them contributes to the development of T2DM. Fatty acids (FAs) may have a key role in the development of IR and T2DM (1-3). However, the long-term effect of FAs on T2DM has yet to be fully elucidated (4).

While genomics, transcriptomics and proteomics have been widely used to improve the current understanding of obesity and T2DM, lipidomics is a tool that has been used comparatively less frequently (5). Lipidomics, which is a subcategory of metabolomics, may enhance the understanding of the contribution of FAs and lipids towards the development of health-related complications, particularly IR and T2DM. Circulating lipids and FAs may reflect an individual's lifestyle (e.g., diet and exercise) and their gene and protein activity, all of which may affect the development of IR and T2DM (6,7). Lipidomic techniques have provided valuable information on obesity and T2DM-related changes in adipocyte (8), macrophage (9), skeletal muscle (10), lipoprotein lipid composition (11) and liver FA metabolism (12), and have allowed researchers to better understand the contribution of obesity towards the development of T2DM. These methods have also enabled researchers to unravel the underlying mechanisms through which exercise, metformin and rosiglitazone improve the status of patients with T2DM (12,13). Lipidomic techniques have revealed that quantifying specific FAs within lipid fractions [e.g., triglycerides (TGs) and phospholipids (PLs)] may provide a more accurate indication of IR and T2DM (13-15). It was demonstrated that specific combinations of FAs within PL and TG exhibited the strongest association with the risk of T2DM, particularly shorter saturated FAs (SFAs) (15).

2. FAs

FAs may exist as free FAs (FFAs) in the body or they may combine with other molecules to form lipids, such as cholesterol esters (CEs), PLs and TGs (16-20). Low-density lipoprotein (LDL), very LDL and high-density lipoprotein consist of different relative amounts of CE, PL and TG. PLs have a hydrophilic phosphate head and two hydrophobic FA tails linked to a glycerol molecule. TGs contain FFAs that are esterified to a glycerol molecule. TG is the main form of fat in the diet. CEs are formed from FA and cholesterol by an ester bond between the carboxylate group of FAs and the hydroxyl group of cholesterol (16-20).

In addition to using fat as an energy source, the human body also synthesizes, desaturates and elongates FAs

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endogenously (21). The synthesis of FAs is low if the dietary intake of fat is moderate or high, whereas a high dietary intake of carbohydrates stimulates *de novo* lipogenesis (22-24).

Several factors affect endogenous FA metabolism and plasma FA composition, such as age and sex, health status, epigenetic changes and genes. Desaturation and elongation are steps of a metabolic pathway in which dietary and endogenous SFAs are elongated and converted to monounsaturated FAs (MUFAs), while highly polyunsaturated FAs (PUFAs) are synthesized from dietary n-3 FAs (e.g., α -linolenic acid) and n-6 FAs (e.g., linoleic acid) in the liver and adipose tissue (25,26). Desaturases and elongases are enzymes that activate these metabolic pathways. Desaturases add a double bond to the FA, whereas elongases lengthen the FA by adding two carbon molecules to the carbon chain. The metabolism of PUFAs is important, as they are the essential FAs of the human body (25,26).

A detailed understanding of the molecular structures and mechanisms implicated in FA synthesis and degradation may enable nutritional investigators to elucidate how and why specific dietary patterns and classes of FAs are associated with IR and T2DM (27). The changes in FA levels in the circulation caused by IR are summarized in Fig. 1. In a normal condition, when insulin binds to the insulin receptor it inactivates the enzyme hormone sensitive lipase (HSL) involved in the hydrolysis of TG to glycerol and FFA. In an insulin resistant state, there is an increase in the activity of HSL releasing free fatty acids into circulation to the liver. In the liver, hepatocytes take up the fatty acids and channel them into secretory pathways. The enzyme lipoprotein lipase in the blood vessels hydrolyses monoglycerides and FFA. As this cycling process continues, FFA also increases (Fig. 1).

Fig. 2 depicts how FFAs affect the insulin signalling pathway by increasing diacylglycerol (DAG), reactive oxygen species and protein kinase C (PKC), which in turn increases insulin receptor substrate-1 (IRS-1) serine phosphorylation and decreases IRS-1 tyrosine phosphorylation, thereby inhibiting the activity of PI3K. This finally leads to disturbance of the fragile balance between β -cell function and peripheral insulin resistance, which eventually results in the clinical manifestation of T2DM.

3. n-3 and n-6 PUFA bioactive mediators

Adipocytes and pancreatic β -cells produce a major group of pro-inflammatory mediators, the eicosanoids. Oxidation of n-3 and n-6 PUFAs [eicosapentaenoic acid (EPA), arachidonic acid (AA) and the linolenic acid (LA) derivative dihomogamma-LA] release major eicosanoids, including prostaglandins (PGs), leukotrienes (LTs), thromboxanes and lipoxins. These may be either pro-inflammatory or anti-inflammatory (28,29). PGs and LTs derived from AA are pro-inflammatory, whereas PGs and LTs derived from EPA are anti-inflammatory (Fig. 3) (16,30,31).

4. FAs and T2DM

A number of physiological pathways are affected by SFAs (32,33). Hepatic *de novo* lipogenesis occurs in response to a high dietary intake of carbohydrates or total calories, thereby

increasing the endogenous levels of SFAs (32,33). According to the Chinese philosophy concept, palmitic and oleic acid were described as the 'Yin' and 'Yang' of FAs by Palomer *et al* (34). Increased palmitic acid levels in subjects with diabetes may be explained via the enhancement of deleterious complex lipid synthesis, impairment of cellular organelle function and promotion of receptor-mediated inflammation (35,36). The rate of FA delivery to non-adipose tissues (liver, muscle, heart and pancreatic islets) depends on the increased plasma non-esterified FA (NEFA) content, promoting lipotoxicity and lipoapoptosis. These conditions raise intracellular palmitic acid levels above their mitochondrial oxidation limit and are converted to harmful complex FA-derived lipids, such as DAG and ceramide.

A high intracellular DAG content activates PKC isoforms, followed by phosphorylation of insulin serine residue 1, attenuating the insulin signalling pathway. Pro-inflammatory signalling cascade inhibitor and ceramide synthesis are, in turn, activated by PKC isoforms. Furthermore, ceramide also inhibits mitochondrial β -oxidation of FAs, induces endoplasmic reticulum (ER) stress and activates the NACHT, LRR and PYD domains-containing protein 3 inflammasome, a major instigator of inflammation (37). The perturbation of ER homeostasis by increased NEFA levels affects the lipid composition of ER due to lipid dysregulation, resulting in ER stress, which affects calcium signalling and attenuation of protein translation. Eventually, these modifications cause metabolic dysregulation and T2DM.

As mentioned above, according to the Chinese philosophy concept, if palmitate is the 'Yin' of FAs in T2DM, oleic acid is the 'Yang', as it elicits beneficial effects on insulin sensitivity (38). These beneficial effects of oleic acid are mediated by several mechanisms. Oleic acid reduces leukotriene B4 (LTB4) levels and increases insulin sensitivity (39). Oleic acid elicits anti-inflammatory effects by increasing the levels of the anti-inflammatory cytokine IL-10 and adiponectin and reducing the levels of pro-inflammatory cytokines (interleukin-6, tumour necrosis factor- α), induces macrophage polarization and reduces the secretion of LTB4 (38). FFA receptor 4 or G protein-coupled receptor (GPR)120 may also mediate these effects of oleic acid.

Unsaturated FAs have a key role in normal tissue function as major components of membrane bilayers, determining factors of cell structure and function and modulators of gene expression. Unsaturated FAs may be MUFAs or PUFAs (38). A previous study demonstrated that, in subjects with high fasting TG levels, MUFAs buffer β -cell hyperactivity and IR (40).

LA and α -LA (ALA) are essential FAs, as the human body lacks the desaturase enzymes catalysing their endogenous production and they may only be obtained from dietary sources (32,36). The relative FA levels in the plasma, serum or erythrocyte membrane reflect the rate of conversion of different FAs catalysed by key enzymes, such as FA desaturases (FADS) and elongases (33,34).

ALA is converted into the long-chain omega-3 polyunsaturated FA EPA or docosahexaenoic acid (DHA) (41). Preclinical data suggested that omega-3 improves insulin signalling (41). The proposed mechanism of how omega-3 improves insulin sensitivity is that omega-3 PUFAs attenuate ER stress, enhance FA β -oxidation in mitochondria and uncouple mitochondria,

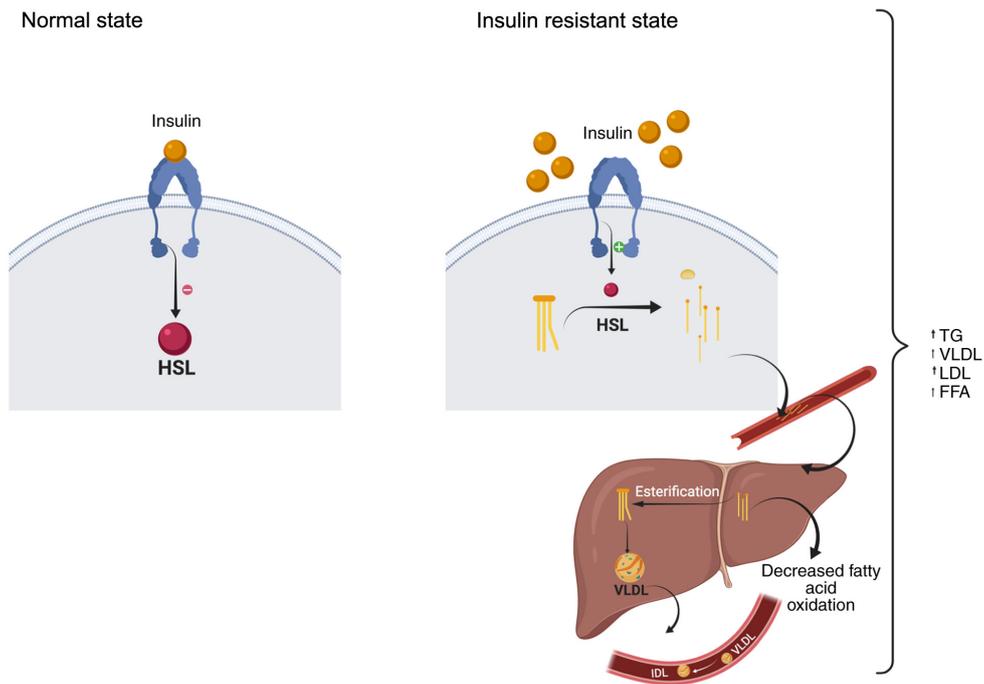


Figure 1. IR and changes in FA composition. In adipose tissue, in the normal state, insulin binds to the insulin receptor, inhibiting the enzyme HSL in the adipocytes of the adipose tissue. This HSL hydrolyses lipids such as TGs. In the state of IR, insulin is unable to bind to insulin receptors, thereby suppressing intracellular signals. In turn, it activates the HSL enzyme, which hydrolyse TGs to glycerol and FFAs, which are released into the circulation towards the liver. Liver hepatocytes take up FFAs to channel them to their secretory pathways. In the case of hyperinsulinemia/IR, esterification is increased. In the blood vessels, the enzyme LPL hydrolyses monoglycerides and FFAs. A certain proportion of these are delivered to liver LPL (hydrolysis). This process continues and more LDL and FFAs are formed (schematic created with BioRender.com). FFA, free fatty acid; HSL, hormone-sensitive lipase; LPL, lipoprotein lipase; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; TG, triglyceride; IR, insulin resistance.

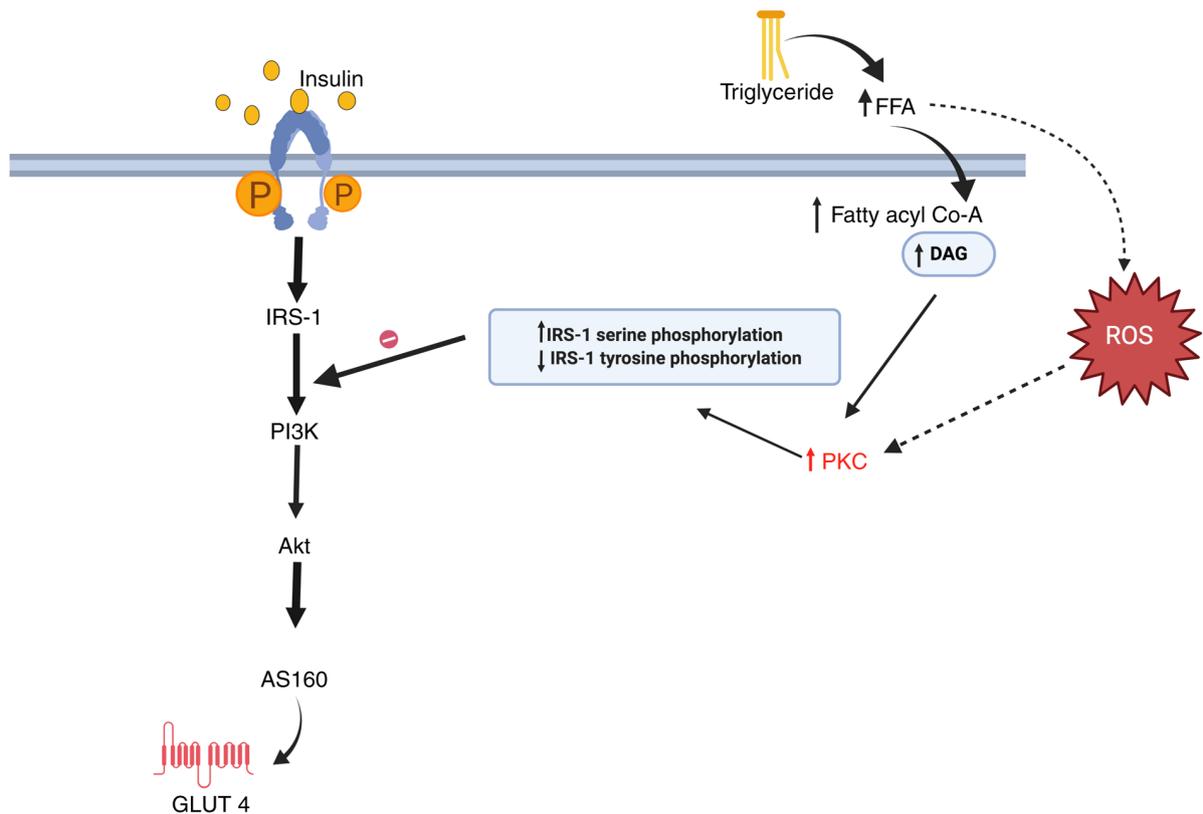


Figure 2. Effect of TG and FFA on the insulin signalling pathway. Elevated TG levels increase FFAs, which leads to accumulation of DAG and fatty acyl Co-A along with increased ROS. All of this together activates PKC, which interrupts the insulin signalling pathway (schematic created with BioRender.com). IRS, insulin receptor substrate; AS160, Akt substrate of 160 kDa; GLUT-4, glucose transporter 4; FFA, free fatty acid; ROS, reactive oxygen species; P, phosphate; PKC, protein kinase C; DAG, diacylglycerol; Co-A, coenzyme A; FFA, free fatty acid.

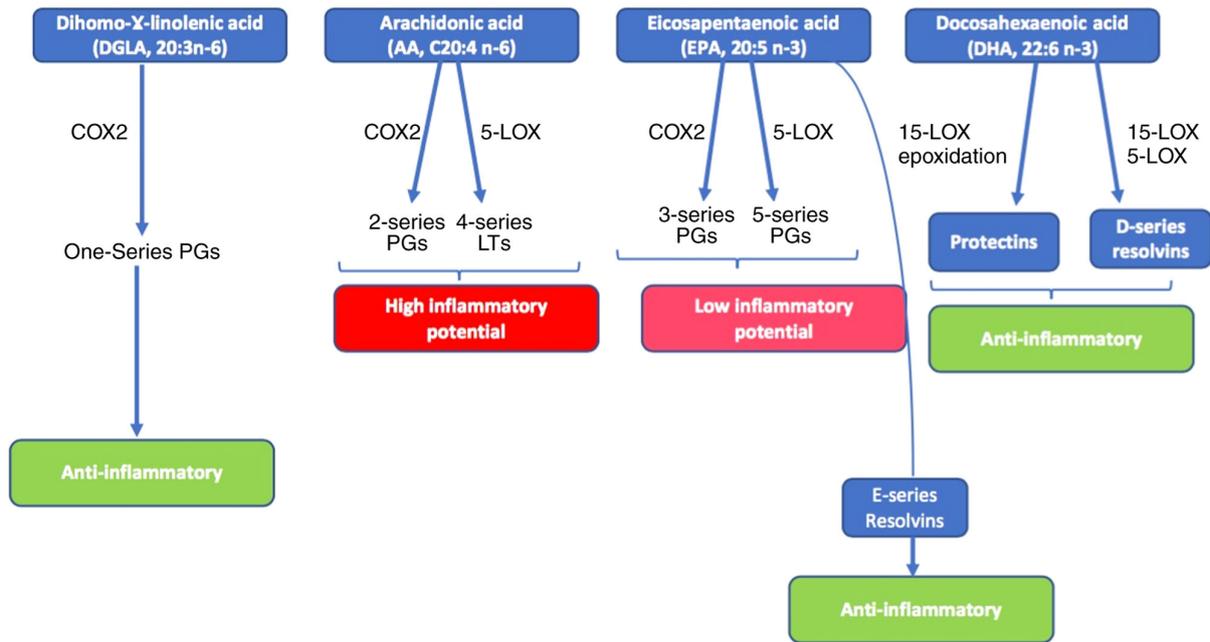


Figure 3. Bioactive mediators from omega-3 and omega-6 fatty acids. COX2, cyclooxygenase-2; LOX, lipoxygenase; PG, prostaglandin; LT, leukotriene.

causing reduction in lipid buildup and reactive oxygen species accumulation (38). In addition, a previous study reported the positive impact of these omega-3 FAs on mitofusin 2, which is involved in mitochondrial dynamics homeostasis and mitochondria-associated membrane integrity maintenance (41).

EPA and DHA regulate insulin sensitivity via Akt phosphorylation, activation of AMP-activated protein kinase (a treatment target for T2DM) and activation of peroxisome proliferator-activated receptor (PPAR)- γ (42). Several studies have demonstrated the role of EPA and DHA in preventing lipotoxicity and insulin sensitivity restoration (43-48). Omega-3 FAs also modulate pancreatic β -cell insulin secretion by exerting a direct effect on the lipid raft function and structure, and indirectly by inhibition of the expression of pro-inflammatory mediators in adipose tissue and the promotion of adipokine production (48). By contrast, omega-6 FAs are pro-inflammatory, as the product of omega-6 desaturation, AA, produces inflammatory cytokines and eicosanoids.

Omega-3 PUFAs inhibit inflammatory cytokine and eicosanoid production from AA and induce adipokine production from adipose tissue, and directly affect β -cell function by binding to PPARs, GPR40 and GPR120, thereby promoting insulin secretion (48). It remains elusive how exactly these PUFAs affect glucose metabolism (49). It has also been reported that a defect in the activity of D6 and D5 desaturases, the key enzymes of the PUFA desaturation pathway, may be a key factor in the development of IR (48), with ensuing public health implications.

Overall, the role of the increase in the FFA content of the body in IR may be explained with the insulin binding to its receptor. Under normal conditions, binding of insulin to its receptor in the adipose tissue cell membrane triggers an intracellular signal that suppresses the activity of hormone-sensitive lipase (HSL), an intracellular enzyme found in adipocytes, which hydrolyses lipids such as TG.

When an individual is insulin-resistant, this intracellular signalling is suppressed, thereby increasing HSL activity, which hydrolyses TG to glycerol and FFAs, which are then released into the circulation and accumulate in the liver. These FAs are taken up by the hepatocytes and are channelled to their secretory pathways. Due to IR, esterification increases. The enzyme lipoprotein lipase in the blood vessels hydrolyses monoglycerides and FFAs. This process continues, thereby increasing the FA content (49).

Omega-3 and omega-6 FAs continuously compete for the desaturation enzymes. ALA is preferred over LA by both FADS1 and FADS2 (50). Therefore, maintaining an optimal balance between omega-6 and omega-3 FAs in the diet is crucial for human health, as the physiological state is anti-inflammatory (51). Unbalanced omega-6/omega-3 ratio in favour of omega-6 PUFAs is highly prothrombotic and pro-inflammatory, contributing to the prevalence of atherosclerosis, obesity and diabetes (51). As previously reported, the target ratio of omega-6/omega-3 should be 1:1 to 2:1 (51). Although the Indian diet is low in fat when compared to the western diet (52), the incidence of coronary artery disease and T2DM are on the increase in this population. As per the previous report by Mani and Kurpad (52) although the Indian diet is rich in PUFAs, the ratio is in favour of omega-6 FAs, since the most abundant PUFA in the majority of plant products is LA. Therefore, the LA intake is high, irrespective of the type of vegetable oil used in a typical Indian diet (52). Therefore, dietary FA interventions specifically aimed at maintaining an optimal omega-6/omega-3 ratio may overcome the risk of developing T2DM.

5. Conclusion

Taken together, the present review indicated that the desaturation pathway appears to be highly important for maintaining

lipid homeostasis in the human body, the key to which may be ensuring a healthy omega-6/omega-3 ratio. This suggests that, in T2DM research, lipidomics may represent a useful approach to improve the understanding of the effect of different lipids on the risk of developing T2DM.

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Competing interests

The authors declare that they have no competing interests.

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