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Knowledgebase Development and Review for the Function of Omega-3 Polyunsaturated Fatty Acid and Polysaccharide in Diabetes

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Abstract

It was well studied that omega-3 polyunsaturated fatty acid (PUFA) or polysaccharides have beneficial effects on the prevention and amelioration of human diseases including diabetes mellitus (DM). However, the effect of combination of these two components on DM has seldom been reported. Our aim was to study the research progress and discuss the potential synergistic effect of omega-3 PUFA and polysaccharides on DM. Based on the literature review, we developed a database named Database of Omega-3 PUFA and Polysaccharide in Diabetes (DOPD), which was freely available at http://bioinfo.life.hust.edu.cn/DOPD/. Users can browse and search the studies and their reported information about Omega-3 and polysaccharide in diabetes. Then we proposed some potential combinations of omega-3 PUFA and polysaccharide which would be better for DM based on their specific functions. The database and the potential combinations will provide useful resource for further studies on diabetes.

Introduction

Diabetes Mellitus (DM) is a chronic disease characterized by the absolute or relative shortage of insulin, leading to chronic hyperglycemia [1, 2]. There were 366 million people with DM in 2011 [3], and a lower life expectancy by approximately 12 years has been expected in people with DM [4]. Type 2 Diabetes Mellitus (T_2DM) causes macro vascular and micro vascular complication such as cardiovascular, cerebrovascular, retinopathy, nephropathy and neuropathy diseases [5]. It is well known that both environmental and genetic factors led to DM. The predominant cause of T_2DM is due to lifestyle factors including diet, insufficient physical activity, overweight and stress [2]. The genetic susceptibility to T_2DM has been demonstrated with at least 36 diabetes-associated genes identified, yet only about 10% of the heritability of T_2DM can be explained [6]. Medical nutrition therapy, physical activity and education have an important contribution to the general management of patients with DM [7]. Diets with specific foods and nutrients have been shown to exert a protective effect on T_2DM [8].

Omega-3 Poly Unsaturated Fatty Acid (PUFA) has potential beneficial impacts on the prevention of cognitive disorders and Cardio Vascular Disease (CVD), and synergistically improves metabolic parameters associated with weight loss [9-12]. Omega-3 PUFA decreases blood triglyceride levels and improves insulin sensitivity in humans [13-15]. Also, regular intake of omega-3 may reduce the DM complications [16, 17]. Similarly, polysaccharides, such as Astragalus Polysaccharide (APS) [18, 19], β-D-fructan polysaccharide (MDG-1) [20], *Ganoderma lucidum* polysaccharide (GL-PS/PSG-l) [21], levan polysaccharide [22], can also inhibit hyperglycemia and oxidative stress, and improve insulin sensitivity.

Although there have been many studies on omega-3 PUFA and polysaccharides, there were no studies on their combinatorial effects on DM. The aim of this article was to discuss whether the combination of omega-3 FUFA and polysaccharide has the potential synergistic effects on DM. Firstly, the research of omega-3 FUFA and polysaccharide on the prevention and amelioration of DM were simply summarized. Then the database of Omega-3 PUFA and Polysaccharide in Diabetes (DOPD, http://bioinfo.life.hust.edu.cn/DOPD/) was developed and discussed. Then combinations of omega-3 PUFA and polysaccharide such as the combination of APS and each of α-linolenic acid (ALA), Eicosapentaenoic (EPA) and Docosahexanoic Acids (DHA) were proposed by the specific function, which were increasing insulin secretion, hypoglycemic activity, and anti-inflammatory activity or improving lipid metabolism.

Material and Methods

Data source and database content

The Database of Omega-3 PUFA and Polysaccharide in Diabetes (DOPD) were built from articles collected in PubMed (http://www.ncbi.nlm.nih.gov/pubmed). We extracted the omega-3 PUFA or polysaccharide components that were effective in preventing or ameliorating DM. The current version of DOPD contained 197 articles related to omega-3 PUFA and 76 articles related to polysaccharides. The data were categorized with Pubmed ID, purpose, study object, component, method, study process, results and conclusion [Figure 1].

Database function and interface

DOPD was built on Apache server 2.2.22 (http://www.apa-che.org/) with PHP scripts (http://www.php.net/) and the data were stored in My SQL relational database. My SQL and PHP technologies were preferred due to the open source of the software and the platform-independent characteristics.

Results and Discussion

Omega-3 PUFA on DM

The most important components of omega-3 PUFA are ALA, EPA and DHA. ALA has a plant origin and is the precursor of EPA and DHA [23]. The consumption of omega-3 PUFA has been shown to reduce risk factors for CVD and T_2DM, such as hypertension, hyperlipidaemia, insulin resistance and inflammation [24-26].

Omega-3 PUFA Ameliorate the Insulin Resistance

Insulin resistance is a sign of diabetes, and its development involves several adipokines, including leptin, tumor necrosis factor-α (TNF-α), interleukin-6, adiponectin, and resistin [27]. Adiponectin regulates the lipid and glucose metabolism, increases insulin sensitivity, and protects against a chronic inflammation [28]. Leptin is an adipokine involved in the regulation of satiety and energy intake [29]. Haugen [30] reported that ALA could reduce resistin mRNA levels in 3T3-L1 adipocytes. Thus omega-3 PUFA could make the levels of adipokines increase or decrease, which all contributed to ameliorate insulin resistance. Kazemian [31] proposed that omega-3 PUFA could bind to a G-protein coupled receptor, resulting in reduced cytokine production and thus improving signaling in adipocytes, leading to a reduction in insulin resistance.

Omega-3 PUFA Can Exert Anti-Inflammatory Effects

T_2DM is considered as an inflammatory disease [32]. Increasing evidences have demonstrated that EPA and DHA can suppress inflammation and have a beneficial role in a variety of inflammatory diseases including diabetes, atherosclerosis, and arthritis [33]. It has been reported that stimulation of macrophages with omega-3 PUFA abolished NLRP3 inflammasome activation and reduced the production of interleukin-1/ 2/ 6 (IL-1/ 2/ 6) and TNF-α [34, 35]. EPA and DHA-derived resolvins and protectins are key inflammation resolution agonists [36]. It also has been demonstrated that EPA and DHA exert anti-inflammatory effects through several mechanisms, including activation of AMPK [37] and PPARG [38], as well as suppression of toll-like receptors (TLRs) and NF-κB pathway [39, 40]. Omega-3 also can reduce blood pressure and oxidative stress in T_2DM patients [41, 42].

As discussed above, omega-3 PUFA can prevent or ameliorate DM and its complications through multiple mechanisms, such as increasing insulin secretion, improving lipid or glucose metabolism. Omega-3 PUFA also can exert anti-oxidant and anti-inflammatory activity in DM and its complications. The number of publications on the effects of omega-3 PUFA on DM was summarized in Figure 2a, which showed a gradually increasing trend in last fifteen years. The allocation of publications for different omega-3 PUFA components was shown in Figure 2b.

Polysaccharide on DM

Polysaccharides such as APS and Lycium barbarum polysaccharide (LBP) can not only inhibit hyperglycemia and oxidative stress, but also improve insulin sensitivity. Here, we focused on the two polysaccharide components which have beneficial effects on DM.

The Beneficial Effects of LBP on DM

LBP as one of the traditional oriental medicines can significantly reduce the blood glucose levels and serum total cholesterol and thyroglobulin concentrations in alloxan-induced diabetic animals [43, 44]. The effects of LBP on the improvement of insulin resistance were investigated in a rat model of Non-Insulin Dependent Diabetes Mellitus (NIDDM) [45]. The mechanism involved was that LBP increased the level of Glucose Transporter 4 (GLUT4), improving GLUT4 trafficking and intracellular insulin signal. Additional study also indicated LBP could control the blood glucose levels and modulate the metabolism of glucose, leading to significant decrease of Malonaldehyde (MDA) and increase of SOD (Superoxide Dismutase). Furthermore, LBP could decrease levels of DNA damage possibly through decreasing in oxidative stress levels in rats with NIDDM [46].

The Beneficial Effects of APS on DM

Protein tyrosine phosphatase 1B (PTP1B) was a key negative

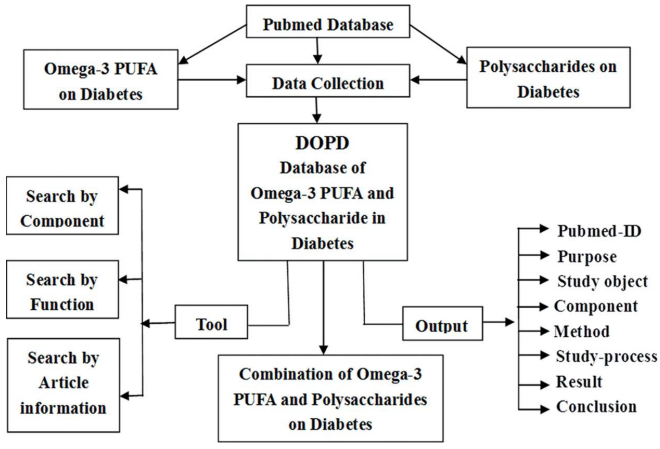

Figure 1: The schematic representation of architecture of database DOPD

regulator of insulin signaling and emerged as an attractive target for therapeutic intervention of T_2DM [47]. APS increased the insulin sensitivity by decreasing the expression of PTP1B [48, 49] and two other pathways including ROS-ERK-NF-κB [50] and PKB/GLUT4 [51]. APS exerted anti-inflammatory effects by inducing IL-10 gene expression and inhibiting IL-1β protein production and most of the pro-inflammatory genes expression [52]. APS showed beneficial effects to lower body weight, blood glucose and triglyceride levels in mice with insulin resistance and DM [53]. Besides, APS partially improved myocardial glucose and lipid metabolism disorders in diabetic hamsters and protected myocardium [54].

Thus, polysaccharides exert anti-diabetes effect or have beneficial effects on DM complications through different ways. The number of publications on the effects of polysaccharides on DM was summarized in Figure 2c, which showed a gradually increasing trend in recent years. The allocation of publications for different polysaccharide components was shown in Figure 2d.

The development of DOPD database

The database interface includes the following sections: HOME, SEARCH, SUMMARY 1, SUMMARY 2, SUMMARY 3, and HELP.

In the search interface, there are three methods for search: 1) search by a specific omega-3 PUFA and polysaccharide components; 2) search by one or two functions which both omega-3 PUFA and polysaccharide have; and 3) search by article information, such as PMID, title, publication time and so on. Furthermore, a combination search of the components and functions can also be carried out.

To better understand the function and mechanism of omega-3 PUFA and polysaccharide on DM, we categorized the potential functions into 7 types [Figure 2e]. The SUMMARY 1 section includes some basic statistics of the publications in the database [Figure 2]. The SUMMARY 2 and SUMMARY 3 sections are the combined article information of both PUFA and polysaccharide in each function category showed in different way [Figure 2e], which may indicate the study trend and status of omega-3 PUFA and polysaccharides on DM and its complications intuitively. Users can click the article number to browse the detail information. On SUMMARY 2 page, users can filter by keywords or rank each column by the number.

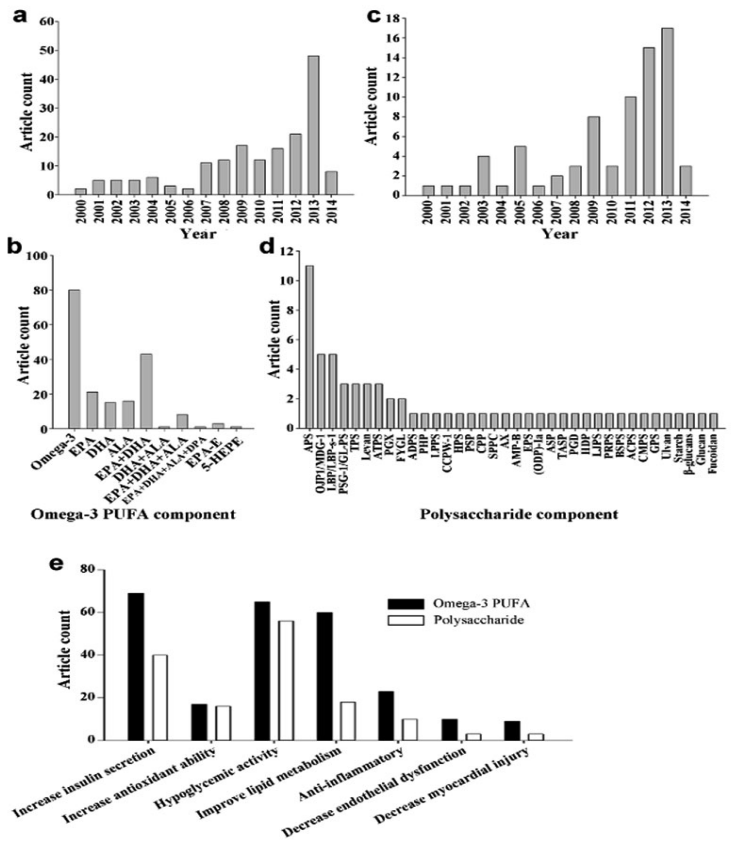

Figure 2: The number of articles of different years and components of omega-3 PUFA and polysaccharides on DM
a. The number of annual articles for omega-3 PUFA on DM after 2000.The number of the year 2014 is only for the first two months.
b. The number of publications for different omega-3 PUFA components on DM. Omega-3 column means the article only mentioned omega-3 and no specific components.
c. The number of annual article for polysaccharides on DM after 2000. (The number of 2014 is only for the first two months)
d. The number of publications for different polysaccharide components on DM. e. The number of articles correlated with different functions.

The prediction of combined effects of omega-3 PUFA and polysaccharide

Amir Abdolahi [55] reported that the ingestion of fish oil, both alone and in combination with aspirin, reduced Lysophosphatidylcholine (LPC) and Lysophosphatidic Acids (LPA) plasma concentrations, which may reduce cardiovascular disease risk in diabetic adults. Canetti [56] demonstrated that Essential Fatty Acids (EFA) mainly concluding Linoleic Acid (LA) and ALA can not only reduce pancreas damage, insulin and glucose plasma levels, but also restore the Delta6 desaturase activity in streptozotocin-induced diabetes mice. Iancu [57] pointed out that only the diet supplemented with both flaxseed (which was very rich in omega-3 PUFA) and vitamin E resulted in the significant reduction of platelet aggregation and adhesiveness as compared to diabetic animals fed with control diet in diabetic hamsters. You-Gui Li [58] reported that Deoxynojirimycin-Polysaccharide Mixture (DPM) decreased blood glucose and reversed the damage to pancreatic β-cells in diabetic mice, thus the anti-hyperglycemic efficacy of this combination was better than that of 1-Deoxynojirimycin (DNJ) or polysaccharide alone. However, whether the combination of omega-3 PUFA and polysaccharides can exert synergistic effects on DM is unknown. Thus, based on our developed DOPD database, we predicted the potential synergistic effects on DM combining omega-3 PUFA and polysvaccharides.

In our database, SUMMARY 2 and SUMMARY 3 both show the potential effects on preventing and ameliorating DM and its complications by combining omega-3 PUFA and polysaccharide but with different strategies. Take SUMMARY 3 for an example [Figure 3], each row of the form represents the component of polysaccharides while each column is different components of omega-3 PUFA. In the cross-cell, A, B, C, D, E, F, G represent seven different functions [Figure 2e], numbers in brackets represent the articles number that omega PUFA and polysaccharide have effects on DM respectively. In the cross-cell of EPA and APS, "A" represents function "Increase insulin secretion", so there are 7 articles about EPA and 9 articles about APS on "Increase insulin secretion" in DM, others are as the same principle. Also the numbers take on different color, it is set up according to the number of omega-3 PUFA which the gradient is 10, followed by gray, green, bright green and red. If the number is gray, it indicates that omega-3 PUFA and polysaccharide has no same function. Furthermore, the number can link to related articles.

On the basis of database, several potential combinations of omega-3 PUFA and polysaccharides were suggested to prevent and ameliorate DM [Figure 3]. First, the combination of APS with EPA, DHA or ALA: APS was the most studied polysaccharide on DM, and it shared at least four same functions with EPA, DHA and ALA, including increasing insulin secretion, hypoglycemic activity, and anti-inflammatory activity and decreasing endothelial dysfunction as well as decreasing myocardial injury. Furthermore, APS and EPA, DHA as well as ALA can regulate NF-κB, AMPK, PPAR-ɣ or other translational factors or proteins that involved in DM. Second, the combination of *Ganoderma lucidum* polysaccharide (PSG-1) and each of EPA, ALA and DHA: PSG-1 had the most same functions with EPA, DHA as well as ALA, which could reach to seven functions with EPA and ALA. Third, the combinations of MDG-1 with EPA, both of them had four same functions. All the suggested combinations of omega-3 PUFA and polysaccharides have not been proposed and reported. It was worth pointing out that the database has the capability to find out whether both omega-3 PUFA and polysaccharide can regulate the same genes and the related signal pathways in DM if the deposited sources contain genetic information that omega-3 PUFA or polysaccharide regulated in DM.

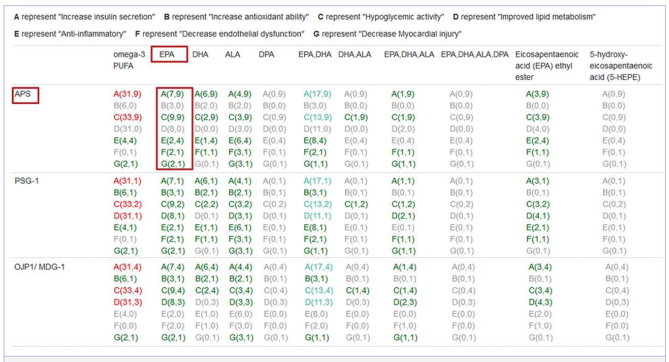

Figure 3: The combination of omega-3 PUFA and polysaccharide connected by functions
The rectangle colored with red is an example of the supported article number of APS and EPA in each function.

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