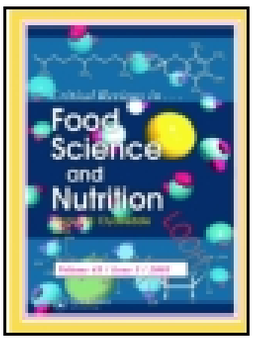

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Title Page

Polyunsaturated fatty acids and type 2 diabetes: impact on the glycemic control mechanism

Olívia Gonçalves Leão Coelho[1*], Bárbara Pereira da Silva[1], Daniela Mayumi Usuda Prado Rocha[1], Lílian Lelis Lopes[1], Rita de Cássia Gonçalves Alfenas[1]

[1]Department of Nutrition and Health, Universidade Federal de Viçosa, Viçosa, Minas Gerais, Brazil.

*Corresponding author: Department of Nutrition and Health, Universidade Federal de Viçosa, Avenida PH Rolfs s/n, 36570-900, Viçosa – MG, Brazil. E-mail: olivia.coelho@ufv.br

Abstract

There is a growing mortality related to co-morbidities associated with diabetes mellitus (DM). Polyunsaturated fatty acids (PUFA) intake has been associated with low cardiometabolic risk and reduction of inflammatory process. The objective of this paper is to review the impact of PUFA intake on glycemic control in diabetic patients, as well as elucidate the possible mechanisms involved. Medline/PubMed electronic database was searched to identify studies published within the last 5 years regarding the effect of PUFA intake on glucose metabolism in type 2 diabetics. The search terms used were: "polyunsaturated fatty acid (s)", “PUFA”, and “diabetes”. We included only intervetion studies that assessed the effects of PUFA intake on glucose metabolism – fasting glucose, serum insulin, HbA1c and HOMA-IR assessment– in type 2 diabetics. Initially, 48 articles were identified, which 1 was not available and 41 did not match the inclusion criteria. Within the selected studies, 3 showed an improvement on fasting blood glucose, 2 showed an increase on fasting glycemia and there was no effect of the intervention in only 1. Based on the analyzed clinical intervention studies, supplementation of 0,42-5,2 g

PUFA/day for at least 8 weeks may be an alternative treatment for T2DM, particularly to Asian people.

Key-words: Diabetes Mellitus, glucose metabolism, glycemic control, treatment, w-3 polyunsaturated fatty acids.

Introduction

The number of people with diabetes mellitus (DM) has increased worldwide. In 2000, DM prevalence was estimated to be 2.8%. In 2030, 4.4% of the population may have the disease. Therefore, in about 15 years there will be about 366 million diabetics in the world (Wild, Roglic, Green, Sicree, & King, 2004). Such pandemic is attributable mainly to population aging, increased obesity and sedentary lifestyle (van Dieren, Beulens, van der Schouw, Grobbee, & Neal, 2010; Wild et al., 2004).

In this scenario, there is a growing mortality directly or indirectly related to co-morbidities associated with DM. Cardiovascular diseases are the main complications of diabetes, accounting for half of the causes of death in type 2 diabetics (van Dieren et al., 2010).

Polyunsaturated fatty acids (PUFA) intake, especially when consumed in substitution of saturated and *trans* fatty acid, has been associated with improved lipid profile leading to attenuated cardiometabolic risk (St-Onge, Aban, & Bosarge, 2007; Zhao et al., 2004). In addition to the lipid-lowering effect, PUFA also exhibit others cardioprotective benefits, including the reduction of inflammatory process (Belchior et al., 2015; Lesná et al., 2013; Zhao et al., 2004).

Recently, the beneficial effect of PUFA on insulin sensitivity has been demonstrated in animal studies (Lamping et al., 2013; Matravadia, Herbst, Jain, Mutch, & Holloway, 2014; Nardi et al., 2014). Some studies have investigated the effect of PUFA on blood glucose level and insulin in diabetic adults (El-Sayed, 2011; Kondo et al., 2014; Miller et al., 2013; Müllner et al., 2014; Ogawa et al., 2013; Sarbolouki et al., 2013). Therefore, we reviewed the impact of PUFA intake on glycemic control in diabetics, as well the possible mechanisms involved, seeking the identification of strategies capable to control diabetes and its complications.

Methodology

Medline/PubMed electronic database was searched to identify studies published within the last 5 years regarding the PUFA intake on glucose metabolism in type 2 diabetics. The search terms used were: "polyunsaturated fatty acid (s)", “PUFA”, and “diabetes”. Articles in English, Spanish or Portuguese, describing human clinical trials were screened based on their titles and abstracts. We included only intervention studies in which the effects of PUFA intake on glucose metabolism – fasting glucose, serum insulin, HbA1c and HOMA-IR assessment– were assessed in type 2 diabetics (Figure 1). Studies involving children, pregnant women, and diabetics that had other diseases associated to DM were excluded. The selected studies are summarized in Table 1, and the particularities of each study will be discussed below.

Impact of polyunsaturated fatty acids consumption on glycemic control in diabetics

Hyperglycemia, insulin resistance, oxidative stress, low intensity chronic inflammation and dyslipidemia are the main complications related to diabetes. Improved insulin resistance and glycemic control are essential targets for t type 2 diabetics treatment (S.-C. Li et al., 2011; Ogawa et al., 2013). According to some authors, PUFA consumption may be beneficial on glycemic control (El-Sayed, 2011; Ogawa et al., 2013; Sarbolouki et al., 2013) insulin sensitivity improvement (Sarbolouki et al., 2013).

The ingestion of low doses of w-3 PUFA (up to 2.0 g/day) for 12 weeks improved fasting glycemia and HbA1c in diabetics (Ogawa et al., 2013; Sarbolouki et al., 2013). A reduction on fasting and postprandial glycemia was also verified when a higher intake of PUFA (5.2g/day) was implemented for a shorter period of time (8 weeks) (El-Sayed, 2011). However, the consumption of fish oil as source of PUFA for 4 to 6 weeks lead to an increase in fasting

glycemia (Kondo et al., 2014; Miller et al., 2013). We believe the variations in these studies methodologies favored the differences in the observed outcomes. Hereafter, we will discuss some aspects involved in these results.

A recent meta-analysis demonstrated that w-3 PUFA intake did not cause any detrimental or beneficial effects on type 2 diabetics (Wu et al., 2012). However, conflicting results were observed in a study (D. Li, 2015), in which the analysis was based on pacients ethnicity. According to that author, among the western population, only asian type 2 diabetics may increase insulin sensitivity in response to w-3 PUFA supplementation (D. Li, 2015). This suggests that the protective effect of w-3 PUFA on type 2 diabetes mellitus (T2DM) development may be affected by ethnicity. In fact, PUFA supplementation (0,42-5,2 g PUFA/day) lead to an improvement on Asians glycemic control was verified (El-Sayed, 2011; Ogawa et al., 2013; Sarbolouki et al., 2013) the studies listed on Table 1. On the other hand, no benefits were verified in the studies involving western population (Miller et al., 2013; Müllner et al., 2014). However, an adverse effect was observed when 12,8g PUFA/day was given to Asian diabetics (Kondo et al., 2014). The results of these studies suggest that PUFA supplementation to Asian diabetics may favor glycemic control up to 5,2 g/day, while this response is not observed when PUFA is administrated in high doses (El-Sayed, 2011; Ogawa et al., 2013; Sarbolouki et al., 2013) .

Hiperglycemia and oxidative stress, commonly observed in diabetics, contribute for advanced glycation end products (AGEs) formation and accumulation. AGEs are compounds formed by non-enzymatic reducing reaction of sugar molecules, lipids, free amino groups of proteins and nucleic acids (Huebschmann, Regensteiner, Vlassara, & Reusch, 2006). These

compounds are also known as glycotoxins, which are highly oxidants and have pathogenic significance in diabetes and in other chronic diseases (Uribarri et al., 2010). The accumulation of AGEs within the organism over time is associated with microvascular and physiologic changes, especially insulin resistance (Huebschmann et al., 2006; Ottum & Mistry, 2015). The AGEs were highlighted in 1970 through the Hb1Ac, which is still the most researched and evaluated AGE in clinical trials (Ottum & Mistry, 2015).

Fasting glucose and HbA1c concentration reduced in some (Ogawa et al., 2013; Sarbolouki et al., 2013), but remained unchanged in another study (Müllner et al., 2014). These results suggest that PUFA supplementation must be done for at least 12 weeks for a better glycemic control to be observed. In a shorter duration study (4 weeks), fasting glucose increased, but HbA1c concentrations were not affected (Kondo et al., 2014). It is clear that the duration of that study was not enough to lead to changes on HbA1c concentrations. This concentration depends on hemoglobin half-life, which is about 120 days. Therefore, HbA1c reflects the mean blood glucose concentration in the preceding 8-12 weeks (ADA, 2014)

Fasting insulin assessment is a simple method that can be used to evaluate hypoglycemia and has high validity for the diagnosis of insulin-resistant status (Oliveira, Souza, & Lima, 2005). When fasting insulin is an isolated measurement, it has questionable applicability in clinical practice because of the low correlation with *in vivo* insulin action (Olefsky, Farquhar, & Reaven, 1973). Thus, unchanged insulin cocentration can not be useful to evaluate the insulin resistance and insulin sensitivity when it is analyzed alone (Müllner et al., 2014). Serum insulin reduction in diabetics may not indicate low insulin resistance, but pancreatic beta cells failure which affects its capacitiy of secreting hormone (El-Sayed, 2011; Neto & Tambascia, 2002).

Therefore, to assess insulin resistance the concentrations of insulin and of fasting glucose should be assessed to obtain the HOMA-IR (Kondo et al., 2014; Matthews et al., 1985; Sarbolouki et al., 2013).

The consumption of 2.0 g/day of EPA capsules over 12 weeks reduced HOMA-IR, while serum insulin and QUICKI index remained unchanged (Sarbolouki et al., 2013). The increase of HOMA-IR and serum insulin was observed after the consumption of 12.8 g/day (6.5% of total caloric value) during 4 weeks (Kondo et al., 2014). Although the studies have adopted a PUFA intake within the recommended range (6 - 10% of daily energy intake) (WHO, 2003), the intervention with the highest dose (6,5% of total energy intake) and for the shortest period of time appeared to be unfavorable with regard to peripheral action of insulin in diabetic subjects. HOMA-IR and QUICKI indices assess plasma insulin concentrations compared to glucose blood level and reflects the degree of insulin resistance and insulin sensitivity, respectively (Katz et al., 2000). These indices have good correlations with glycemic control markers, including insulin resistance and glucose tolerance (Chen, Sullivan, & Quon, 2005).

Given these results, it is suggested that the consumption of up to 5.0 g/day of PUFA for at least 8 weeks improves glycemic control in type 2 diabetics. However, the results of the studies are controversial, indicating a need to elucidate the possible mechanisms involved in glucose control in order to identify an effective and safe dose of PUFA as an alternative therapy for patients with T2DM. Figure 2 summarizes the mechanisms by which the PUFA may contribute to glycemic control.

Possible mechanisms involved in blood glucose control

T2DM is characterized by insulin resistance in skeletal muscle and adipose tissue, as well as by hepatic gluconeogenesis dysregulation and uncontrolled insulin secretion in order to compensate the insulin sensitivity default (Gannon, Conn, & Vaughan, 2015). Inflammatory pathway activated by a chronic stimulus contributes significantly to the insulin resistance pathogenesis. In addition, the relation between macrophage and adipocyte plays an important role in the mechanism involved on decreasing insulin sensitivity (Schenk, Saberi, & Olefsky, 2008). Substances produced by adipose tissue in the inflammatory status, like tumor necrosis factor alfa (TNF-α), interleukin-6 (IL-6), resistin, among other pro-inflammatory cytokines and chemokines are able to activate intracellular pathways that trigger insulin resistance (Shoelson, Lee, & Goldfine, 2006). Therefore, w-3 PUFA anti-inflammatory potencial could lead to insulin sensitivity improvement (Berger et al., 2013; Sarbolouki et al., 2013).

Besides being an energy source, fatty acids can also act as signaling molecules in important cell processes (Hirasawa et al., 2005) and immunological processes (Oh et al., 2010). G-protein-coupled receptor (GPCR) excites and induces various cell responses through secondary messengers. Studies show the role of fatty acids stimulating G-protein-coupled receptor (GPCR) (Hirasawa et al., 2005; Itoh et al., 2003; Oh et al., 2010). GPCR receptors such as GPR40, GPR41, GPR43, GPR84 and GPR120 are activated by free fatty acids. Particularly, long chain fatty acids (EPA, DHA and arachidonic acid) (Briscoe et al., 2003; Hirasawa et al., 2005) are GPR40 and GPR120 ligands (Oh et al., 2010). Binding of w-3 PUFA binding to these receptors can directly and indirectly stimulate insulin secretion.

Insulin is secreted in response to elevated plasma glucose concentration. GPR40 is significantly expressed in pancreatic β-cells and also has a direct effect on insulin secretion.

When glucose concentrations are high as observed in diabetics, there is an increase in insulin release stimulated by linoleic acid (Itoh et al., 2003).

GPR120 is expressed in the adipose tissue, pro-inflammatory macrophages and gastrointestinal tract, especially in the enteroendocrine L cells (Hirasawa et al., 2005; Oh et al., 2010). Once the receptor binds to PUFA, those molecules have indirect effect on insulin secretion by promoting the release of glucagon like peptide-1 (GLP-1), an incretin peptide hormone. This stimulatory effect has a dose-dependent relationship with the concentration of free fatty acids in the blood, illustrating the powerful action of α-linolenic acid and DHA PUFA on this stimulus (Hirasawa et al., 2005).

T2DM subjects have reduced concentrations of glucose transporter type 4 (GLUT4) (Gannon et al., 2015). Another beneficial effect of the PUFA binding to GPR120 is the increase on GLUT4 translocation, which enhances glucose uptake by adipocytes (Oh et al., 2010). Insulin also promotes the translocation of intracellular vesicles containing GLUT4 and increases its expression in the muscle cells plasma membrane (Gannon et al., 2015). Hence, the consumption of PUFA increases insulin secretion directly and indirectly, as well as stimulates glucose uptake via GLUT4 in adipocytes. We emphasize the relevance of the role of these tissues in the pathogenesis of T2DM, particularly the skeletal muscle, since it is the major tissue involved on glucose uptake (70-80%) stimulated by insulin (Oh et al., 2010).

Insulin promotes the translocation of intracellular vesicles containing GLUT4 thus,allowing its integration with the plasma membrane. It has been shown that GLUT4 levels are lower in skeletal muscle of type 2 diabetics as well as in severe insulin resistant patients (Gaster, Staehr, Beck-Nielsen, Schrøder, & Handberg, 2001; Kampmann et al., 2011).

The role of GPR120 activation has been elucidated integrating its anti-inflammatory and insulin sensitizing effect through in vitro and in vivo studies. When PUFA binds to GPR120, it recruits the protein β-arrestin2 to the cytoplasm, leading the discontinuation of the inflammation cascade (Oh et al., 2010). It is known that there are several triggers for the onset of inflammatory process, however, in the mechanism involving β-arrestin2 we feature the lipopolysaccharide (LPS) and TNF-α (Kawai & Akira, 2006). LPS binds to toll-like receptors 4 (TLR4) while TNF-α binds to its receptor TNFR, and both links activate growth factor-βactivated kinase 1 (TAK1), which associates to TAK1 binding protein 1 (TAB1) and this initiates the inflammatory process. β-arrestin2 activation through GPR120 allows TAB1-β-arrestin2 link and blocks TAK1/TAB1 association, which is a crucial stage for factor nuclear kappa B (NfkB) activation and inflammation beginning (Oh et al., 2010). Considering the tissue chronic inflammation as a relevant component in insulin resistance (Schenk et al., 2008), PUFA anti-inflammatory action through GPR120 exerts potent insulin sensitizing effects.

Moreover, toll-like receptors (TLRs) are linked to the pathogenesis of insulin resistance and diabetes. In T2DM patients, the TLR2 and TLR4 activation are increased, which in turn contribute to systemic inflammation observed in those subjects (Dasu, Devaraj, Park, & Jialal, 2010). However, w-3 PUFA supplementation can suppress the TLR-induced signaling pathways and target gene expression, exhibiting an anti-inflammatory effect, probably by inhibition of TLR4 dimerization and recruitment into lipid rafts (Lee, 2003; Wong et al., 2009).

Peroxisome proliferator-activated receptors (PPARs) regulate the gene expression of proteins involved in glucose and lipid metabolism. Those transcriptional factors include PPARα, PPARβ/δ and PPARγ, which are receptors for fatty acids and their metabolites. W-3 PUFA are

considered natural pan-PPAR agonists (Moller & Berger, 2003). Therefore, w-3 PUFA can improve lipid profile and exhibit an anti-inflammatory response, thus enhance insulin action by PPARα activation (Evans, Lin, & Goldfine, 2005). In addition, the activation of PPARβ/δ, predominantly expressed in skeletal muscle, up regulates the expression of genes involved in fatty acid oxidation, leading to increased insulin sensitivity through improvement of lipid profile and reduced adiposity (Evans et al., 2005). PPARγ, highly expressed in adipose tissue, also contribute to increase systemic insulin action. Agonists of PPARγ can induce the fatty acid clearance in adipose tissue, lowering the circulating free fatty acids and reducing its transport to liver and muscle tissue, which enhances insulin sensitivity. Besides, PPARγ ligands mediate the down regulation of the expression of pro-inflammatory markers (e.g. TNFα) promoting insulin sensitization [6, 45, 46]. Moreover, adiponectin, an adipocyte-derived hormone with insulin sensitizing activity, is induced by PPARγ agonists (Evans et al., 2005; Moller & Berger, 2003).

Conclusion

Despite the controversial results of the analyzed studies, Asian T2DM subjects seem to be more likely to be benefited by PUFA supplementation in terms of improvement on glycemic control. Therefore, based on these clinical intervention studies, supplementation of 0,42-5,2 g PUFA/day for at least 8 weeks may be an alternative treatment for T2DM, particularly to Asian people. It is still necessary to investigate how the genetic background can modulate the mechanisms involved in the glycemic control, either improving inflammation and insulin sensivity or glucose uptake.

The authors have declared no conflict of interest.

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Table 1– Studies that evaluated the effect of polyunsaturated fatty acids intake on glucose metabolism in type 2 diabetics

Subjects and treatments	Ethnicity	Study design	Duration	Source of PUFA	Main results	Ref.
30 subjects (40 ± 3,2 y): -Test: 5,2 g PUFA /d (seed powder); -Control: 3 doses of 500mg of metformin/d	Asian	Randomized, controlled, double-blind	8 W	*Portulaca oleracea L* seed (52% of w-3 PUFA)	Test group: ↓ fasting glucose, ↓ post-prandial glucose and ↓ insulin after intervention.	(El-Sayed, 2011)
92 subjects (63 y): - Test: 6,7g PUFA /d - Control: 5,7 g PUFA /d	European	Randomized, paralell, and double-blind	10 W	Almond oil	↔ fasting glucose, ↔ HbA1c, ↔ insulin between groups and after intervention	(Müllner et al., 2014)

					(test group).	
67 subjects (45 ± 4,4 y): - Test: 2g/d PUFA (pills); - Control: 2g corn oil/d (pills)	Asian	Randomized, controlled, double-blind	12 W	EPA	Test group: ↓ fasting glucose, ↓ HbA1c, ↓ HOMA-IR, ↔ insulin and QUICKI comparing to control.	(Sarbolouki et al., 2013)
29 subjects (67,4 ± 11,5 y): - Test: 4g PUFA/d (pills); - Control: 4g corn oil/d (pills)	American	Randomized, controlled, crossover	6 W	Fish oil	Test group: ↑ fasting glucose comparing to control.	(Miller et al., 2013)
23 women (69,7 ± 6,6 y):	Asian	Randomized, crossover	4 W	Fish	Test group: ↑ fasting	(Kondo et al., 2014)

- Test: 12,8g PUFA/d - Control: 10,9g PUFA/d					glucose, ↑ insulin, ↑ HOMA-IR, ↔ HbA1c after intervention.	

HbA1c: glycated hemoglobin; HOMA-IR: insulin resistance index; QUICKI: quantitative insulin-sensitivity check index; y: years old; d: day; W: week↔: unchanged; ↑: increased; ↓: reduced.

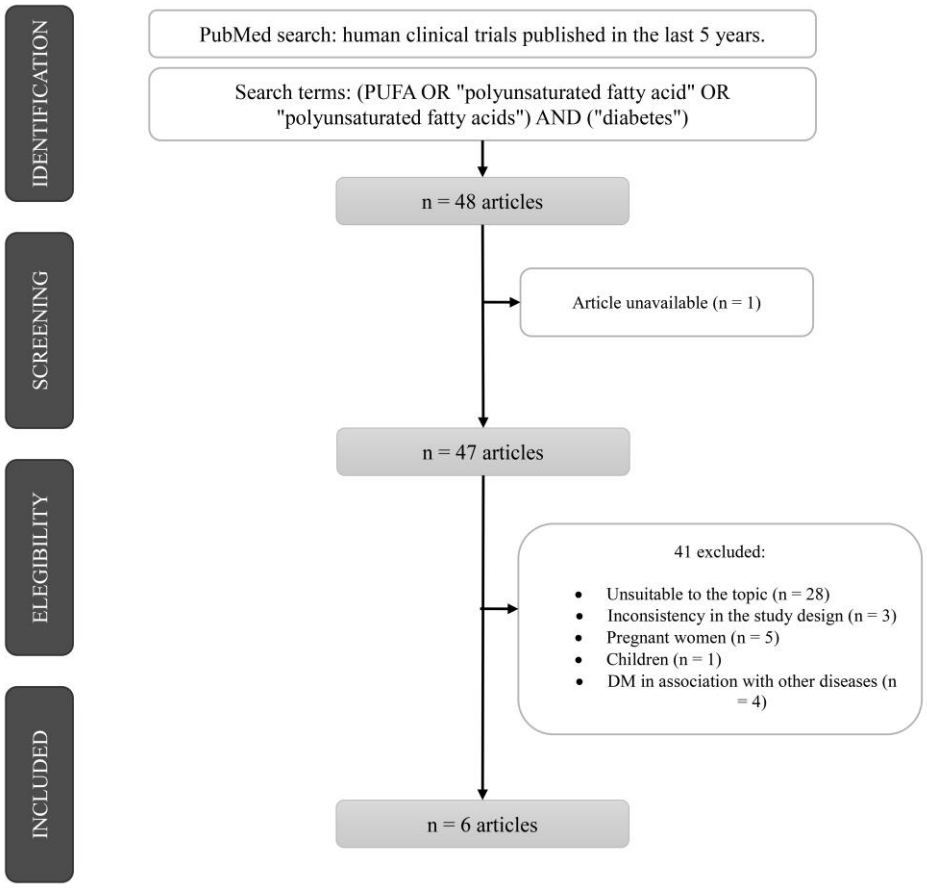

Figure 1 – Flowchart of studies selection.

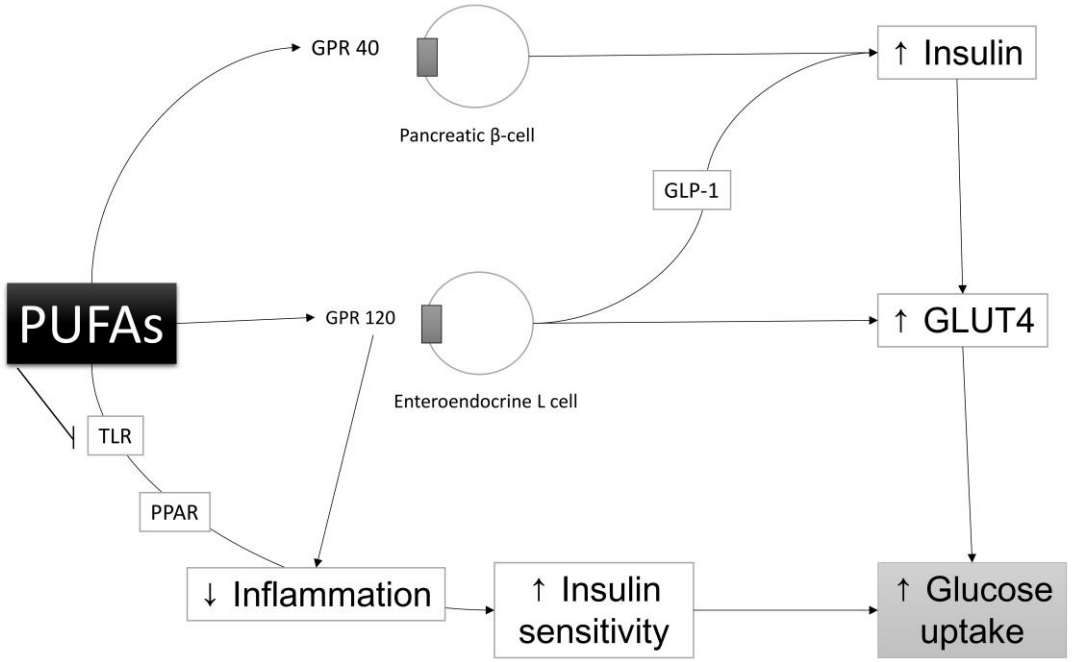

Figure 2 – PUFA potential mechanisms to improve glycemic control. PUFA is a GPR40 and GPR120 (mainly located in pancreatic beta-cells and enteroendocrine cells, respectively) ligand. Both act increasing insulin secretion either in a direct or indirect way (through GLP-1). Insulin increment promotes GLUT4 translocation in the muscle cells membrane. GPR120 increases the rate of adipocytes GLUT4, increasing glucose uptake. GRP120 also reduces the concentration of inflammatory mediators, increasing insulin sensitivity and glucose uptake. In addition, PUFA also has anti-inflammatory effects through TLR inhibition and PPAR activation.